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Is it time for medical therapy for aortic valve disease?

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Abstract

Calcific aortic stenosis is the most common indication for surgical valve replacement. Currently there are no medical therapies approved for the treatment of this disease. This review will summarize the clinical and experimental studies published over the past 5 years that indicate that medical therapy may be an option for this patient population.

Keywords

angiotensin-converting enzyme; inhibitors; aortic valve; calcification; statins

Calcific aortic stenosis is the primary cause of valvular heart disease in developed countries. Currently, the only established treatment for calcific aortic stenosis is surgical valve replacement. Due to the increasing number of ongoing basic scientific and clinical studies, the cellular mechanisms responsible for this disease clearly demonstrate that medical therapy may be an option for these patients. Furthermore, due to the aging population in the USA, developing primary prevention strategies is becoming increasingly necessary to potentially delay or avoid surgical valve replacement in the future [101]. In order to understand this rapidly evolving field, this review will focus on the following subject areas:

- Etiology and risk factors of calcific aortic valve disease
- Natural history of aortic valve disease
- Current management for calcific aortic stenosis: American College of Cardiology (ACC) and American Heart Association (AHA) guidelines
- Emerging clinical and experimental data for the atherosclerotic hypothesis
- Studies indicating the potential for cholesterol-lowering therapy and angiotensin-converting enzyme (ACE) inhibitors to prevent or slow the progression of aortic valve calcification

Etiology & risk factors of calcific aortic valve disease

Calcific aortic stenosis is the primary cause of aortic valve disease in developed countries. This condition increases in prevalence with advancing age of the population in the USA, affecting 2 to 3% by the age of 65 years [1]. The aging population of the USA has led to an increasing number of valve replacements each year, which, in turn, costs the USA billions of dollars. The pathologic changes that develop along the valve surface, including nodules and

valve leaflet thickening are shown in FIGURE 1. It is these pathologic changes that are responsible for the progressive decrease in the valve area over time, which results in valvular aortic stenosis. This narrowing of the aortic valve is responsible for the symptoms of shortness of breath, lightheadedness and chest pain in patients who have aortic stenosis [2]. For years, the etiology of calcification in the aortic valves has been thought to be due to a passive accumulation of calcium attaching to the valve leaflet, causing eventual stenosis. In 1854, William Stokes described in his textbook *'The Diseases of the Heart and the Aorta'*, specific pathologic descriptions of calcific aortic valves, which include stenosis of the aortic valve, ossific bone growth along the valve surface and atheromatous changes in the valve and heart [3]. Currently, the hypothesis that valve calcification is not a passive phenomenon, but an active biology similar to the description by William Stokes in 1854, is being reconsidered. In order to understand the mechanism by which calcification occurs, it is helpful to review a list of the different etiologies of aortic valve stenosis. The primary and secondary causes of aortic valve stenosis, including degenerative calcific, bicuspid aortic valves, rheumatic valvular heart disease, a number of secondary systemic diseases and medication-induced valvular heart disease are listed in BOX 1. Emerging epidemiological studies have revealed convincing clinical evidence towards an atherosclerotic hypothesis for the cellular mechanism of this valvular lesion (TABLE 1) [4]. The growing evidence for the etiology of degenerative calcific aortic valve disease points towards a response-to-injury mechanism similar to that which has been described for vascular atherosclerosis. A list of current retrospective studies demonstrates that the risk factors for this disease are similar to those of vascular disease, which include elevated low-density lipoproteins, hypertension, male gender and smoking [4,5].

The atherosclerotic hypothesis associated with valvular heart disease has also been implicated in patients with homozygous familial hypercholesterolemia (FH). In the current lipid-lowering era, it is difficult to demonstrate the association of atherosclerosis of the heart valve in this patient population. Prior to the lipid-lowering era, autopsy studies of FH patients demonstrated that these patients develop a particularly severe form of atherosclerosis often with supra-aortic narrowing in children and involvement of the aortic surface of the valve [6]. The left circumflex artery of a patient who had a myocardial infarction at the age of 7 years due to FH is shown in FIGURE 2A. The aortic valve from the same patient, demonstrating the atherosclerotic changes along the aortic valve surface is shown in FIGURE 2B [7]. Autopsy studies in this patient population are valuable to provide the link between atherosclerosis and high lipid levels.

Reviewing the emerging data for preclinical markers for aortic valve disease will potentially target patient populations that are at risk of developing this disease in the future. One important marker to identify patients is aortic valve sclerosis. The hallmark of this valve lesion is a soft early systolic murmur heard over the base of the heart. This was once thought to be a benign precursor lesion for aortic valve stenosis. However, Otto and colleagues, in the Cardiovascular Health Study, have reported that aortic sclerosis – which is described as focal areas of increased echogenicity and thickening of aortic valve leaflets, without restricted leaflets – is found in 29% of subjects [8]. In the 5-year follow-up of this study, aortic sclerosis was associated with a 50% increased risk of death from cardiovascular causes and the risk of myocardial infarction in the absence of hemodynamic significant obstruction to left ventricular outflow [9].

Although aortic sclerosis can be seen as a precursor step to aortic stenosis, it is still not clear which patients will develop aortic stenosis. In a study of over 2000 patients with aortic sclerosis, progression to aortic stenosis occurred in only 16% [10]. Furthermore, most only developed mild stenosis, and in a small subset of patients (2.5%) who developed severe stenosis, the average time interval from diagnosis of aortic sclerosis to severe aortic stenosis

was 8 years; a longer time frame than encompassed by the epidemiologic studies showing the association demonstrating aortic sclerosis and clinical outcome. These studies, combined with the clinical risk-factor data for aortic valve sclerosis [11], provide further evidence to include this early valve lesion in the approach to the primary prevention of aortic valve calcification.

Additional emerging preclinical risk factors for vascular atherosclerosis are:

- C-reactive protein (CRP)
- The extent of calcification in the aortic valve

Galante and colleagues have demonstrated an increase in CRP levels in patients with aortic valve stenosis [12]. Rosenhek and colleagues have found that the extent of aortic valve calcification is an important predictor of poor outcome in patients with aortic stenosis [13]. The clinical studies that list the risk factors of cholesterol, hypertension, male gender, increasing age and elevated CRP suggest that aortic valve calcification is an inflammatory process promoted by atherosclerotic risk factors and treating this disease with medical therapy may be an important strategy in the future.

Natural history of aortic valve disease

Patients with severe calcific aortic stenosis develop left ventricular obstruction, which occurs gradually over several years. Over time, the left ventricle compensates for the persistent gradient between the left ventricle and aorta, resulting in left ventricular hypertrophy and in an increase in left ventricular mass. Eventually, as the aortic stenosis becomes more severe, the left ventricle begins to fail. When the preload reserve is diminished and no further compensatory mechanisms are available, heart failure ensues, leading to death within approximately 1 year. There are a number of studies demonstrating the hemodynamic progression of this valvular lesion. Defining the rate of progression of aortic stenosis prior to the onset of symptoms provides the optimal windows for intervention for these patients. Doppler echocardiography has provided an accurate, noninvasive measurement of the severity of stenosis, which has replaced invasive cardiac catheterization in most cases [14]. The incidence of the development of symptoms in asymptomatic patients is as high as 38% in patients with Doppler outflow velocities over 4 m/s after 2 years and 79% after 3 years [9]. Therefore, patients with severe aortic stenosis should be monitored closely for the development of symptoms and progression of disease.

The natural history of severe symptomatic aortic stenosis is associated with 50% mortality within 5 years [15]. In 1968, Ross and Braunwald established the only current class I therapeutic intervention for aortic stenosis listed in the ACC/AHA guidelines [2]. This landmark paper describes the critical importance of the timing of valve replacement at the onset of symptoms. Currently, no medical treatment is indicated for the asymptomatic patient with valvular aortic stenosis, only clinical observation for progression of the disease.

Current management for calcific aortic stenosis

ACC/AHA guidelines

The ACC/AHA guidelines have defined severe aortic stenosis as an aortic valve area of under 1.0 cm² and a mean gradient of over 50 mmHg [2]. The decision to replace the valve is dependent upon the presence or absence of symptoms with unequivocal evidence of severe stenosis, but still remains a complex issue that should be individualized, particularly in younger active patients [2]. The class I to III indications for the management of severe calcific aortic stenosis are listed in BOX 2. These guidelines have been developed to provide a framework to manage valvular heart disease in patients who have multiple variables in

their clinical presentation that need to be included in the decision making towards the treatment and management of their disease process.

Emerging experimental data for the atherosclerotic hypothesis

Despite the increasing prevalence of this condition and the growing epidemiological evidence demonstrating the clinical risk factors, very little is known regarding the cellular mechanisms of calcific aortic stenosis. Furthermore, there are no established medical treatments indicated for calcific aortic stenosis. If cholesterol is a causative risk factor, then medications may play a pivotal role in the management of aortic valve disease. The understanding of medical therapy in aortic valve disease may slow the progression of stenosis and will decrease the number of aortic valve replacements in the future. For years, degenerative aortic valve disease was hypothesized to be a passive accumulation of calcium binding to the aortic surface of the valve leaflet. The histology of aortic stenosis has been well described in a number of studies evaluating human calcified aortic valves from surgical valve replacement or autopsy. Studies indicate that aortic valve sclerosis is a precursor of aortic stenosis and critical as an initiating lesion in this disease. *Ex vivo* analysis of human aortic valves have redefined the paradigm that aortic valve disease is not just a passive phenomena but an active cellular process, that ranges from early atherosclerosis to calcification associated with an increase in bone matrix expression [16]. Studies evaluating heavily calcified aortic valves describe mature lamellar bone formation [17] and expression of specific bone markers as important in the development of osteoblast bone formation [18]. These studies that define the presence of actual bone within the valve provide further evidence that the development of stenosis occurs secondarily to an active biological process. Histologic studies in the early valvular sclerotic lesions demonstrated chronic inflammatory cell infiltrates (macrophages and T-lymphocytes) and lipids (apolipoprotein [apo] B, [a] and E) and α -actin-expressing cells in lesion and in adjacent fibrosa and thickening of fibrosa with collagen and elastin [19]. These studies provide critical information regarding the pathogenesis of this disease.

Another potential approach to treating this disease would be the ACE signaling pathway. O'Brien and colleagues have identified the presence of ACE, angiotensin (AT)1 and 2 receptors that colocalize with lipoproteins in stenotic aortic valves [20]. These studies implicate the first signaling mechanism present in this tissue. The immunohistochemistry of AT1 receptors along the aortic valve surface colocalizing with ApoE lipoproteins is shown in FIGURE 3. It is important to note that the use of ACE inhibitors is contraindicated in the treatment of patients with severe asymptomatic aortic stenosis [2]. However, there are studies that have examined the use of ACE inhibitors to manage symptomatic atherosclerosis, with remarkable clinical improvement in subjects with generally preserved left ventricular function [21]. These studies also propose that the tissue level antiproliferative effects of ACE inhibitors may be responsible for this acute benefit in symptoms and effort tolerance [21]. There are also interesting new data concerning the role of vasodilation with nitroprusside, which improves cardiac output by afterload reduction in New York Heart Association (NYHA) class IV patients with critical atherosclerosis and left ventricular dys-function [22]. There have been smaller studies over the past 20 years that have also reported encouraging results for the potential use and safety of ACE inhibitors in this patient population [23,24]. Future prospective studies in the area are needed in order to determine if inhibition of this signaling pathway is required to slow the progression of atherosclerosis. These data corroborate the growing number of epidemiologic studies defining similar risk factors for aortic valve disease and vascular atherosclerosis.

Human *ex vivo* studies have provided the foundation for future basic science studies in this field. Experimental studies have tested the hyperlipidemic hypothesis of valvular disease.

The growing body of literature suggests that hypercholesterolemia may play a role in aortic valve calcification. Experimental hypercholesterolemia animal models demonstrate that the atherosclerotic lesion that develops in the aorta also develops along the aortic surface of the aortic valve [25–27]. These studies have been further analyzed to demonstrate a potential mechanism of how calcification may develop in the aortic valve and how treatment with statin agents may slow the progression and development of this disease. A description of a potential mechanism by which lipids may contribute to the valvular biologic changes that occur early on in the disease process prior to calcification can be seen in FIGURE 4 [28]. In the presence of lipids and the other risk factors associated with valvular heart disease (TABLE 1), an inflammatory reaction is initiated along the surface of the valve leaflet. In turn, foam cell formation and the release of growth factors and cytokines occurs. Finally, the valve myofibroblast cell undergoes cellular proliferation and synthesis of bone matrix proteins and eventually calcifies. The valve develops stenosis, which eventually causes symptoms in this patient population.

Potential for medical therapy to slow the progression of aortic valve calcification

A summary of studies thus far that provide the foundation for potential targeted drug therapy to slow the progression of this disease, is shown in BOX 2. Two leading candidates for drug therapy are the drugs inhibiting ACE and 5-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitors as indicated from the human studies. ACE inhibitors interfere with the renin–angiotensin system and exert beneficial actions on vascular tissues beyond their blood pressure-lowering effects. ACE inhibitors may reduce atherogenesis in experimental models through various protective mechanisms. The biologic effects of ACE inhibitors act by multiple pathways including:

- Inhibiting the conversion of inactive angiotensin I to active angiotensin II
- Decreasing the bradykinin levels, which in turn releases nitric oxide

The beneficial effects of this mechanism are [30]:

- Improved endothelial function
- A decrease in smooth muscle proliferation

Studies demonstrating the presence of ACE in the cardiac valve endothelium provide the biological basis for this therapy; however, experimental studies are necessary to determine the timing and effects of ACE inhibition on calcification in the valve.

HMG CoA reductase inhibitors (statins) have emerged as another target for treating aortic valve calcification. The changes in the aortic valves from a 2-month experimental hypercholesterolemia study with and without atorvastatin are demonstrated in FIGURE 5 [30]. Histologic analysis has demonstrated that the effects of cholesterol on the aortic valve are characterized by foam cell formation, aortic valve myofibroblast cell proliferation and bone matrix protein expression. Further analysis at the gene level indicates that specific osteoblast bone markers are expressed in the aortic valve from these samples [30]. Finally, this study demonstrates that statins may decrease the atherosclerotic cellular effects, inhibit osteoblast gene markers and inhibit calcification. Statins also have potent low-density lipoprotein-lowering and nonlow-density lipoprotein-lowering effects via inhibition of the rate limiting step in cholesterol synthesis, which improves the cellular pathways that modify the atherosclerotic process [31]. The evidence to date suggests that multiple nonlipid-lowering mechanisms may contribute to the beneficial effects of HMG-CoA reductase inhibitors in coronary artery disease.

There are a growing number of retrospective studies demonstrating that medical therapy is a potential approach for the treatment of aortic valve disease. The magnitude of the effect of therapy is similar to previous studies with all showing an approximately 50% annual reduction in measurable disease progression, whether quantified by Doppler echocardiographic jet velocity or valve area, or by electron beam tomographic valve calcium scores [32–36]. Currently, there is an ongoing prospective trial in Europe for the use of cholesterol-lowering medications and slowing the progression of aortic valve stenosis [37]. Results of this study will be helpful in developing the different therapies for this disease. The cellular features of calcific aortic stenosis and the potential drug targets to slow the progression of this disease are shown in FIGURE 6.

Valve replacement is, and will remain, the treatment of choice for severe symptomatic critical aortic stenosis. Future insights into the mechanisms of calcification and its progression may indicate a role for ACE inhibition, and/or lipid-lowering treatment in slowing the rate of progression of stenosis. The need for more experimental models to define the disease process and timing of therapy are critical for the development of future clinical trials for this disease. Is there medical therapy for aortic stenosis? In 1942, James B Herrick posed a similar question regarding the future of medical therapy for vascular disease in his monograph entitled '*A Short History of Cardiology*'. Herrick predicted the advent of experiments in vascular biology that have changed the way we treat atherosclerosis and acute coronary syndromes in 2004.

'...heart disease...this is the story of a bad disease...the outlook for the dread angina...is thought to be more favorable than it was first thought...though the cause...has not been discovered, and...vascular change may never be warded off or cured, research may unearth secrets by which premature or old age may be postponed.' [38].

A similar prediction can be made for the future for the medical treatment of aortic valve disease.

Expert opinion

The current treatment for symptomatic calcific aortic stenosis is surgical valve replacement. There are ongoing clinical trials testing the effects of HMG CoA reductase agents and future studies in preparation for the use of ACE inhibitors for this disease. The results of these and future studies will have major implications in the treatment of calcific aortic stenosis. At this time, it is important to follow the preventive cardiology guidelines for the treatment of lipids and blood pressure until future recommendations are made for the treatment of calcific aortic valve disease.

Five-year view

Calcific aortic stenosis is the most common indication for surgical valve replacement. During the next 5 years, the treatment of calcific aortic stenosis will change and primary prevention strategies will be in place for preventing and treating early markers of valvular heart disease. Electron beam computed tomography and cardiac magnetic resonance imaging will also emerge as tools for assessing the extent of calcification and monitoring treatment strategies in the future.

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Box 1. Etiologies of aortic valve disease [28]

- Congenital
- Degenerative
- Rheumatic
- Endocarditis
- Hyperuricemia
- Inflammatory – secondary to chronic infection
- Homozygous type II
- Hypercholesterolemia
- Pseudoxanthoma elasticum
- Histocompatibility leukocyte antigen, B27, valvulitis
- Alkaptonuria
- Gaucher
- Hyperparathyroidism
- Calciphylaxis
- Fabry's
- Drug induced
- Incontinentii pigmentii
- Paget's
- Cardiac valve tumors
- Carcinoid heart diseases
- Histocompatibility leukocyte antigen, B27, valvulitis
- Alkaptonuria

Box 2. Recommendations for aortic valve replacement in aortic stenosis [2]**Box 2**

Recommendations for aortic valve replacement in aortic stenosis [2].

Indication	Class
• Symptomatic patients with severe AS	I
• Patients with severe AS before undergoing coronary artery bypass surgery	I
• Patients with severe AS undergoing surgery on the aorta or other heart valves	I
• Patients with moderate AS undergoing coronary artery bypass surgery or surgery on the aorta or other heart valves	IIa
• Asymptomatic patients with severe AS and:	
- LV systolic dysfunction	IIa
- Abnormal response to exercise (e.g. hypotension)	IIa
- Ventricular tachycardia	IIb
- Marked or excessive LV hypertrophy (> 15 mm)	IIb
- Valve area <0.6 cm ²	IIb
• Prevention of sudden death in asymptomatic patients with none of the findings listed under the fifth indication, shown above	III

AS: Atherosclerosis; LV: Left ventricular.

Key issues

- Calcific aortic stenosis is the primary cause of aortic valve disease in developed countries. Pathologic changes along the valve surface are responsible for the progressive decrease in valve area over time, which results in valvular aortic stenosis. The hypothesis that valve calcification is not a passive phenomenon, but an active biology is currently being reconsidered.
- Patients with severe calcific aortic stenosis develop left ventricular obstruction gradually over several years. Over time, the left ventricle compensates for the persistent gradient between the left ventricle and aorta, resulting in left ventricular hypertrophy and in an increase in left ventricular mass. Eventually, as the aortic stenosis becomes more severe, the left ventricle begins to fail. When the preload reserve is diminished and no further compensatory mechanisms are available, heart failure ensues, leading to death within approximately 1 year.
- Current management for calcific aortic stenosis is included in the American College of Cardiology/American Heart Association guidelines.
- There are emerging clinical and experimental data for the atherosclerotic hypothesis.
- Studies have been carried out that indicate the potential for cholesterol-lowering therapy and angiotensin-converting enzyme inhibitors to prevent or slow the progression of aortic valve calcification.

Figure 1. Calcified human aortic valve

Photograph of an aortic valve removed at the time of valve replacement. The arrow indicates bone-like nodules on the aortic surface of the aortic valve. The leaflets also demonstrate increased thickening.

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Figure 2. Cardiovascular features of a patient with familial hypercholesterolemia
Left circumflex artery and aortic valve demonstrating atheromatous changes along the aortic valve surface. Copyright© 2004, Massachusetts Medical Society. All rights reserved [7].

Figure 3. Angiotensin 1 receptors and apo E in a calcified aortic valve

Demonstrates immunohistochemistry for angiotensin 1 receptors, ACE and apo E, which localize along the surface of the aortic valve leaflet.

Reproduced with permission from O'Brien KD, Shavelle DM, Caulfield MT *et al.*

Association of angiotensin converting enzyme with low-density lipoprotein in aortic valvular lesions and in human plasma. *Circulation* 106(17), 2224–2230 (2002).

ACE: Angiotensin converting enzyme; AngII: Angiotensin II;

Apo: Apolipoprotein;

Figure 4. Potential mechanism for aortic valve calcification

The cell within the valve develops osteoblast-like features that synthesize bone matrix proteins involved in the calcification process within the valve leaflet.

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Cbfa: Core binding factor alpha-1; LDL: Low-density lipoprotein;

PDGF: Platelet-derived growth factor; TGF: Tissue growth factor.

Figure 5. Experimental hypercholesterolemia and atorvastatin treatment in aortic valves
 Demonstrates the effects of elevated cholesterol with and without atorvastatin in rabbit aortic valves. **(A1,B1)** The normal aortic valve surface is thin and intact, with a smooth endothelial layer in the spongiosa layer of the valve, **(C1,D1)** and there are no macrophages or proliferation. **(A2)** On a cholesterol diet, foam cells converge to form a large lipid-laden lesion on the valve leaflet, **(C2)** collagen is formed, **(B2)** and is stained blue, **(D2)** foam cells stain positive for macrophage cells, and there is a marked increase in myofibroblast proliferation cell nuclear antigen staining. **(A3–D3)** Animals on a cholesterol diet and treated with atorvastatin have a marked decrease in abnormal findings **(A2–D2)** seen in animals on only the cholesterol diet.

Reproduced with permission from Rajamannan NM, Subramaniam M, Springett M *et al.* Atorvastatin inhibits hypercholesterolemia-induced cellular proliferation and bone matrix production in the rabbit aortic valve. *Circulation* 105(22), 2260–2265 (2002).

Figure 6. Potential therapeutic approach for aortic valve disease

Demonstrates the signaling pathways important in the treatment of aortic valve disease [38].

ACEI: Angiotensin-converting enzyme inhibitor; AT: Angiotensin; ENOS: Endothelial nitric oxide synthase; LDL: Low-density lipoprotein; NO: Nitric oxide.

Table 1

Risk factors for calcific aortic valve disease [4].

Author	Study design	n	Mean age (years)	Positive risk factors
Deutscher <i>et al.</i> (1983)	Case control	54 cases 359 controls	NA NA	Hypercholesterolemia, diabetes
Hoagland <i>et al.</i> (1987)	Case control	105 cases 439 controls	66	None
Aronow <i>et al.</i> (1991) [§]	Hospital survey	571	82	Hypertension, hypercholesterolemia, diabetes, low HDL-cholesterol
Mohler <i>et al.</i> (1994)	Retrospective	39 BAV 30 degenerative	62 72	Race, gender, low triglyceride, smoking
Lindroos <i>et al.</i> (1997) [§]	Retrospective echo database	501	>75	Hypertension, low BMI
Boon <i>et al.</i> (1997)	Retrospective	515 cases 562 controls	67	Age, hypertension, hypercholesterolemia
Stewart <i>et al.</i> (1997) [§]	Prospective	5201	73	Gender, age, hypertension, lipoprotein(a), LDL-cholesterol
Wilms <i>et al.</i> (2001)	Prospective case control	20 cases (6 BAV) 20 controls	66	Cholesterol
Chan <i>et al.</i> (2001)	Prospective case control	48 cases (all BAV) 52 controls	56	Cholesterol, history of hypertension
Aronow <i>et al.</i> (2001)	Retrospective	180 cases	82	Gender, smoking, hypertension, diabetes, cholesterol, not on statins
Chui <i>et al.</i> (2003)	Retrospective case control	43 cases 40 controls	66	Cholesterol
Peltier <i>et al.</i> (1985)	Prospective case control	220 cases 220 controls	68	Hypertension, smoking, high BMI, cholesterol

BAV: Bicuspid aortic valve; BMI: Body mass index; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; NA: Not available.

[§]Includes cases with sclerotic changes of the aortic valve and/or aortic root.