CARDIOLOGY Rounds®

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Statin Therapy for Valvular Aortic Stenosis: Opportunities and Challenges

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Calcification of the aortic valve is the third leading cause of heart disease in adults. While indications for aortic valve replacement are well established, potential medical interventions to treat valvular aortic stenosis (VAS) have only recently been explored. The approach to treatment of VAS should focus on minimizing its progression and preventing pathological ventricular remodeling, myocardial ischemia, and heart failure. Given the similar pathophysiology between atherosclerosis and VAS, and the impressive benefit of statin therapy in atherosclerotic cardiovascular disease, statin therapy has been proposed to reduce VAS progression and several retrospective trials have confirmed this recommendation. However, a recent, prospective, randomized, controlled trial – the Scottish Aortic Stenosis and Lipid-Lowering Trial, Impact on Regression (SALTIRE) study – failed to show that atorvastatin prevents the progression of VAS. Given the limited sample size and short follow-up in this trial, the results of future prospective trials, eg, the Canadian Aortic Stenosis Progression Observation Measuring Effects of Rosuvastatin (ASTRONOMER) and European Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trials, are eagerly awaited. This issue of *Cardiology Rounds* discusses the pathophysiology of VAS, reviews the evidence that statin therapy may slow the progression of VAS, and discusses current clinical trials that are examining this treatment.

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."[1,2] Calcification of the aortic valve is the third leading cause of heart disease in adults and VAS is the most common acquired valvular disease in developed countries.[2,3] Aortic sclerosis is common, occurring in approximately 25% of people aged 65 to 74 years and in 48% of those aged >84 years. It is defined echocardiographically by focal areas of valve thickening, typically located in the leaflet center with commissural sparing and normal leaflet mobility.[4] With aortic sclerosis, valvular area and hemodynamics are within normal limits with a peak transvalvular velocity <2.5 m/sec; it is considered a precursor lesion to VAS.

In the past, VAS was thought to be a degenerative disease because of time-dependent wear-and-tear of the leaflets with passive calcium deposition. However, there are now compelling histopathologic and clinical data suggesting that calcific aortic valve disease is an active disease process similar to atherosclerosis, with lipoprotein deposition, chronic inflammation, and active leaflet calcification. The overlap in the clinical factors associated with calcific VAS and atherosclerosis, and the correlation between the severity of coronary artery and aortic valve calcification provide further support for a shared disease process.[2] While treatment for patients with symptomatic aortic stenosis remains aortic valve replacement,[5] there is now emerging evidence that pharmacological therapies may potentially retard the progression of aortic stenosis.

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Table 1: Classification of valvular aortic stenosis

	Peak transvalvular jet velocity (m/sec)	Aortic valve area (cm^2)	Mean transvalvular pressure gradient (mm Hg)	Aortic valve area index (cm^2/m^2)*
Sclerosis AS	<2.5	Normal (2-4)	Normal	
Mild AS	2.5-<3.0	1.5-2		>0.9
Moderate AS	3.0-<4.0	1.0-1.5		0.6-0.9
Severe AS	>4.0	<1.0	>50	<0.4-0.6

AS = aortic stenosis

* calculated as aortic valve area divided by body surface area (m^2)

Classification and pathophysiology of VAS

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
- the fibrosa, on the aortic side of the leaflet, comprises primarily fibroblasts and collagen fibers arranged circumferentially
- the spongiosa, a layer of loose connective tissue at the base of the leaflet, between the fibrosa and ventricularis, is composed of fibroblasts, mesenchymal cells, and a mucopolysaccharide-rich matrix.[2]

These layers work in concert to provide tensile strength and pliability to the aortic valve. The classification of VAS is based on echocardiographic (calculated valve area and aortic jet velocity) and hemodynamic (mean pressure gradient) parameters (Table 1). Although the classic echocardiographic description of severe valvular stenosis is a valve area <0.7 cm^2, the American Heart Association/American College of Cardiology guidelines have taken a more conservative approach and consider an absolute valve area <1.0 cm^2 as severe aortic stenosis.[5] The aortic valve area index attempts to correlate the size of the aortic valve to the size of the patient by dividing the aortic valve area by the body surface area. For example, in large patients, a valve area of 1.0 cm^2 may be severely stenotic, whereas a valve area of 0.7 cm^2 may be adequate for smaller patients.

Histopathologic studies of aortic sclerosis reveal focal subendothelial plaque-like lesions on the aortic side of the leaflet that extend to the adjacent fibrous layer. These lesions have features that are similar to the lesions associated with atherosclerosis, with prominent accumulation of "atherogenic" lipoproteins, including low-density lipoprotein (LDL) and lipoprotein(a), evidence of LDL oxidation, inflammatory cell infiltrates, and microscopic calcification.[6] Several studies have documented that the clinical factors traditionally associated with atherosclerosis overlap with those associated with calcific aortic valve disease (Figure 1).[2] In the prospective, population-based Cardiovascular Health Study, which included 5621 adults aged >65 years, clinical factors associated with calcific aortic valve disease included older age, male gender, smoking, hypertension, and hyperlipidemia; the strength of these associations were comparable to those seen with atherosclerotic disease.[2,7] Inflammatory cells are predominant early in the course of the disease process, with infiltration by T-lymphocytes and macrophages, while aortic sclerosis lesions have also been shown to contain angiotensin-converting enzyme (ACE), with local production of angiotensin II.[2] A key distinguishing feature of VAS is the early and pronounced transformation of fibroblasts into an osteoblast-like phenotype with associated calcification of valve leaflets (Figure 1).[8]

Figure 1: Comparison of the risk factors of calcific aortic stenosis and atherosclerosis. The boxed areas indicate key differences between atherosclerosis and calcific aortic valve disease

	Calcific aortic valve disease	Atherosclerosis
Histopathologic features		
Lipoprotein accumulation	++++	++++
Lipid oxidation	++++	++++
Calcification	+++++	++
Inflammatory changes	++++	++++
Systemic inflammatory markers	+	++
C pneumoniae 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	++	++++

(Modified from Freeman and Otto[2])

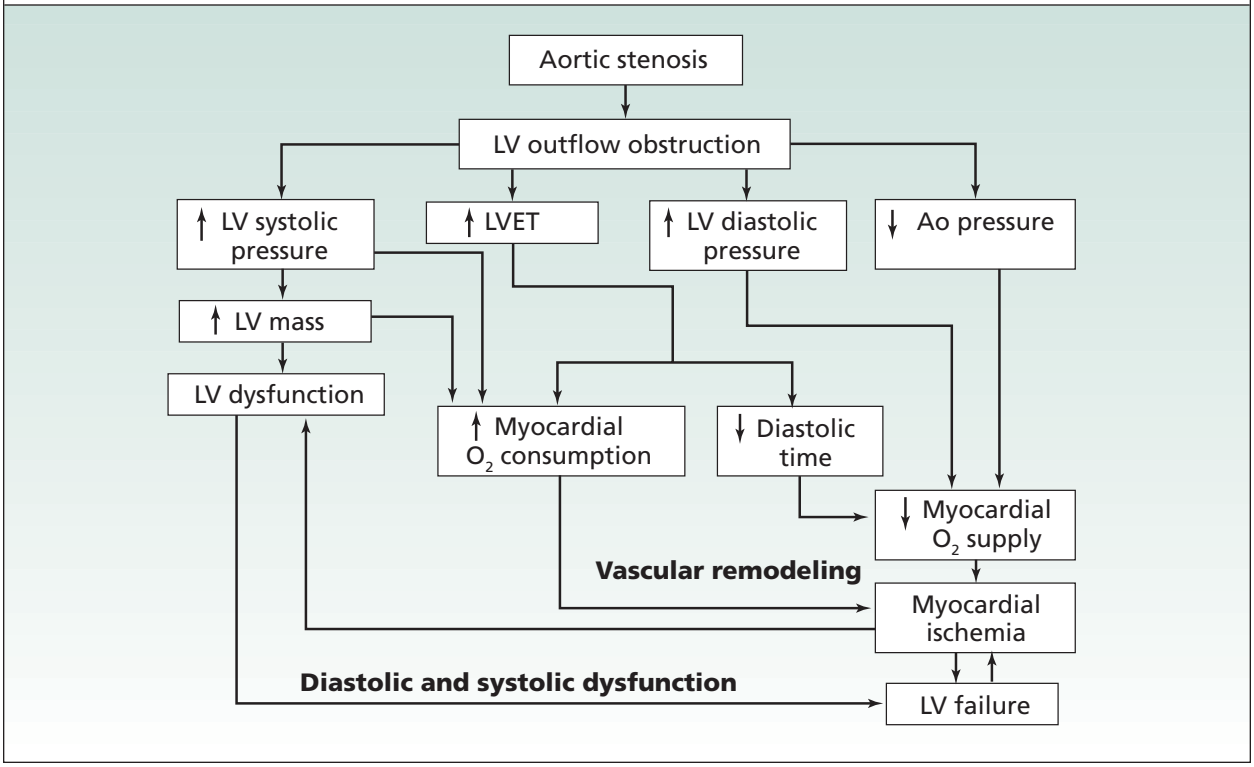
Progression of aortic sclerosis to stenosis

There have been few prospective studies examining the progression of hemodynamic rates spanning the disease spectrum from aortic sclerosis to aortic stenosis. In a study of >2000 patients with aortic sclerosis, 16% developed aortic stenosis, with:

- mild stenosis developing in 10.5% (peak transvalvular velocity 2 to 3 m/sec)
- moderate stenosis developing in 3% (peak transvalvular velocity 3 to 4 m/sec)
- severe stenosis developing in 2.5% (peak transvalvular velocity >4 m/sec).[9]

The average time interval from diagnosis of aortic sclerosis to severe aortic stenosis was 8 years.[9] Similar findings were observed in a smaller study in 400 subjects with aortic sclerosis, of which 5% developed moderate aortic stenosis and 2.5% developed severe aortic stenosis.[10]

Figure 2: Pathophysiology of heart disease in patients with valvular aortic stenosis



LV = left ventricular; LVET = left ventricular ejection time; Ao = aorta

(Modified from Braunwald *Textbook of Cardiovascular Medicine*, 7th Edition, 2004)

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 increases in tandem with longer durations of follow-up. These data highlight the need for close clinical follow-up and serial evaluation of patients once aortic sclerosis is identified.[2,9] Indeed, although patients with aortic sclerosis are usually asymptomatic, its presence is associated with increasing morbidity and mortality.[2,11] In asymptomatic patients with aortic stenosis, it appears to be relatively safe to delay surgery until symptoms develop. However, outcomes vary widely.[2] The presence of moderate or severe valvular calcification, together with a rapid increase in aortic-jet velocity, identifies patients with a very poor prognosis[2] and they should be considered for earlier valve replacement rather than delaying surgery until after symptoms develop.[12] As such, in clinical trials, aortic valve calcification (assessed by computerized tomography) and aortic jet velocity (assessed by transthoracic echocardiography) are the two surrogates used to monitor the progression of valvular aortic stenosis.

Pathological remodeling of the heart due to VAS

Hypertrophic remodeling in response to increased afterload provides a compensatory mechanism in which the left ventricle normalizes systolic wall stress, while maintaining a normal ejection fraction (Figure 2).[13,14] There is an inverse relationship between chronically elevated wall stress and the ejection fraction, such that the presence of afterload excess results in a gradual decline in the ejection fraction. Aortic valve replacement can increase the ejection fraction by correcting the afterload excess created by a truly stenotic valve.[5] A second mechanism that can produce a depressed ejection fraction in patients with aortic stenosis is a decline in the intrinsic contractility of the myocardium.[14] In patients who have had aortic valve replacement for aortic stenosis, poorer outcomes were related to preoperative excessive left ventricular hypertrophy and indices of underlying irreversible myocardial disease.[15] Symptoms of aortic stenosis develop with larger valve area and lower stroke work loss in hypertensive patients because of the additional overload due to hypertension, suggesting that hypertension should be treated aggressively in these patients.[16] The increased incidence of myocardial ischemia in patients with aortic stenosis is due to several related factors, including increased myocardial oxygen demand, endothelial dysfunction, and the high burden of atherosclerotic coronary artery disease (Figure 2). In addition to systolic dysfunction, diastolic heart failure may result from myocardial hypertrophy and ischemia that often coexist in patients with severe aortic stenosis.

Table 2: Clinical studies examining the relationship between statin therapy and progression of valvular aortic stenosis

	Aronow[22]	Novaro[23]	Shavelle[24]	Bellamy[25]	Rosenhek[26]	Cowell[27]
Study design	Retro	Retro	Retro	Retro	Retro	Prospect
Method	Echo	Echo	EBCT	Echo	Echo	Echo +CT
Follow-up (months)	33	21	30	44	24	25
# of patients	180	174	65	156	211	134
# with statin	62	57	28	38	50	65
Mean age (yr)	82±5	68±12	67±10	77±12	70±10	68±11
Female (%)	69	56	NA	42	49	30
HTN (%)	73	69	35	66	80	51
Diabetes (%)	27	25	12	24	21	4
CAD (%)	NA	59	51	35	27	20
ACEi (%)	NA	NA	NA	NA	62	13
Mean LDL (mg/dL)	NA	130	NA	143	142	135
Peak AJV (m/s)	NA	2.65	NA	2.95	3.96	3.42
Slowed AVS	Yes	Yes	Yes	Yes	Yes	No

Retro = Retrospective; Prospect = Prospective; Echo = Echocardiography; EBCT = Electron beam computed tomography; CT = Computed tomography; ACEi = ACE inhibitor; LDL = Low-density lipoprotein; HTN = Hypertension; CAD = Coronary artery disease; AVS = Aortic valve stenosis; AJV = Aortic jet velocity; NA = data not available.

The most common symptom of aortic stenosis is exertional dyspnea or decreased exercise tolerance due to the heart's inability to adequately increase stroke volume to meet increased metabolic demands. The classic presentation of heart failure, chest pain, and syncope develops late in the disease process and heralds a poor prognosis.[5,17] As such, there has been interest in developing a more objective marker of "symptom onset" to identify those who would benefit from earlier valve replacement. Recent studies measuring serum neurohormone levels, such as B-type or brain natriuretic peptide (BNP), demonstrate an association between increased levels and disease severity. There is a progressive association of serum BNP with the severity of aortic stenosis and left ventricular dysfunction.[18] Asymptomatic patients with more hemodynamically significant aortic valve disease had higher serum BNP levels, suggesting that BNP may potentially serve to discriminate between normal exercise tolerance and early symptoms of heart failure.[18] Serum N-terminal pro-BNP level was also an independent predictor of postoperative clinical outcome defined by survival and ejection fraction.[19] Serum BNP levels may be a helpful adjunct in identifying patients with equivocal complaints at risk of rapid progression to symptom onset. Larger prospective trials are necessary before advocating that these measures be used on a routine basis.

Statin therapy and valvular aortic stenosis – clinical trial evidence

Given the large overlap in the pathophysiology of atherosclerosis and calcific aortic stenosis, and the impressive benefit of statin therapy on atherosclerotic cardiovascular disease, statin therapy has also been proposed to reduce the progression of aortic valve stenosis. Statin therapy may also improve endothelial dysfunction and reduce the ischemic burden in these patients. In addition to the potential beneficial effects in slowing the progression of aortic stenosis, emerging evidence suggests that statin therapy may reduce the progression to ventricular dilation and heart failure in response to pressure overload.[20,21]

Several retrospective studies have revealed that protracted use of a statin may retard the progression of aortic stenosis. These "hypothesis-generating" studies have created a great deal of excitement in the scientific community (Table 2).[22-26] However, a recent, prospective, randomized, controlled clinical trial performed in the United Kingdom – the SALTIRE study – failed to confirm the results of these retrospective analyses.[27] Nevertheless, there were several limitations in SALTIRE, including too few subjects (77 patients in each arm), a short follow-up (median of 25 months), a high drop-out rate (30% at 24 months), and the inclusion of patients with moderate/severe aortic stenosis.[27,28] The inclusion of

patients with severe aortic stenosis in the SALTIRE trial may have limited the potential therapeutic benefit of statin therapy. These limitations were compounded by the inherent variability of the outcome variables, namely, aortic jet velocity and aortic valve calcium score.

Currently, there are two ongoing prospective clinical trials, the Canadian ASTRONOMER study and the European SEAS study that will provide a more definitive answer to this important clinical question.[1,2]

The ASTRONOMER study is a multicentre, double-blind, placebo-controlled, randomized, controlled trial with a 2-year recruitment period, a treatment duration of 3-5 years, and a common close-out date 3 years from the time the last patient is randomized. The subjects will be randomized to receive either placebo or a fixed-dose of active drug, rosuvastatin, 40 mg daily. The main objective is to determine whether patients taking rosuvastatin 40 mg will have a smaller increase in their aortic transvalvular gradient and a smaller decrease in their aortic valve area compared to those taking placebo over a period of 3 years. A total of 300 patients will be recruited; those eligible include men and women between the ages of 18 and 82 years with mild-to-moderate aortic stenosis defined by peak Doppler aortic valve velocity 2.5 to 4.0 m/sec. Baseline low-density lipoprotein cholesterol and triglycerides levels must be within target levels for the risk categories according to Canadian Guidelines. There are currently 23 centres recruiting patients across Canada.

The SEAS study is a multicentre, randomized, controlled trial that is being conducted in 7 European countries, involving 1873 patients from 173 sites. The main goal of the study is to determine whether treatment with simvastatin and ezetimibe versus placebo reduces a composite endpoint of major cardiovascular events, including aortic valve replacement in patients with aortic stenosis.

Until the results of these trials become available, statin therapy cannot be specifically recommended to slow the progression of disease in patients with VAS. Nevertheless, given the widespread use of statins and the high incidence of atherosclerotic disease in patients with aortic stenosis, a large proportion of patients with aortic stenosis will have a conventional indication for statin therapy that renders recruitment of patients to these trials difficult.

Summary and conclusions

Valvular aortic stenosis leads to a considerable burden on the heart and is a common cause of heart disease in adults. Although surgical replacement of the aortic valve is the gold-standard for management of those indicated, recent studies have started to unravel the complex pathophysiology of VAS and the ventricular remodeling that ensues. These studies have provided a strong basis for statin therapy that is supported by numerous retrospective clinical studies. Given the limitations of a recent randomized clinical trial (the SALTIRE study), there is a clear need for large-scale randomized clinical trials with larger sample sizes and longer durations of follow-up. Indeed, two current trials, the Canadian-based ASTRONOMER Study and the European-based SEAS trial, will provide the critical data to better understand the efficacy and safety of statin therapy in patients with VAS. Until the results of these trials become available, statin therapy can only be specifically recommended based on conventional indications.

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Abstract of Interest

Prevention of cardiac hypertrophy by atorvastatin in a transgenic rabbit model of human hypertrophic cardiomyopathy.

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Cardiac hypertrophy, a major determinant of morbidity and mortality in hypertrophic cardiomyopathy (HCM), is considered a secondary phenotype and potentially preventable. To test this hypothesis, we screened 30 5- to 6-month-old beta-myosin heavy chain Q403 transgenic rabbits by echocardiography and selected 26 without cardiac hypertrophy. We randomized the transgenic rabbits to treatment with atorvastatin (2.5 mg/Kg/d), known to block hypertrophic signaling or a placebo. We included 15 nontransgenic rabbits as controls. Cardiac phenotype was analyzed serially before, 6 and 12 months after randomization. Serum total cholesterol levels were reduced by 49% with atorvastatin administration. Left-ventricular mass, wall thickness; myocyte size, myocardial levels of molecular markers of hypertrophy, lipid peroxides, and oxidized mitochondrial DNA; and the number of terminal deoxynucleotidyltransferase-mediated dUTP-biotin nick end labeling (TUNEL)-positive myocytes were increased significantly in the placebo but not in the atorvastatin group. Myocardium catalase mRNA levels were decreased by 5-fold in the placebo but were normal in the atorvastatin group. Catalase protein level and activity were not significantly changed. Levels of membrane-bound Ras and phospho-p44/42 mitogen-activated-protein kinase (MAPK) were increased in the placebo group (approximately 2.5 fold) but were reduced in the atorvastatin group. Levels of GTP- and membrane-bound RhoA and Rac1, phospho-p38, and phospho-c-Jun NH2-terminal kinases were unchanged. Thus, atorvastatin prevented development of cardiac hypertrophy; determined at organ, cellular, and molecular levels, partly through reducing active Ras and p44/42 MAPK. The results indicate potential beneficial effects of atorvastatin in prevention of cardiac hypertrophy, a major determinant of morbidity in all forms of cardiovascular diseases, and beckon clinical studies in humans with HCM.

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