Hydroxymethylglutaryl Coenzyme-A Reductase Inhibitors Delay the Progression of Rheumatic Aortic Valve Stenosis

A Long-Term Echocardiographic Study

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Objectives
This study sought to assess the effect of hydroxymethylglutaryl coenzyme-A reductase inhibitors (statins) on the progression of rheumatic aortic valve stenosis.

Background
The possible role of statins in slowing the progression of degenerative aortic valve stenosis (AS) is still debated. No information about the role of statin treatment in patients with rheumatic AS is available yet.

Methods
From our 1988 to 2008 echocardiographic database, we retrospectively identified all patients with rheumatic AS, with a baseline peak aortic velocity /H11350/ 1.5 m/s and at least 2 echocardiographic studies /H11350/ 2 years apart. Exclusion criteria were: severe aortic regurgitation, bicuspid aortic valve, and left ventricular ejection fraction /H11021/ 40%.

Results
The study population consisted of 164 patients (30 treated with statins) followed up for 8.5 ± 4.2 years. Peak aortic velocity at baseline was not different in patients treated with statins versus untreated patients (2.3 ± 0.8 m/s vs. 2.3 ± 0.7 m/s, p = 0.84). There were no significant differences in sex, age, or follow-up duration between the 2 groups. Progression of AS severity was slower in patients receiving statins compared with untreated patients (annual change of peak aortic velocity: 0.05 ± 0.07 m/s/year vs. 0.12 ± 0.11 m/s/year, p = 0.001). An annual rate of peak velocity progression ≥0.1 m/s was found in 10% of statin-treated patients and in 49% of untreated patients (p < 0.0001).

Conclusions
This is the first observation of a positive effect of statin treatment in reducing the progression of rheumatic AS. The underlying mechanisms remain to be clarified. (J Am Coll Cardiol 2009;53:1874–9) © 2009 by the American College of Cardiology Foundation

Rheumatic heart disease still represents a major public heart problem, especially in developing countries (1–4). Even if during the last decades the prevalence of rheumatic heart disease has greatly decreased in industrialized countries, recently, because of increasing migration of people from areas where rheumatic heart disease is still endemic, we encounter again patients with rheumatic heart disease in our echocardiographic laboratories. Echocardiography represents the gold standard imaging technique in patients with suspected or known rheumatic heart disease (2–5). It is well known that nowadays the degenerative etiology of aortic valve disease is the most prevalent one, but there are still cases of rheumatic aortic valve disease, mostly aortic regurgitation but also aortic stenosis (AS). The hypothesis that statin treatment could slow the progression of degenerative aortic valve stenosis is still controversial (6), and the recent SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study did not show any benefit of statins plus ezetimibe in reducing AS progression (7). However, information about the role of statins in patients with rheumatic AS is not yet available. Therefore, the goal of this study was to assess the effect of statin treatment on the long-term hemodynamic progression of AS in a large group of patients with rheumatic heart disease.
Methods

Study population. A systematic retrospective analysis of our adult echocardiography computerized database was performed. All patients examined over the last 20 years (between 1988 and 2008) who were found to be affected by rheumatic heart disease (confirmed history of rheumatic fever and/or classical signs of rheumatic mitral valve disease and typical echocardiographic aspect of the aortic valve) were selected. All patients who had a baseline peak aortic velocity ≥1.5 m/s and at least 2 echocardiographic studies ≥2 years apart were considered for the study. Patients with previous aortic valve surgery, bicuspid aortic valves, reduced left ventricular function (ejection fraction <40%), severe aortic regurgitation, symptoms at first examination, or lack of detailed information on medical therapy were excluded. Demographic, clinical, and laboratory data (when available) were obtained by review of the patient’s medical records.

Clinical data. The following clinical data were collected: age, sex, history of hypertension, diabetes mellitus, hypercholesterolemia, prior evidence of coronary artery disease (CAD) (history of myocardial infarction, coronary revascularization, or CAD by angiography) and end-stage renal disease requiring dialysis. Information regarding medication and specifically the use of statin treatment (type of drug, dose, and treatment duration), was also obtained. We considered a patient to be statin treated only if the information about statin treatment was present in serial medical records during the entire follow-up period (between the first and the last available echocardiographic examination).

Echocardiographic examination. Echocardiography was performed with commercially available ultrasound systems by experienced staff cardiologists. Interpretation of the echocardiographic studies was conducted without knowledge of the present study. All patients underwent a comprehensive examination, including 2-dimensional, pulsed- and continuous-wave, and color Doppler echocardiography. Peak velocity, peak instantaneous gradient, and mean gradient across the aortic valve were measured according to the American Society of Echocardiography guidelines (8).

The primary end point was the annual change in peak aortic velocity (m/s/year) calculated by dividing the difference between the last and the first measurements by the time between examinations. Annualized changes in peak and mean gradients (mm Hg/year) were also calculated. In our laboratory, the interobserver coefficient of reproducibility (9) for recording and measuring peak aortic velocity, in a group of 50 patients, was 0.20 m/s.

Statistical analysis. Continuous variables were expressed as mean ± SD and categorical variables as percentages. The chi-square test was used for the comparison of dichotomous variables, and the Student t test was used for continuous variables. A value of p < 0.05 was considered statistically significant. A multiple linear regression analysis was used to determine the independent predictors of AS hemodynamic progression. The variables introduced in the analysis were: age, sex, hypercholesterolemia, diabetes, CAD, hypertension, baseline peak aortic velocity, and use of statin therapy. The analyses were performed using SPSS for Windows, version 13.0 (SPSS Inc., Chicago, Illinois).

Results

The final study population consisted of 164 patients (mean age 61 ± 10 years, 126 women), 30 of which were treated with statins. Mean follow-up duration was 8.5 ± 4.2 years (range 2 to 20 years). Hypertension was present in 65 patients (40%), hypercholesterolemia in 48 (29%), diabetes mellitus in 24 (15%). Only 1 patient was undergoing dialysis. There were no significant differences in sex distribution, age, and follow-up duration between the 2 groups but, as expected, the prevalence of hypercholesterolemia was higher in the statin group (Table 1). Echocardiographic characteristics at baseline and at follow-up are shown in Table 1. Peak aortic velocity at baseline was similar in patients treated with statins versus untreated patients (2.3 ±
0.8 m/s vs. 2.3 ± 0.7 m/s, p = 0.84). No patient had more than mild AS at baseline. Progression of AS severity was slower in patients receiving statins compared with untreated patients (annual change in peak aortic velocity: 0.05 ± 0.07 m/s/year vs. 0.12 ± 0.11 m/s/year, p = 0.001) (Fig. 1). The absolute change in peak aortic velocity between baseline and last follow-up was higher in untreated patients compared with patients treated with statins (Fig. 2). A fast AS progression was defined as an annual rate of peak aortic velocity progression ≥ 0.1 m/s. Fast AS progression was found in 10% of statin-treated patients and in 49% of untreated patients (p < 0.0001) (Fig. 3).

At multivariate analysis (including age, sex, hypercholesterolemia, diabetes mellitus, CAD, hypertension, baseline peak aortic velocity, and statin therapy) only statin therapy (p = 0.001) and baseline peak aortic velocity (p < 0.001) were independently related to rheumatic AS progression.

During follow-up, worsening of aortic regurgitation (≥1 degree/3) was found in 17% of statin treated patients and in 19% of untreated patients (p = 0.93). An analysis of statin treatment effect on mitral valve stenosis was not possible because of the large number of previous surgical or interventional procedures performed on the mitral valve.

The statins used and the mean ± SD daily dosages were: simvastatin, 10 patients (18 ± 9.2 mg); atorvastatin, 14 patients (15 ± 8.5 mg); pravastatin, 3 patients (23 ± 15.3 mg); fluvastatin, 1 patient (40 mg); rosuvastatin, 2 patients (10 ± 0 mg).

With similar distribution in the statin and nonstatin groups, 67 patients (41%) were treated with angiotensin-converting enzyme inhibitors (ACEIs). The use of ACEIs did not influence progression of rheumatic AS (rates of peak aortic velocity progression were 0.09 ± 0.11 m/s/year in patients treated with ACEIs and 0.11 ± 0.11 m/s/year in untreated patients, p = 0.44).

**Discussion**

Rheumatic heart disease is a major public health problem in developing countries. Up to 1% of school children in Africa, Asia, the Eastern Mediterranean region, and Latin America show signs of this disease. It has been estimated that worldwide 15.6 million people are affected by rheumatic heart disease, and every year there are about 470,000 new cases of rheumatic fever and 233,000 deaths attributable to rheumatic heart disease (1–3). There are about 2 million people with rheumatic heart disease requiring repeated hospitalization, and 1 million are likely to require surgery globally (4). However, these estimates are based on conservative assumptions. In recent echocardiographic studies the prevalence of aortic valve involvement in rheumatic valve disease ranged between 5% and 24% in developing countries (10,11). The prevalence of rheumatic heart disease in developed countries decreased during the last decades. The most common cause of AS in adults is calcification of a normal trileaflet or congenital bicuspid valve. This calcific
disease progresses from the base of the cusps to the leaflet margins, eventually causing a reduction in leaflet mobility and effective valve area, without commissural fusion. Rheumatic AS caused by fusion of the commissures with scarring and calcification of the cusps is less common and is invariably accompanied by mitral valve disease (12). Nowadays, although degenerative AS is the most prevalent form of aortic valve diseases, cases of rheumatic AS are still present in our echocardiographic laboratories. Echocardiography represents the gold standard imaging technique in patients with suspected or known rheumatic heart disease (2,5). Typical aspects of aortic valve involvement in rheumatic valve disease are represented by adhesions and fusions of the commissures, cusp retraction, and stiffening of the free borders of the cusps (13). These macroscopic features are the result of the pathogenic mechanism: autoimmune humoral and cellular responses directed toward the cardiac structure, triggered by the response to beta-hemolytic group A streptococci. The precise pathogenic mechanisms of rheumatic heart disease have never been clearly defined. It has been postulated that chronic rheumatic valve disease is usually the result of repeated episodes of carditis and is characterized by deposition of fibrous tissue. The debate continues about whether the anatomical changes in chronic rheumatic valve disease result from a smoldering rheumatic process or, once the valve has been deformed by turbulent flow, this leads to progressive fibrosis, thickening, and calcification (14). Recent studies indicate that calcification is not merely an inactive process but involves a regulated inflammatory process associated with expression of osteoblast markers and neoangiogenesis. Also, inflammatory cytokines have been involved as mediators in the immune response in rheumatic aortic valve disease (15). Recent data suggest that oxidative stress and high-sensitivity C-reactive protein (CRP) plasma levels as a marker of systemic inflammation could be involved in the pathogenesis of rheumatic valve disease (16,17). Therefore, the role of inflammation in rheumatic valve disease progression should be considered. Indeed, the persistence of high levels of high-sensitivity CRP has been shown in patients with chronic rheumatic valve disease, particularly in patients with multivalvular disease, who showed significantly higher plasma levels of CRP (18).

Degenerative AS is no longer considered an unmodifiable process, but rather an active, atherosclerosis-like inflammatory process (19). Thus, it was reasonable to hypothesize that pharmacological strategies effective in atherosclerosis, such as statin treatment, might also be an effective therapy in AS. This hypothesis has been tested in several studies (20–25), with either positive or negative results. Some retrospective studies have shown that statin use may be associated with a decreased rate of degenerative AS progression (20–23). Similar results were also obtained in a recent prospective open-label study (RAAVE [Rosuvastatin Affecting Aortic Valve Endothelium] trial) (24). However, the 2 double-blind randomized controlled trials (the SALTIRE [Scottish Aortic Stenosis and Lipid Lowering Therapy, Impact on Regression] and SEAS [Simvastatin and Ezetimibe in Aortic Stenosis] trials) failed to show a benefit of intensive lipid-lowering therapy on calcific AS progression (7,25). The SEAS study involved 1,873 patients with mild to moderate asymptomatic AS (peak aortic velocity between 2.5 and 4 m/s) who received either 40 mg of simvastatin plus 10 mg of ezetimibe or placebo daily. The trial, having a median follow-up of 52.2 months, concluded that intensive lipid lowering did not reduce AS progression, but as expected, it reduced the incidence of ischemic events (7). In a very recent retrospective study assessing the long-term impact of statin treatment on degenerative AS progression in 1,046 patients, we have shown a positive effect of statins in patients with aortic valve sclerosis and mild AS, but not in moderate to severe AS (26), suggesting that early treatment could be more effective. The benefit of statin treatment in slowing the progression of degenerative AS could be related to both its lipid- and nonlipid-lowering effects, including anti-inflammatory properties (27), especially through CRP lowering (28), partial inhibition of cellular proliferation (29), or improvement in endothelial function (30) and reduction of the oxidative processes (28).

The present study is the first one analyzing the possible effect of statin treatment in rheumatic valve disease. Currently, the treatment of chronic rheumatic heart disease is mainly directed at preventing acute attacks of rheumatic fever, but there is no specific treatment aimed at preventing the progression of valvular damage. The high level of CRP in the chronic phase raises the idea of using anti-inflammatory therapy (18). It has been suggested that...
statins may inhibit the inflammatory and noninflammatory processes that induce the acute phase response, and are thus able to reduce CRP levels (31). Furthermore, CRP levels were found to be increased in patients with chronic degenerative AS (32) and degenerated bioprosthesis (33). Skow- asch et al. (33) suggested that serum CRP concentrations may reflect inflammatory processes within the aortic valve. Because statins have not only cholesterol-lowering properties but also pleiotropic and anti-inflammatory properties, the use of statins may be useful for preventing degeneration of native aortic valve and bioprosthesis.

In view of these facts, the hypothesis that statin treatment could also be beneficial in rheumatic AS is a sound one. Our study tested this hypothesis retrospectively in a group of patients with documented rheumatic valve disease, dividing the study population into 2 groups (with or without statin treatment) and assessing the impact of statins on AS progression (increase in peak aortic velocity) during long-term follow-up. The study protocol is similar to those used in previous retrospective studies on the role of statins in degenerative AS (20–23,26).

The 2 groups were similar with respect to age, sex, prevalence of hypertension, diabetes mellitus, CAD, and baseline echocardiographic parameters of AS severity, which was mild in both groups at baseline (Table 1). As expected, the prevalence of hypercholesterolemia was significantly higher in the statin group. Our results showed a significant difference between groups regarding annual change in peak aortic velocity and overall change in velocity between baseline and last follow-up (Figs. 1 and 2). In addition, a pattern of fast progression was found in untreated patients more frequently than in statin-treated patients. Usually, in degenerative AS a pattern of fast progression is considered to be present when the annual change in peak aortic velocity is ≥0.3 m/s/year (34). Because the velocity of AS progression is lower in rheumatic AS, we chose a cutoff of 0.1 m/s/year for identifying fast progression, and a significant difference between statin-treated and untreated patients was noted (Fig. 3). These results are similar to those recently reported by our group (26) showing that statins slow the progression of aortic valve sclerosis and mild AS.

**Study limitations.** This study has the inherent limitations of a retrospective, observational study. However, we tried to reduce the potential sources of selection bias by including a large number of patients for this particular etiology and by having a long-term follow-up.

For the lack of complete aortic valve area measurements (as a consequence of the retrospective nature of the study and of the inclusion of patients with mild disease [peak aortic jet velocity >1.5 m/s]), we only analyzed peak aortic jet velocity for assessing aortic valve disease progression. Nevertheless, peak aortic jet velocity is a well-validated and widely used parameter of AS severity in the absence of significant left ventricular dysfunction (as is the case in our study). This measurement also shows a lower variability when compared with other measures of AS severity. In our study, both initial and final ejection fractions were similar in the 2 groups (treated and untreated patients); therefore, we believe this factor does not influence our results. Complete information regarding the lipid profiles of these patients was not available. Therefore, we could not analyze the possible relationship between changes in lipid profile and aortic disease progression.

**Conclusions**

This is the first study to assess the role of statin treatment in patients with rheumatic AS. It provides evidence for a positive effect of statins in reducing the progression of rheumatic AS. These findings may have important implications for the early management of this progressive disease. The underlying mechanisms, not yet fully understood, remain to be clarified.

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