Calcific Aortic Stenosis

A Disease of the Valve and the Myocardium

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Although aortic stenosis is a common condition associated with major morbidity, mortality, and health economic costs, there are currently no medical interventions capable of delaying or halting its progression. Re-evaluation of the underlying pathophysiology is therefore required so that novel therapeutic strategies can be developed. Aortic stenosis is characterized by progressive aortic valve narrowing and secondary left ventricular hypertrophy. Both processes are important because in combination they drive the development of symptoms and adverse events that characterize the latter stages of the disease. In this review, the authors examine the pathophysiology of aortic stenosis with respect to both the valve and the myocardium. In particular, the authors focus on the role of inflammation, fibrosis, and calcification in progressive valve narrowing and then examine the development of left ventricular hypertrophy, its subsequent decompensation, and the transition to heart failure. Finally the authors discuss potential therapeutic strategies on the basis of similarities aortic stenosis shares with other pathological conditions. (J Am Coll Cardiol 2012;60:1854–63) © 2012 by the American College of Cardiology Foundation

Calcific aortic stenosis (AS) is the most common form of valve disease in the Western world and represents a major healthcare burden. Over the past decade, the number of aortic valve replacements performed in the United States has doubled, and with an increasingly elderly population, the prevalence of AS is likely to double again in the next 20 years (1). However, the pathophysiology underlying AS remains incompletely defined, and there are currently no effective medical treatments capable of altering its course. Furthermore, we lack reliable markers that can predict disease progression, the future need for surgery, or mortality. There is therefore a pressing need to re-evaluate the underlying pathophysiological processes involved.

AS is characterized by progressive narrowing of the aortic valve that increases the pressure afterload on the left ventricle. Myocytes enlarge and wall thickness increases in a hypertrophic response that initially restores wall stress but ultimately proves maladaptive. The rate at which patients with AS move toward symptoms, adverse events, and the need for surgery is determined both by the severity of the valve narrowing and by the myocardial hypertrophic response (2,3). Both processes are of clinical importance, and although linked, they are under the influence of different

pathological factors. In this review, we discuss each in turn, focusing on the role of inflammation, fibrosis, and calcification in the development of progressive valve narrowing and then on the factors modulating the left ventricular hypertrophic response, its decompensation, and the transition to heart failure. Finally, we review the similarities AS shares with other pathological conditions, with the aim of highlighting potential targets for novel therapeutic interventions.

Valve Narrowing

Anatomy of the normal valve. Normal aortic valves are made up of 3 cusps (Fig. 1), the arrangement of which results in even distribution of mechanical stress to the valve ring and the aorta (4). Each cusp is <1 mm thick and appears smooth, thin, and opalescent, with very few cells. They are composed of 4 clearly defined tissue layers: the endothelium, fibrosa, spongiosa, and ventricularis (Fig. 1). At their base, the valve leaflets are attached to a dense collagenous network, called the annulus, which facilitates their attachment to the aortic root and the dissipation of mechanical force.

Pathology. In calcific AS, the valve cusps become progressively thickened, fibrosed, and calcified. This results in increased valve stiffness, reduced cusp excursion, and progressive valve orifice narrowing that contrasts with the cusp fusion seen with rheumatic heart disease. Historically, calcific AS has been attributed to prolonged "wear and tear" and age-associated valvular degeneration. However, recent evidence suggests that it is instead the result of active

inflammatory processes involving biochemical, humoral, and genetic factors (Fig. 2).

MECHANICAL STRESS AND ENDOTHELIAL DAMAGE. The early stages of AS are in many ways similar to those of atherosclerosis (Table 1). As with atherosclerosis, the initiating event is believed to be endothelial damage resulting from increased mechanical stress and reduced shear stress. This results in a characteristic distribution of lesions within the stenotic valve. Shear stress is highest in the cusps adjacent to the coronary ostia because of the influence of coronary artery flow. Consequently, the noncoronary cusp has lower shear stress and is most frequently involved in AS. Mechanical tissue stress is highest around the flexion areas of the cusps near their attachment to the aortic root, and 50% of lesions can also be observed in this region (5). However, the bicuspid aortic valve perhaps best illustrates the role of mechanical stress in the pathogenesis of AS. This common congenital abnormality is characterized by a 2-cusp structure that results in a less efficient distribution and concentration of mechanical forces within the valve such that AS develops almost invariably and on average 2 decades earlier than in patients with tricuspid valves (6).

INFLAMMATION. Endothelial injury or disruption may allow lipids to penetrate the valvular endothelium and accumulate in areas of inflammation (7,8). The lipoproteins implicated in atherogenesis, including low-density lipoprotein and lipoprotein(a), are present in early aortic valve lesions (7) and undergo oxidative modification (8). These oxidized lipoproteins are highly cytotoxic and capable of stimulating intense inflammatory activity and subsequent mineralization (Fig. 2) (9).

A combination of endothelial damage and lipid deposition triggers inflammation within the valve. The expression of adhesion molecules allows infiltration of the endothelial layer by monocytes that differentiate into macrophages (10) and T cells that release proinflammatory cytokines, including transforming growth factor–beta-1 (11), tumor necrosis factor–alpha, and interleukin-1–beta (12). These inflammatory cells and cytokines ultimately help stimulate and establish the subsequent fibrotic and calcific processes that drive increasing valve stiffness (Fig. 2).

An inflammatory basis for AS is supported by studies demonstrating increased systemic C-reactive protein concentrations in patients with AS (13) and increased temperature in stenotic aortic valve cusps (14) and more recently by noninvasive imaging studies using combined positron emission tomography and computed tomography. Fluorine-18 fluorodeoxyglucose is a positron emission tomographic ligand that serves as a marker of macrophage activity and has become an established means of measuring inflammation in aortic and carotid atheroma (15). More recently, ^{18}F fluorodeoxyglucose levels have been shown to be increased in patients with AS compared with controls, displaying a progressive rise in activity with increasing valve severity (16).

ANGIONEOGENESIS AND VALVE HEMORRHAGE. Histological studies have suggested that these inflammatory processes are sustained by angioneogenesis in the valve. Thin neovessels are commonly observed in regions of intense inflammation surrounding calcific deposits and demonstrate a positive correlation with T-lymphocyte density. Furthermore, both intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 expression is increased in these vessels, suggesting that they act as an important portal of entry for inflammatory cells (17). Hemorrhage related to these vessels also appears to be important, being present in 78% of patients with severe AS and associated with neovascularization,

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme

AS = aortic stenosis

OPG = osteoprotegerin

RANK = receptor activator of nuclear factor kappa B

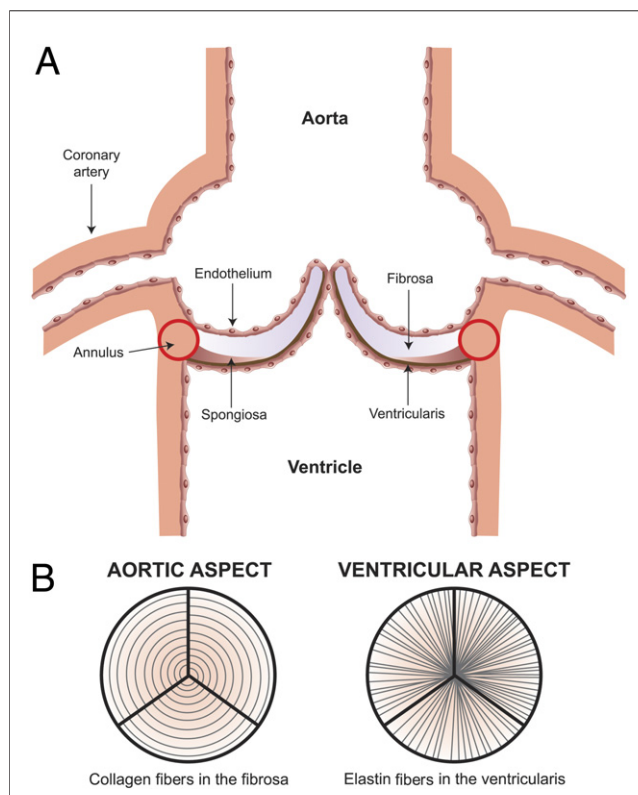**RANKL** = receptor activator of nuclear factor kappa B ligand

Figure 1   **Normal Structure of the Trileaflet Aortic Valve**

(A) The valve cusps have a 4-layered structure. On the aortic and ventricular aspects of the valve is the endothelium, which is continuous with that of the aortic endothelium and left ventricular endocardium. Moving toward the ventricular aspect of the valve is the fibrosa, which consists of fibroblasts and collagen fibers. The spongiosa is predominantly found at the base of the leaflets. It is a layer of loose connective tissue containing mucopolysaccharides, mesenchymal cells, and fibroblasts, whose function is to resist compressive forces within the cusps. Finally, the ventricularis is found on the ventricular aspect of the valve and contains elastin fibers orientated perpendicularly to the collagen. **(B)** Short-axis views of the aortic valve. Aortic aspect of the valve displays the concentric arrangement of collagen fibers in the fibrosa layer of the valve. Ventricular aspect showing the radial arrangement of elastin fibers in the ventricularis.
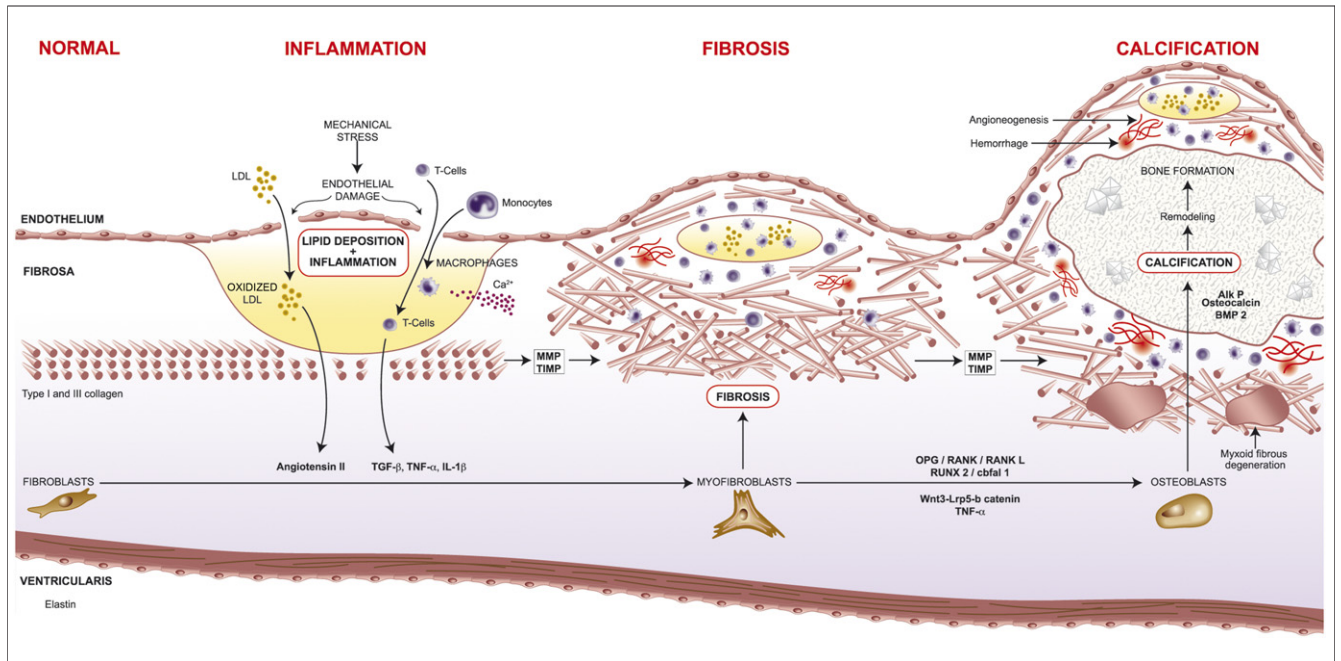
Figure 2   Summary of the Pathological Processes Occurring Within the Valve During Aortic Stenosis

Mechanical stress results in endothelial damage that allows infiltration of lipid and inflammatory cells into the valve. Lipid oxidization further increases inflammatory activity within these lesions and the secretion of proinflammatory and profibrotic cytokines. The latter drives the differentiation of fibroblasts into myofibroblasts that secrete increased collagen under the influence of angiotensin. In combination with the action of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), disorganized fibrous tissue accumulates within the valve. This leads to thickening and increased stiffness of the valve and in the latter stages the development of myxoid fibrous degeneration. Microcalcification begins early in the disease, driven by microvesicle secretion by macrophages. However, calcification accelerates in a proportion of patients because of the differentiation of myofibroblasts into osteoblasts. This occurs under the influence of several procalcific pathways, including osteoprotegerin (OPG)/receptor activator of nuclear factor kappa B (RANK)/RANK ligand (RANKL), Runx 2-cbfal 2, Wnt3-Lrp5-b catenin, and tumor necrosis factor (TNF)-α. Osteoblasts subsequently coordinate calcification of the valve as part of a highly regulated process akin to skeletal bone formation, with expression of many of the same mediators, such as osteocalcin, alkaline phosphatase (Alk P), and bone morphogenic protein (BMP)-2. With time, maturation of valvular calcification occurs so that by the end stages of the disease, lamellar bone, microfractures, and hemopoeitic tissue can all be observed within the valve. These pathogenic processes are sustained by angioneogenesis, with new vessels localizing, in particular, to regions of inflammation surrounding calcific deposits. Hemorrhage in relation to these vessels has also been demonstrated in severe disease and may have a role in accelerating disease progression. IL-1β = interleukin-1–beta; LDL = low-density lipoprotein; TGF = transforming growth factor.

macrophage infiltration, and accelerated disease progression (Fig. 2) (18).

FIBROSIS. The stenotic aortic valve is characterized by extensive thickening due to the accumulation of fibrous tissue and remodeling of the extracellular matrix. In all 3 layers of the valve, abundant fibroblast-like cells are found. They contain vimentin and are commonly referred to as valve interstitial cells. A subpopulation of these cells become activated by the inflammatory activity within the valve and differentiate into myofibroblasts, which are believed to be responsible for the accelerated fibrosis observed in this condition (19). In addition, matrix metalloproteinases are secreted by myofibroblasts and inflammatory cells and have an important and complex role in the restructuring of the valve leaflet matrix (Fig. 2) (12,20).

Table 1   Comparisons Between the Pathological Processes Underlying Aortic Stenosis and Atherosclerosis

	Aortic Stenosis	Atherosclerosis
Initiating event	Increased mechanical stress and reduced shear stress causing endothelial damage	Increased mechanical stress and reduced shear stress causing endothelial damage
Predominant cell types	Macrophages and T helper cells Valve interstitial cells Myofibroblasts Osteoblasts	Macrophages and T helper cells Foam cells Vascular smooth muscle cells
Early pathology	Oxidized lipid deposition, inflammation	Oxidized lipid deposition, inflammation, foam cells
Later pathology	Calcification and fibrosis predominate Neovascularization and hemorrhage	Lipid deposition and pools, inflammation, and calcification Neovascularization and hemorrhage
Disease progression	Fibrosis, calcification, and hemorrhage	Lipid deposition and pools, inflammation, plaque rupture, and thrombosis
Mechanism of adverse events	Progressive valve rigidity due to calcification and fibrosis Decompensation of the hypertrophic response	Plaque rupture due to lipid-rich pool, inflammatory infiltrate, and thin fibrous cap Intravascular thrombosis

The renin-angiotensin system is thought to modify this fibrotic process. Tissue angiotensin-converting enzyme (ACE) and angiotensin II are both up-regulated in stenotic aortic valves, and angiotensin receptors have been identified on valve myofibroblasts (21).

CALCIFICATION. Valve calcification plays a key role in the development of AS and can be quantified using computed tomography. The degree of valvular calcification correlates with valve severity (22), disease progression (23), and the development of symptoms and adverse events (24). Moreover, disorders of mineral metabolism, including Paget disease (25), osteoporosis (26), vitamin D polymorphisms (27), and hemodialysis (28), are all associated with an increased prevalence of AS.

Although other processes predominate, microscopic areas of calcification can be observed in the early stages of aortic sclerosis, co-localizing to areas of lipid deposition. In one-sixth of patients with sclerosis, the calcification process accelerates, hemodynamic obstruction ensues, and the valve becomes stenotic (29). This progression is thought to be driven by the differentiation of myofibroblasts into osteoblasts under the influence of the Wnt3-Lrp5-β catenin signaling pathway (30), the osteoprotegerin (OPG)/receptor activator of nuclear factor kappa B (RANK)/RANK ligand (RANKL) pathway (31) and Runx-2/NOTCH-1 signaling (Fig. 2) (32). Osteoblasts subsequently coordinate calcification as part of a highly regulated process, akin to new bone formation (33), with the local production of many factors more commonly associated with skeletal bone metabolism, including osteopontin, osteocalcin, bone sialoprotein, and bone morphogenic protein 2 (33–36). In addition, serum concentrations of fetuin A, an inhibitor of calcification, are reduced in patients with AS (37).

In the early stages of AS, calcification is composed of nodules containing hydroxyapatite deposited on a bonelike matrix of collagen, osteopontin, and other bone matrix proteins (34,35,38). Remodeling of this calcification occurs as AS progresses until by the later stages of disease, lamellar bone, microfractures, and hemopoeitic tissue can all be identified within the valve (35). Combined positron emission tomographic and computed tomographic imaging has confirmed the pathogenic role of calcification in AS using ^{18}F sodium fluoride (16). This tracer exchanges with hydroxyl groups on hydroxyapatite crystal and is believed to detect areas of developing or remodeling calcification. Uptake of ^{18}F sodium fluoride is increased within stenotic and sclerotic aortic valves compared with control subjects, displaying a progressive rise in activity with increasing disease severity. This rise accelerates and is disproportionate to that displayed by ^{18}F fluorodeoxyglucose, with 97% of patients with moderate AS and all patients with severe disease displaying increased ^{18}F sodium fluoride activity (16). In our opinion, this tracer holds considerable potential as a biomarker of disease activity, and the extent of its uptake adds

further support to calcification as the key process in the pathogenesis of aortic valve narrowing.

Left Ventricular Hypertrophy

AS causes an increase in pressure afterload and ventricular wall stress that stimulates hypertrophy of the left ventricular myocardium. Myocytes enlarge and wall thickness increases in a response that initially restores wall stress and preserves left ventricular function (39,40). However, evidence is accumulating that increasing levels of hypertrophy may in fact be maladaptive. The landmark Framingham studies first linked increasing hypertrophy with the progression to heart failure (41), and left ventricular hypertrophy is now considered a marker of an adverse prognosis across a number of cardiac conditions (42,43). In AS, patients display a marked variation in the magnitude of their hypertrophic response. This has recently been demonstrated to be of prognostic importance (3) and might explain the marked heterogeneity between symptom onset and the severity of valve narrowing that is observed.

Variation in the degree of left ventricular hypertrophy. It is perhaps surprising that in patients with AS, the degree of left ventricular hypertrophy is only weakly related to the severity of valve obstruction (44–46). This was first established with echocardiography but has recently been confirmed using cardiac magnetic resonance, with which no correlation between peak aortic valve velocity and indexed left ventricular mass was observed (47). Instead, the magnitude of the hypertrophic response appears to be more closely associated with other factors, such as advanced age, male sex, and obesity (44,48,49). Genetic factors modulate the degree of hypertrophy in response to a wide range of physiological and pathological triggers (50,51), and in AS, polymorphisms of the *ACE 1/D* gene have been associated with variation in left ventricular mass (49).

Other contributors to an increased afterload frequently coexist in patients with AS and are likely to modulate the hypertrophic response. Hypertension is common in this patient group, and an analysis of participants in the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) trial showed that coexistent hypertension was associated with increased left ventricular mass and a higher prevalence of hypertrophy (52). Increased arterial stiffness is also frequently observed because of a combination of advanced age, coexistent atherosclerosis, diabetes, and high blood pressure. This results in increased afterload and contributes to the development of left ventricular dysfunction in AS (53). On this basis, a global measure of afterload, Z_{VA}, has been proposed that is derived from both the mean valve gradient and the systemic arterial compliance. This variable predicts an adverse prognosis among patients with moderate and severe AS and has been proposed as a means of improving risk stratification and clinical decision making (54).

The variation in the hypertrophic response has important clinical consequences. In a study of 218 patients with

asymptomatic severe disease, Cioffi et al. (3) demonstrated that subjects with inappropriately high left ventricular mass had increased mortality compared with patients with comparable valve narrowing but more moderate hypertrophy. The mechanism for this adverse prognosis is likely to relate to premature decompensation of the hypertrophic process.

From hypertrophy to heart failure. The transition from hypertrophy to heart failure marks the tipping point at which the left ventricle fails in the face of an increased pressure afterload and is no longer able to maintain forward flow through the valve. This heralds the onset of symptoms, adverse events, and a poor prognosis. Hein et al. (55) established that this key progression is associated with increased myocyte apoptosis and fibrosis and postulated that these two processes were responsible for the transition (Fig. 3).

MYOCYTE APOPTOSIS. The rate of apoptosis in the hypertrophied myocardium has been estimated at 5% to 10% of myocytes per year (56). Apoptosis is usually balanced by myocyte regeneration, but in hypertrophy there appears to be a net loss of cells. Increased apoptotic rates may simply be a response to the direct mechanical forces associated with increased afterload (57,58). However, angiotensin II has also been implicated, and angiotensin receptor blockers reduce apoptosis in patients with hypertension, even at doses that do not reduce blood pressure (59,60). Ischemia may also be important. In AS, myocardial oxygen demand is increased by a combination of the elevated myocardial mass and increased afterload. In contrast to physiological hypertrophy, the density of the coronary capillary network does not expand sufficiently to meet this demand and coronary flow reserve is impaired (Fig. 3) (61). Galiuto et al. (62) demonstrated impaired myocardial perfusion in patients with severe AS and normal coronary arteries and that this was associated with increased cardiomyocyte apoptosis.

FIBROSIS. Histopathological studies have confirmed fibrosis to be an integral part of the hypertrophic process (63,64). Myofibroblasts infiltrate the myocardium and secrete extracellular matrix proteins, including collagen types I and III (65). Areas of fibrosis are observed to co-localize with areas of myocyte apoptosis (66), and it has been suggested that fibrosis occurs as a form of scarring after myocyte death and injury. As with fibrosis in the valve, the renin-angiotensin system, transforming growth factor–beta, and an imbalance in matrix metalloproteinase and tissue inhibitor of matrix metalloproteinase activity have all been implicated in this process (Fig. 3) (67,68).

Cardiac magnetic resonance imaging using late gadolinium enhancement allows the noninvasive visualization of replacement fibrosis within the myocardium. A midwall pattern of fibrosis has been observed in the myocardium of up to 38% of patients with moderate or severe AS and has been associated with a more advanced hypertrophic response (69). Importantly, there is also an 8-fold increase in mortality associated with midwall fibrosis (69). This tech-
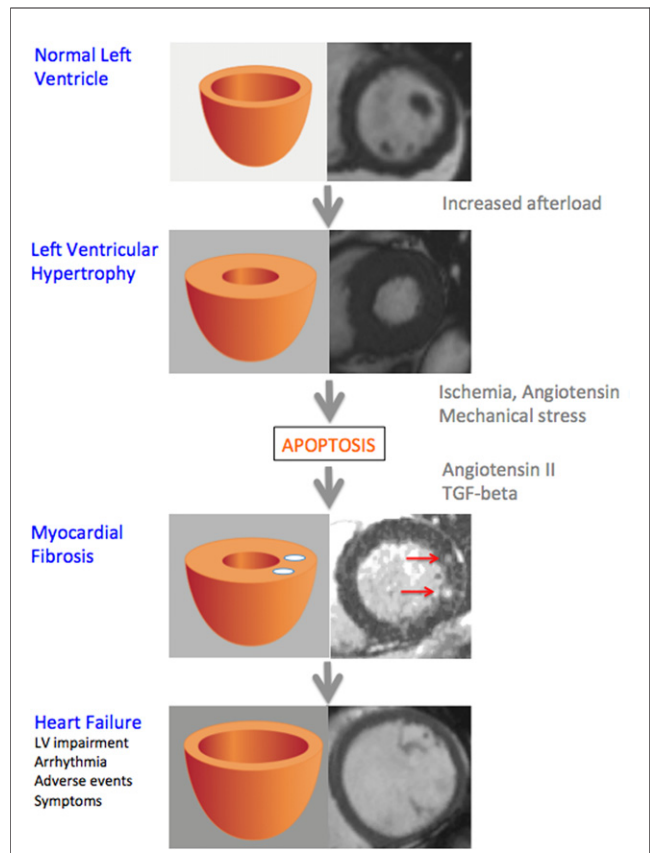

Figure 3 The Development and Subsequent Decompensation of LV Hypertrophy in Response to Aortic Stenosis

Aortic valve narrowing imposes increased afterload and wall stress on the left ventricle. This stimulates a hypertrophic response, which initially restores wall stress and maintains cardiac performance. However, this process ultimately becomes decompensated. Myocyte apoptosis is triggered by a combination of myocardial ischemia, direct mechanical forces, and the actions of angiotensin. This triggers a fibrotic response in the myocardium under the influence of profibrotic mediators such as angiotensin and transforming growth factor (TGF)–beta, which can be visualized using the late gadolinium enhancement technique (**red arrows** show regions of midwall fibrosis on short-axis views of the left ventricle). Increasing myocardial fibrosis leads to progressive systolic and diastolic impairment and the progression to heart failure. Symptoms and adverse events ensue perhaps in part because of an increased tendency to arrhythmia. LV = left ventricular.

nique can therefore serve as a prognostic marker and a means of detecting decompensation of the hypertrophic response before heart failure intervenes (Fig. 3). The mechanism for the adverse prognosis, however, remains unclear. In part, it is likely to reflect the systolic and diastolic impairment associated with myocardial apoptosis and fibrosis, the former leading to a reduction in the ventricular contractile mass and the latter resulting in increased ventricular stiffness (55,70,71). However, arrhythmia may also contribute (72). Late gadolinium enhancement has been associated with ventricular arrhythmia in other cardiac conditions (73), and fibrosis predisposes to arrhythmia by impairing electrical conduction, encouraging the development of re-entry circuits and increasing ventricular refractoriness and myocyte excitability (74,75). Importantly, pa-

tients with AS remain predisposed to sudden death even after aortic valve replacement, and this has been related to advanced left ventricular hypertrophy (76,77). Although potentially interesting, this hypothesis requires further work, as the contribution of malignant arrhythmia to sudden cardiac death in AS is incompletely defined.

The late gadolinium enhancement technique is limited by the fact that it identifies only regional differences in replacement myocardial fibrosis. It will therefore miss diffuse interstitial fibrosis, which is evenly distributed throughout the myocardium and the predominant fibrotic response in AS. However, cardiac magnetic resonance T1 mapping systems have recently been developed that enable the detection and quantification of this form of fibrosis. These are likely to become the preferred method of assessment in AS, having already undergone histological validation and been shown to correlate with symptomatic status (78,79).

Clinical Correlates and Future Treatment Strategies

To date, there are no effective medical treatments for AS. These are urgently required, because they might eliminate the need for invasive cardiac surgery in patients who are often elderly and not ideally suited to a major operation. Similarities exist between the pathogenesis of AS and several other common medical conditions that provide a rationale for possible novel therapeutic strategies (Fig. 4).

Inflammation, atherosclerosis, and statin therapy. Atherosclerosis and AS share many common risk factors, and are both characterized by endothelial damage, lipid deposition, angioneogenesis, and inflammation (Table 1). Statin therapy slows the progression of coronary and carotid atheroma and reduces major adverse cardiac events, leading to the hypothesis that statins might also delay progressive valve narrowing in AS (Fig. 4). However, this strategy has proved disappointing, with 3 major prospective randomized controlled trials failing to demonstrate any impact on disease progression or clinical outcomes (80–82). These results probably reflect important pathophysiological differences between the development and progression of AS and atherosclerosis (Table 1). In atherosclerosis, inflammation and lipid deposition are key components in both the development of arterial plaque and its stability. Adverse events are predominantly related to plaque rupture, and much of the benefit from statin therapy is due to plaque stabilization and a thickening of the fibrous cap. In contrast, in AS, adverse events are related to progressive narrowing of the aortic valve. This is predominantly driven by increasing calcification, a process that statins have consistently failed to affect, even in the context of coronary atherosclerosis (83–85).

It is our opinion that the early stages of AS are established in a manner akin to atherosclerosis. However, once osteoblast activity has been established in the valve, progressive calcification predominates in a manner that is quite distinct from the
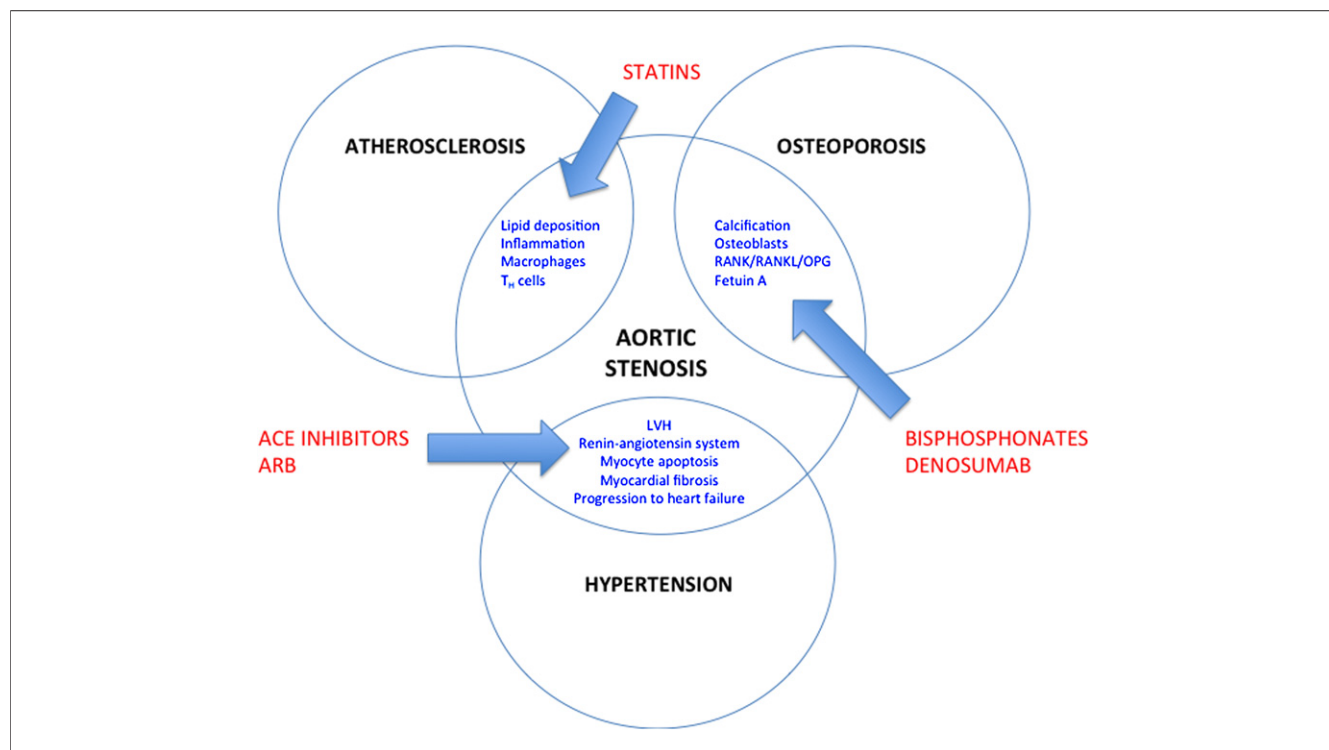

Figure 4   **Similarities Between Aortic Stenosis and Other Medical Conditions and Potential Therapeutic Strategies**

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; LVH = left ventricular hypertrophy; OPG = osteoprotegerin; RANK = receptor activator of nuclear factor kappa B; RANKL = receptor activator of nuclear factor kappa B ligand.

pathogenesis of atherosclerosis. Consequently, disease progression in these patients is more likely to be regulated by the mediators of calcium homeostasis than atherogenesis. In support of this concept, although atherosclerotic risk factors and serum C-reactive protein concentrations predict the development of AS, they do not predict subsequent disease progression (86,87). Rather, this is best predicted by the degree of valvular calcification at baseline (87).

Fibrosis, hypertension, and antifibrotic medication. In a similar fashion to AS, hypertension is characterized by an increased pressure afterload and left ventricular hypertrophy under the influence of the renin-angiotensin-aldosterone system. It is therefore encouraging that in patients with hypertension, ACE inhibitors and angiotensin receptor blockers reduce left ventricular hypertrophy beyond their effects on blood pressure, with favorable effects on myocardial fibrosis, diastolic function, and clinical outcomes (88,89).

The impact of ACE inhibitors and angiotensin receptor blockers in AS is less well studied. Beneficial effects with respect to hypertrophy have been observed in experimental animal models (90–92), whereas results on valve narrowing have been conflicting in 2 retrospective human studies (93,94). More encouragingly, a reduction in mortality and cardiovascular events was observed in a recent observational study in patients with AS maintained on ACE inhibitors (95). Despite prior concerns, published research suggests that ACE inhibitors are well tolerated even in patients with severe AS (96,97), and large-scale prospective randomized controlled trials of this therapeutic strategy are now required (98) (Fig. 4).

Calcification and osteoporosis. Patients with osteoporosis have an increased incidence of AS and display more rapid rates of disease progression (26,99). Both conditions are characterized by abnormalities in calcium metabolism and are governed by common systemic regulatory systems, which coordinate calcium homeostasis via the action of osteoblasts and osteoclasts.

In particular, the OPG/RANK/RANKL axis appears to have a central role in both conditions. OPG is a decoy receptor for RANKL: a potent stimulator of osteoclast differentiation and bone resorption (100). Increased expression of RANKL and reduced levels of OPG have been observed in osteoporosis and have led to the development the anti-RANKL monoclonal antibody denosumab as a highly efficacious and well-tolerated osteoporosis treatment (101). Similarly, increased RANKL and reduced OPG have also been observed within stenotic aortic valves (31) (Fig. 2), while mice with targeted inactivation of OPG develop extensive vascular calcification alongside high-turnover osteoporosis (102).

Calcification is the critical process in determining the progression of aortic valve stenosis and is therefore likely to be a crucial treatment target. The overlap in pathophysiology between AS and osteoporosis provides a strong rationale for drugs, such as bisphosphonates, that are already known to have beneficial effects with regard to vascular calcification

(103). These agents have also been shown to reduce valvular calcification in patients with renal failure and bioprosthetic valves (103,104) and appeared to slow disease progression in a small observational study of patients being treated for osteoporosis (26). Given the central regulatory role of the OPG/RANK/RANKL system, novel medications such as denosumab also hold promise, and there is therefore a strong rationale for randomized controlled trials of these treatments in AS.

Conclusions

AS is a common condition associated with major morbidity and mortality, due to both progressive valve narrowing and consequent left ventricular hypertrophy. However, to date, there are no effective medical therapies that can halt or delay disease progression. Calcification is believed to be the predominant mechanism by which progressive valve narrowing occurs, while fibrosis appears to drive decompensation of the hypertrophic myocardial response. We believe that osteoporotic and antifibrotic interventions hold considerable promise as future treatment strategies and that efforts should now be focused on their development.

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