Progression of aortic valve sclerosis and aortic valve stenosis: what is the role of statin treatment?

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Background. **It has recently been suggested that statins could slow the progression of aortic stenosis, but this hypothesis has not been validated in large series. Moreover, there is little information about the role of statin treatment in patients with aortic valve sclerosis.**

Methods. **From our database 1988-2002, we retrospectively identified 1136 consecutive patients with aortic valve sclerosis (peak aortic velocity [Vmax] > 1.5 and < 2 m/s), or mild to moderate aortic stenosis (Vmax 2.0-3.9 m/s) and with ≥ 2 echocardiographic studies ≥ 6 months apart; 121 (11%) were treated with statins. As a control group we randomly selected 121 age-gender-matched patients not treated with statins, with similar initial Vmax.**

Results. **The mean follow-up duration was 54 ± 34 months in the statin group, and 50 ± 33 months in controls (p = 0.35). There were no differences between statin-treated patients and controls with respect to age, gender, and prevalence of hypertension. More patients in the statin group had documented hypercholesterolemia, diabetes, or had proven coronary artery disease. Overall, the rate of change of Vmax was not different between statin-treated patients and controls (0.13 ± 0.24 vs 0.14 ± 0.19 m/s/year, p = 0.72). However, in the subgroup of patients with aortic valve sclerosis (n = 52, 26 statin-treated, 26 controls), the rate of change of Vmax was significantly lower in statin-treated patients (0.04 ± 0.04 vs 0.08 ± 0.06 m/s/year, p = 0.007).**

Conclusions. **The results of our retrospective study show that statins could be beneficial in retarding the progression of valvular aortic sclerosis to aortic stenosis. This suggests that statins retard the progression of aortic valve lesion in its early stage, a finding that may have important implications in the management of this very common disease.**

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Aortic valve sclerosis and aortic valve stenosis, characterized by an increased leaflet thickness, stiffening and calcification, are common in the elderly. The disease shows a progressive course even in asymptomatic patients, especially after the threshold to mild stenosis has been crossed. To date, there is no proven medical therapy able to modify significantly the natural history of aortic stenosis. Given the similarities between atherosclerosis and aortic stenosis, it has recently been hypothesized that hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) might reduce the progression of mild and moderate aortic stenosis. Indeed, some retrospective studies, performed with a small sample size of patients, reported that statins might be effective in slowing the progression of mild and moderate aortic stenosis[1-3].

The aim of this study was to test this hypothesis in a larger group of patients and, in particular, to address the question of whether statin treatment is beneficial in patients with aortic valve sclerosis, the earliest stage of aortic valve lesion. We performed a retrospective analysis of a group of consecutive patients with aortic sclerosis or mild and moderate aortic stenosis.

Methods

Study population. A systematic retrospective analysis of our adult echocardiography computerized database was performed. All the patients with aortic valve sclerosis or mild to moderate aortic valve stenosis (thickened aortic leaflets with reduced systolic opening on two-dimensional imaging and increased peak aortic velocity [Vmax, range 1.5-3.9 m/s] on Doppler echocardiography) who were studied between 1988 and 2002 were screened for inclusion in the study.

Patients were required to have at least two complete transthoracic echocardiographic examinations ≥ 6 months apart. Patients with coexisting more than mild aortic regurgitation were excluded. Demographic, clinical, and laboratory data were obtained by review of the patients' medical records and/or by interviews. The use of an HMG-CoA reductase inhibitor (statin) was identified and information regarding type of the drug, dose, and duration of treatment was obtained. Treatment with a lipid-lowering agent was done at the discretion of the patient's physician.

The entire study population consisted of 1136 patients. Among them, 121 (11%) received statins throughout the follow-up (75 males, 46 females, mean age 67 ± 9 years). As a control group, from the remaining 1015 patients not treated with statins but with a similar initial Vmax, 121 age-gender-matched subjects (75 males, 46 females, mean age 67 ± 9 years) were randomly selected. The follow-up duration was similar in the two groups (54 ± 34 months in the statin group and 50 ± 33 months in the control group, p = 0.35). Patients were divided into three groups according to the initial Vmax: group A, aortic valve sclerosis (initial Vmax > 1.5 and < 2 m/s); group B, mild aortic stenosis (initial Vmax ≥ 2 and < 3 m/s); group C, moderate aortic stenosis (initial Vmax ≥ 3 and < 4 m/s).

Clinical data. The following clinical data were recorded: the clinical status; history of hypertension, hypercholesterolemia, diabetes mellitus, current smoking, and end-stage renal disease requiring dialysis. Also, prior evidence of coronary artery disease (CAD) (history of myocardial infarction, coronary revascularization, or CAD at coronary angiography) was recorded. The major clinical events were defined as death or aortic valve replacement.

Echocardiographic examination. All echocardiographic data were acquired and interpreted by an experienced staff cardiologist. Interpretation of the echo studies was conducted without knowledge of the present study. Comprehensive examinations were performed on all study patients, including two-dimensional, pulsed- and continuous-wave, and color Doppler echocardiography.

Commercially available echocardiographic systems equipped with 2.5-3.5 MHz phased-array transducers were used. Standard views and techniques were used according to the guidelines of the American Society of Echocardiography[4]. Vmax was measured by continuous-wave Doppler, systematically sampling the flow from different windows, and selecting the highest profile envelope. The peak instantaneous gradient across the valve was derived from Vmax by the simplified Bernoulli equation. The Doppler data of the last examination were compared with the initial ones, and the progression of aortic stenosis was calculated as the annual rate of increase in Vmax. The pattern of progression was compared between the statin group and the control group to evaluate the influence of statin therapy. A pattern of rapid progression of aortic stenosis was defined as a rate of increase in Vmax ≥ 0.3 m/s/year, as previously suggested[5].

The inter- and intraobserver variability in our laboratory for recording and measuring Vmax is low (coefficient of variation < 10% in 100 consecutive patients with aortic stenosis).

Statistical analysis. Changes in Vmax were measured. Rates were calculated both in absolute terms and on an annualized basis (dividing the absolute change by time in the study). Continuous data were expressed as means ± SD, and categories data as percentages. For comparisons between patients treated with statins and controls, the χ^2 test was used for dichotomous variables and the Student's t-test for continuous variables. A p value < 0.05 was considered as statistically significant.

Results

Patient characteristics. The patients' clinical characteristics are summarized in table I.

There were no significant differences between the statin-treated group and the control group with respect to age, gender, or follow-up duration. The prevalence of systemic hypertension and end-stage renal disease requiring dialysis was also similar in both groups. As expected, more patients in the statin group had documented hypercholesterolemia, diabetes, or had CAD (Table I). Five different statins were used in the statin group. The agent used, the number of patients and the mean ± SD daily dosage were: simvastatin, 75 patients,

Table I. Clinical characteristics of the statin and control groups.

Variables	Statin group (n=121)	Control group (n=121)	p
Hypertension	78 (64%)	67 (55%)	0.19
Hypercholesterolemia	111 (92%)	17 (14%)	< 0.001
Diabetes	32 (26%)	17 (13%)	0.025
Current smoking	6 (5%)	2 (2%)	0.28
Dialysis	4 (3%)	4 (3%)	0.72
Coronary artery disease	87 (72%)	25 (21%)	< 0.001

15 ± 5 mg; atorvastatin, 25 patients, 13 ± 7 mg; pravastatin, 15 patients, 21 ± 8 mg; fluvastatin, 4 patients, 50 ± 20 mg; cerivastatin, 2 patients, 0.3 ± 0.1 mg (both patients completed their follow-up period before drug withdrawal from the market).

Hemodynamic progression of aortic valve sclerosis/stenosis. The baseline and follow-up echocardiographic data and clinical events in the two groups are shown in table II. The baseline echocardiographic parameters were similar for both groups and remained not significantly different at the end of the study. When all stages of aortic valve lesion were considered together, no significant differences between the two groups regarding progression of aortic stenosis were found. The rate of increase in Vmax, and the presence of a pattern of rapid progression of aortic stenosis were similar in the two groups. However, considering separately the effect of statin treatment on patients with different stages of aortic lesion, a significant effect of slowing lesion progression was demonstrated in the statin-treated patients with aortic valve sclerosis (Fig. 1): the rate of increase in Vmax was 0.04 ± 0.04 m/s/year in the statin-group and 0.08 ± 0.06 m/s/year in controls (p = 0.007) (Table III).

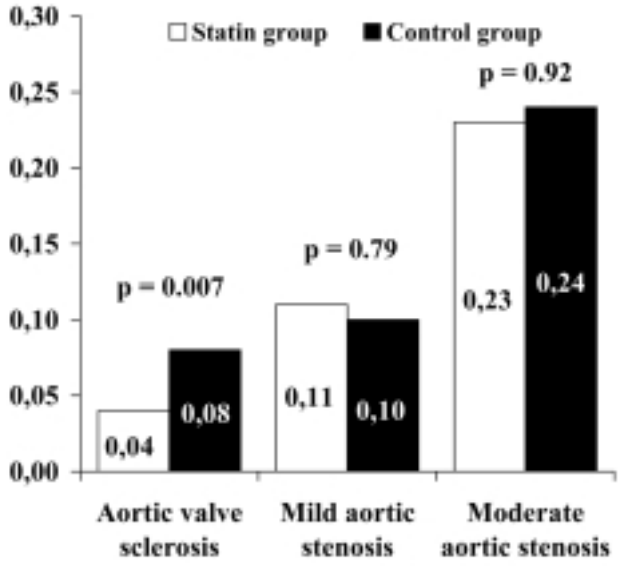

Figure 1. *Rate of progression of the disease in the three study groups: group A, aortic valve sclerosis (n = 26); group B, mild aortic stenosis (n = 63); group C, moderate aortic stenosis (n = 32), expressed as the rate of annual increase in peak aortic velocity (m/s/year) in the statin group and the control group. There was a significant difference between statin-treated patients and controls only in the aortic valve sclerosis group (p = 0.007).*

Relation between clinical factors and progression of aortic valve sclerosis/stenosis. The influence of several clinical factors on aortic stenosis progression is presented in table IV. No significant association between age, gender, hypertension, diabetes, hypercholesterolemia, current smoking, documented CAD, and progression of aortic sclerosis or stenosis was found, even though there was a trend for more rapid progression in the presence of hypertension and older age. Only dialysis was significantly associated with a faster progression of aortic stenosis (Table IV).

Clinical events. During follow-up, the occurrence of a major clinical event was similar in both groups. There were 3 cardiac deaths and 18 aortic valve replacement procedures in the statin group, compared to 3 cardiac

Table II. Changes in echocardiographic data and major clinical events during the study period.

Variable	Statin group (n=121)	Control group (n=121)	p
Initial LV ejection fraction	0.59 ± 0.13	0.58 ± 0.14	0.56
Final LV ejection fraction	0.54 ± 0.14	0.55 ± 0.14	0.58
Initial peak aortic velocity (m/s)	2.45 ± 0.66	2.44 ± 0.65	0.95
Final peak aortic velocity (m/s)	3.0 ± 1.0	2.9 ± 1.0	0.44
Initial peak aortic gradient (mmHg)	25.8 ± 13.9	25.7 ± 13.7	0.94
Final peak aortic gradient (mmHg)	38.2 ± 25.8	37.6 ± 27.2	0.85
Rate of increase in peak velocity (m/s/year)	0.13 ± 0.24	0.14 ± 0.19	0.72
Rapid progression (rate ≥ 0.3 m/s/year)	15 (12%)	20 (16%)	0.46
Major clinical events (death/AVR)	21 (17%)	13 (11%)	0.20

AVR = aortic valve replacement; LV = left ventricular.

Table III. The rate of annual increase in peak aortic velocity (m/s/year) in the three subgroups.

Subgroup	Statin group	Control group	p
Aortic valve sclerosis (n=26)	0.04 ± 0.04	0.08 ± 0.06	0.007
Mild aortic stenosis (n=63)	0.11 ± 0.25	0.10 ± 0.17	0.79
Moderate aortic stenosis (n=32)	0.23 ± 0.27	0.24 ± 0.23	0.92

Table IV. Influence of clinical factors on aortic sclerosis or aortic stenosis progression (expressed as the rate of annual increase in peak aortic velocity, m/s/year).

Variable	Present	Absent	p
Hypertension	0.15 ± 0.24 (n=145)	0.10 ± 0.14 (n=97)	0.07
Diabetes	0.13 ± 0.17 (n=48)	0.13 ± 0.21 (n=194)	0.95
Hypercholesterolemia	0.13 ± 0.25 (n=128)	0.13 ± 0.17 (n=114)	0.91
Current smoking	0.18 ± 0.19 (n=8)	0.13 ± 0.21 (n=234)	0.51
Advanced age (> 70 years)	0.16 ± 0.28 (n=92)	0.11 ± 0.16 (n=150)	0.08
Dialysis	0.39 ± 0.38 (n=8)	0.14 ± 0.19 (n=234)	< 0.001
Male gender	0.12 ± 0.20 (n=150)	0.15 ± 0.23 (n=92)	0.29
Coronary artery disease	0.14 ± 0.24 (n=112)	0.12 ± 0.18 (n=130)	0.46

deaths and 10 aortic valve replacement procedures in controls (p = 0.20) (Table II). No non-cardiac deaths occurred and no significant adverse effects of statin treatment were recorded during follow-up.

Discussion

Aortic stenosis is a common public health problem in western countries, and it is now the most frequent valve disease in the elderly cohort. The prevalence of aortic stenosis and aortic valve sclerosis increases with age; in adults > 65 years it is estimated at 2-3 and 25%, respectively[6]. It has been suggested that valvular calcium is a form of the spectrum of atherosclerotic disease[7-9]. The hypothesis is supported by several lines of evidence, including: the histological similarity between early lesions of aortic stenosis and CAD, such as lipoprotein deposition[10,11]; the association between aortic valve lesion and atherosclerotic risk factors, such as increased serum total cholesterol[12-14], serum low-density lipoprotein (LDL)[1,15] and lipoprotein(a) concentrations[6,16], decrease in high-density lipoproteins (HDL)[1]; or the coexistence of CAD and aortic stenosis in some patients, suggesting similar mechanisms of the two diseases. Therefore it seems reasonable to hypothesize that atherosclerotic risk factor modification may lead to slower progression of aortic stenosis.

This hypothesis has recently been supported by an experimental animal model[17]. In this rabbit model, hypercholesterolemia was proven to produce atherosclerotic lesions in the aortic valve, and treatment with atorvastatin influenced the pathogenic mechanism and reduced the extent of atherosclerotic changes in the aortic valve.

Furthermore, in recent years, some retrospective studies reported in humans that statin therapy might slow the progression of aortic stenosis. Aronow et al.[1] analyzed Doppler echocardiographic data of 180 patients with mild aortic stenosis and reported that LDL cholesterol ≥ 125 mg/dl and HDL cholesterol ≤ 35 mg/dl were independent predictors of aortic stenosis progression, which was significantly slowed in 62 patients by statin treatment. Novaro et al.[2] found a significant reduction in the rate of aortic stenosis progression in 57 patients treated with statins as compared to untreated patients. Recently, Bellamy et al.[3] found similar results in 38 statin-treated patients. Pohle et al.[15] studied the progression of aortic valve calcification using electron beam computed tomography. They found that a serum LDL cholesterol ≥ 130 mg/dl was an independent predictor of progression of aortic valve calcification, while the use of statins in 54 patients significantly decreased the rate of aortic valve calcium accumulation. Shavelle et al.[18] reported similar results in 28 statin-treated patients.

Very recently Rosenhek et al.[19] observed in 82 statin-treated patients a positive effect of statins on the progression of aortic stenosis, while angiotensin-converting enzyme inhibitors were ineffective.

Our study enrolled more patients, had a longer follow-up, and is the first one to specifically address the question of statin treatment benefit in patients with aortic sclerosis. Although we could not confirm the positive effect of statin treatment on slowing disease progression across the whole range of aortic stenosis severity, our study demonstrates a beneficial effect of statins in patients with aortic valve sclerosis. On the other hand, given the higher baseline risk profile for stenosis progression in the statin-treated group (hypercholesterolemia, diabetes, and prevalence of CAD were significantly more prevalent in this group), the fact that Vmax did not increase in statin-treated patients with aortic stenosis could also be interpreted as a beneficial effect of statins since one might expect to find a faster progression in this group.

Nevertheless, the current study suggests that statin treatment benefit might be stage-related. Thus, patients with the early morphological lesion of aortic sclerosis may derive a significant benefit from statin treatment.

It must be emphasized that aortic valve stenosis and aortic valve sclerosis are morphologically different. In aortic valve sclerosis there is a deposition of lipids, which are oxidized similarly to atherosclerosis, whereas in aortic valve stenosis there is mainly calcium overgrowth, which may have its own determinants, inde-

pendent of cholesterol levels[3]. This could also represent one possible explanation for the differences in statin treatment effect between patients with aortic sclerosis and those with aortic stenosis.

The possible mechanism of statin treatment benefit in slowing aortic stenosis progression is not clear. The correlation between lipid levels and aortic stenosis progression is controversial. Two studies[1,15] found a significant correlation, while other studies[2,3,20,21] showed lack of correlation between lipid levels and aortic stenosis progression. Palta et al.[12] reported a faster aortic stenosis progression with cholesterol levels ≥ 200 mg/dl, but overall showed no correlation between cholesterol and aortic stenosis progression. The Cardiovascular Health Study[6], enrolling 5201 subjects ≥ 65 years of age, detected only a very weak association between increased LDL cholesterol and aortic stenosis. Aortic stenosis is certainly a multifactorial disease. Other atherosclerotic factors are also associated with aortic stenosis, including age, male gender, hypertension, obesity and homocysteine levels[1,6,20,21]. Smoking[1,6,13] and diabetes mellitus[1,13] were also reported as risk factors for aortic stenosis, although less consistently. Additionally, an elevated left ventricular systolic pressure[22] and a higher transaortic velocity[12,22] seem to be associated with accelerated aortic stenosis progression. The difference in prevalence between aortic stenosis and CAD suggests that other non-atherosclerotic risk factors may play an important role in the development of aortic stenosis[23]. The coexistence and the interaction of all these factors and mechanisms make this clinical condition more complex. In fact, it is virtually impossible to predict the rate of aortic stenosis progression in an individual patient[24]. Cholesterol lowering may then be only one part of clinical therapy, and its effect may be difficult to evaluate if other coexisting variables are ignored.

On the other hand, statins exhibit pleiotropic effects over and above lipid-lowering, including anti-inflammatory effects[25], with a reduction in C-reactive protein independent of lipid changes[26]. They retard extraosseous calcifications, as for coronary vessels[27], and decrease native aortic valve calcium accumulation[15,18]. The high prevalence of *Chlamydia pneumoniae* in degenerative aortic valves[28] and the anti-inflammatory effects of statins, independent of their lipid-lowering effects, may influence the active subendothelial process that occurs in diseased aortic valves. Given these mechanisms, one might expect statins to be effective in modifying the histologic architecture of the aortic leaflets especially during the early stages, before the appearance of gross nodular calcifications and significant flow obstruction.

The present study is the first one to analyze the effect of statin treatment on different degrees of aortic lesion severity and to demonstrate a beneficial effect of statins in slowing progression specifically in the group of patients with aortic valve sclerosis. As this early lesion is the most prevalent one in the general population, estimated to be present in approximately 25% of elderly adults[6] ("the body of the iceberg"), the findings of this study may have important implications in the management of this very common disease.

Study limitations. The retrospective study design suffers from the usual limitations of this type of study. In addition a small change in velocity progression was observed only in the sclerosis subgroup (26 patients) and the subgroup analysis could be fraught with bias. On the other hand, previous studies demonstrated a positive effect of statin treatment in similar small populations.

Due to the retrospective nature of the study and to its inclusion criteria (patients with Vmax < 1.5 m/s) there was a lack of complete information regarding aortic valve area and therefore only Vmax was analyzed. Nevertheless, this is a simple, widely used parameter of aortic stenosis severity in the absence of significant left ventricular dysfunction. In our study, more than mild aortic regurgitation was an exclusion criteria, and both initial and final ejection fractions were very similar in the two groups. Furthermore, the benefit of statin treatment was identified in the subgroup of patients with aortic sclerosis, in whom usually only Vmax is used as the measure of severity. Therefore, we believe this does not alter significantly the meaning of our study results. Because of the retrospective nature of the study, complete information regarding the lipid profile of these patients was not available. Therefore, we could not test for a relation between changes in lipid profile and disease progression, and so the mechanism of statin treatment benefit in patients with aortic sclerosis remains speculative. Nevertheless, this limitation only relates to the mechanism of statin treatment benefit, and does not affect the conclusion that statin treatment slows the progression of aortic valve sclerosis.

In conclusion, the results of our retrospective study suggest that statins could be beneficial in retarding the progression of valvular aortic sclerosis to aortic stenosis. We could not confirm the positive effect of statin treatment on slowing the disease progression in patients with mild and moderate aortic stenosis. This suggests that statins retard the progression of aortic valve lesions in their early stage, a finding that may have important implications in the management of this very common disease. A large, prospective, randomized controlled trial of statins in patients with aortic sclerosis and different stages of aortic stenosis is in our opinion warranted to determine whether the indications of statins should be extended to this group of patients.

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