Effect of Hydroxymethylglutaryl Coenzyme-A Reductase Inhibitors on the Long-Term Progression of Rheumatic Mitral Valve Disease

Francesco Antonini-Canterin, MD; Luis M. Moura, MD; Roxana Enache, MD; Elisa Leiballi, MD; Daniela Pavan, MD; Rita Piazza, MD; Bogdan A. Popouloscu, MD, PhD; Carmen Ginghină, MD, PhD; Gian Luigi Nicolosi, MD; Nalini M. Rajamannan, MD

Background—At present, no medical therapy is known to affect the progression of rheumatic mitral stenosis (MS). We sought to assess the effect of statin treatment on long-term progression of MS in a large population.

Methods and Results—From our 20-year database, we identified all patients with rheumatic MS with ≥2 echocardiographies ≥1 year apart. Exclusion criteria were previous intervention on the mitral valve, more than moderate aortic regurgitation, or symptoms at first examination. The study sample included 315 patients (mean age, 61 ± 12 years; 224 women); 35 patients (11.1%) were treated with statins, and 280 (88.9%) were not. Mean follow-up period was 6.1 ± 4.0 years (range, 1 to 20). The rate of decrease in mitral valve area was significantly lower in the statin group compared with the untreated group (0.027 ± 0.056 versus 0.067 ± 0.082 cm²/y; \( P = 0.005 \)). The annualized change in mean transmitral gradient was lower in statin-treated patients (0.20 ± 0.59 versus 0.58 ± 0.96 mm Hg/y; \( P = 0.023 \)). The prevalence of fast MS progression (annual change in mitral valve area >0.08 cm²) was significantly lower in the statin group (\( P = 0.008 \)). An increase in systolic pulmonary artery pressure of ≥10 mm Hg was found in 17% of patients in the statin group versus 40% of untreated patients (\( P = 0.045 \)).

Conclusions—Our study shows a significantly slower progression of rheumatic MS in patients treated with statins. These findings could have an important impact in the early medical therapy of patients with rheumatic heart disease. (Circulation. 2010;121:2130-2136.)

Key Words: mitral valve ■ rheumatic heart disease ■ statins ■ stenosis
1988 and March 2009). Rheumatic etiology of MV involvement was identified with the use of 2 compulsory criteria: the presence of confirmed history of rheumatic fever in the patients' medical records and the echocardiographic diagnosis of rheumatic MV disease. The echocardiographic diagnosis of rheumatic MV disease was based on the typical aspect of rheumatic MV and subvalvular apparatus involvement (eg, commissural fusion with doming of the MV leaflets in diastole; thickening at the leaflet tips and variable degrees of thickening and/or calcification of the remainder of the leaflets; fusion, shortening, fibrosis, and calcification of the mitral chordae) and also on excluding all other possible etiologies of MS (eg, calcific MS with thin and mobile mitral leaflet tips, congenital MS, and various systemic disorders). All patients who had a baseline measured MV area (MVA) and at least 2 echocardiographic studies ≥1 year apart were considered eligible for the study. Exclusion criteria were as follows: previous MV replacement or MV commissurotomy, previous mitral balloon valvuloplasty, more than moderate aortic regurgitation, or symptoms at first examination and lack of detailed information on medical therapy. Demographic, echocardiographic, and clinical data were obtained by reviewing the patient's medical records. Our group has recently published a study about the role of statins in rheumatic aortic stenosis progression. The actual study sample differs significantly from the previous study; many patients in that study had had a previous intervention on the MV and were not included in the present study. In addition, many patients of the present study did not have aortic valve involvement.

Clinical Data
The following clinical data were collected: age, gender, history of smoking, hypertension, diabetes mellitus, hypercholesterolemia, prior evidence of coronary artery disease (CAD) (history of myo-cardial infarction or coronary revascularization or documented CAD by coronary angiography). Information regarding the use of statin treatment (type of drug, dose, and treatment duration) was obtained. The available medical records did not indicate the number of rheumatic fever attacks/rheumatic carditis events before the first echocardiographic examination and the previous antibiotic prophylaxis treatment and duration. No patient was on antibiotic prophylaxis at the time of the echocardiographic examinations.

Echocardiographic Examination
Echocardiography was performed with commercially available ultrasound systems. MVA was assessed by both the pressure half-time method and direct planimetry whenever possible. To determine MVA by the pressure half-time method, transmitral inflow velocities were recorded by continuous-wave Doppler echocardiography from the apical 4-chamber view, and valve areas were calculated as an average of 3 beats in sinus rhythm and of 5 beats in atrial fibrillation. Mean gradient across the MV was measured. The Wilkins score was calculated as described previously. Presence of mitral and aortic regurgitation was evaluated qualitatively, and the severity of regurgitation was estimated by a semiquantitative evaluation: mild, moderate, and severe, according to the width and depth of the regurgitant jet. Left atrial (LA) dimension was reported as anteroposterior diameter measured in the parasternal long-axis view. Right ventricular systolic pressure was estimated from tricuspid regurgitation with the use of the modified Bernoulli equation and addition of 5 to 15 mm Hg for the estimated right atrial pressure. In the absence of pulmonary stenosis, systolic pulmonary artery pressure was considered equal with right ventricular systolic pressure. All echocardiograms were analyzed by an investigator blinded to the medical treatment of patients.

The study sample was divided into 2 subgroups according to statin treatment (statin and nonstatin group, respectively). Primary end point was the annual change in MVA, referred to as rate of MS progression (cm²/y; calculated by dividing the difference between the last and the first measurements by the time between examinations). Fast MS progression was defined as an annual change in MVA >0.08 cm²/y, corresponding to the 75th percentile of annualized MVA change reported in our entire study sample. Secondary end points were the pattern of fast MS progression and changes in mitral regurgitation severity. The progression of pulmonary hypertension was defined as an increase in systolic pulmonary artery pressure >10 mm Hg during follow-up. Annualized changes in mean transmural gradient (mm Hg/y) and LA dimension were also calculated.

Statistical Analysis
Continuous variables were expressed as mean±SD and categorical variables as percentages. The χ² test was used for the comparison of dichotomous variables and the Student t test for continuous variables. Wilcoxon rank sum test was used for comparison of nominal variables. To identify parameters that could predict MS progression rate, single-variable correlation analysis and multivariable linear regression analysis were performed. A P value <0.05 was considered statistically significant. The analyses were performed with the use of SPSS for Windows, version 13.0 (SPSS, Inc, Chicago, Ill).

Results
At baseline, 736 patients had rheumatic MS and the MVA measured (the query of the database was for rheumatic MS on native valves with MVA measured); 266 patients were excluded because they had only 1 echocardiographic examination or an echocardiographic follow-up examination at <1 year. From the remaining 470 patients, we excluded 12 patients for the presence of more than moderate aortic regurgitation, 81 patients for the lack of detailed information on medical therapy, and 62 patients for previous mitral commissurotomy or balloon valvuloplasty, and the final study sample consisted of 315 patients (mean age, 61±12 years; 224 women). Mean follow-up period was 6.1±4.0 years. Of all patients, 35 (11.1%) were receiving statin treatment, and 280 (88.9%) were not. Statins employed and mean daily dosages were as follows: simvastatin (18 patients, 16.7±8 mg), atorvastatin (10 patients, 16±5 mg), pravastatin (4 patients, 30±12 mg), and rosuvastatin (3 patients, 10±0 mg). There were no significant differences in age, gender distribution, and follow-up period between the 2 subgroups of patients. Patients in the statin group, as expected, had more frequently hypercholesterolemia (89% versus 14%; P<0.001), hypertension (49% versus 28%; P=0.018), and previous evidence of CAD (71% versus 41%; P=0.001) (Table 1). Baseline echocardiographic characteristics of the entire study sample and of the 2 groups are shown in Table 2. MVA assessment at baseline and at follow-up was available by the pressure

### Table 1. Baseline Demographic and Clinical Characteristics of Patients in the Entire Study Sample and in the 2 Subgroups of Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n=315)</th>
<th>Statin Group (n=35)</th>
<th>Nonstatin Group (n=280)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61±12</td>
<td>60±9</td>
<td>61±13</td>
<td>0.66</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>224 (71)</td>
<td>23 (66)</td>
<td>201 (72)</td>
<td>0.64</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>119 (38)</td>
<td>9 (28)</td>
<td>110 (39)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>70 (22)</td>
<td>31 (89)</td>
<td>39 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>94 (30)</td>
<td>17 (49)</td>
<td>77 (28)</td>
<td>0.018</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>48 (15)</td>
<td>5 (14)</td>
<td>43 (15)</td>
<td>0.93</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>139 (44)</td>
<td>25 (71)</td>
<td>114 (41)</td>
<td>0.001</td>
</tr>
<tr>
<td>Follow-up, y</td>
<td>6.1±4.0</td>
<td>7.1±4.2</td>
<td>5.9±4</td>
<td>0.097</td>
</tr>
</tbody>
</table>

*P value for comparisons between statin group and nonstatin group.
half-time method in all patients and by planimetry in 101 patients. In those 101 patients, the correlation between the 2 methods was very high ($r=0.90$, $P<0.001$), and the Bland-Altman analysis confirmed a good correlation between these 2 methods of MVA estimation in our study sample. Therefore, for all analyses in the study, we used MVA assessment by the pressure half-time method.

MVA and mean transmitral gradient values at baseline were similar in patients in the statin and nonstatin groups; the initial severity of mitral regurgitation was also similar in the 2 subgroups (Table 2).

The mean rate of MS progression in the entire study sample was 0.062±0.079 cm²/y. At subgroup analysis (Table 3), the rate of MS progression, expressed as the rate of decrease in MVA, was significantly lower in statin-treated patients (0.027±0.056 versus 0.067±0.082 cm²; $P=0.005$). An annual change in MVA $>0.08$ cm²/y, referred to as fast MS progression, was found in 3 patients (8.6%) treated with statins and in 83 untreated patients (29.6%) ($P=0.008$) (Figure). Similarly, the annualized change in mean transmitral gradient was lower in statin-treated patients (0.20±0.59 versus 0.58±0.96 mm Hg/y; $P=0.023$).

During follow-up, worsening of mitral regurgitation severity was more important in the nonstatin group ($P=0.038$) (Table 3), and, when a ≥1 degree worsening of mitral regurgitation was considered, significantly fewer patients treated with a statin reached this end point ($P=0.008$). Only 17% of patients in the statin group presented an increase in systolic pulmonary artery pressure of $>10$ mm Hg during follow-up versus 40% in the nonstatin group ($P=0.045$). The annualized change of LA diameter was not different in the 2 groups (Table 3).

During follow-up, no patient in the study sample was identified as experiencing recurrences of rheumatic fever and/or diagnosed streptococcal infection, as assessed by a review of all of their medical records.

On single-variable analysis, statin treatment, presence of CAD, baseline MVA, baseline mean transmitral gradient, and baseline LA dimension were significantly correlated with MS progression rate. On multivariable regression analysis (including the parameters significantly correlated to MS progression rate on single-variable analysis), baseline MVA,
Table 4. Single-Variable and Multivariable Analysis of Predictors of MS Progression Rate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Single-Variable Analysis</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pearson Coefficient</td>
<td>P</td>
</tr>
<tr>
<td>Age</td>
<td>-0.002</td>
<td>0.97</td>
</tr>
<tr>
<td>Gender</td>
<td>0.05</td>
<td>0.38</td>
</tr>
<tr>
<td>Baseline MVA</td>
<td>-0.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline mean mitral gradient</td>
<td>0.18</td>
<td>0.001</td>
</tr>
<tr>
<td>Baseline mitral regurgitation degree</td>
<td>-0.06</td>
<td>0.29</td>
</tr>
<tr>
<td>LA dimension</td>
<td>-0.15</td>
<td>0.007</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0.06</td>
<td>0.29</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.07</td>
<td>0.22</td>
</tr>
<tr>
<td>CAD</td>
<td>0.15</td>
<td>0.009</td>
</tr>
<tr>
<td>Statin treatment</td>
<td>0.16</td>
<td>0.005</td>
</tr>
</tbody>
</table>

baseline LA dimension, and statin treatment emerged as independent predictors of MS progression rate (Table 4).

Discussion

This is, to our knowledge, the first study that seeks to assess the potential role of statin treatment in slowing the progression of rheumatic MS. Although the global prevalence of RHD seems to be decreasing, this condition remains an important cause of morbidity and mortality in some areas of the world. To 1% of schoolchildren in Africa, Asia, the Eastern Mediterranean region, and Latin America show signs of RHD, and it is possible that this prevalence could be even higher because the estimates are not necessarily established with the use of echocardiographic studies. Currently, the treatment of chronic RHD is directed mainly at secondary prevention of acute rheumatic cardiacitis and symptomatic medical treatment, percutaneous balloon valvuloplasty, or surgical valvotomy/MV replacement when significant valve disease develops. There is no specific treatment aimed at preventing the progression of valvular damage.

The most frequent rheumatic valve involvement is the MV; an echocardiographic screening performed in children from geographic areas with high prevalence of RHD showed an extremely high prevalence of MV involvement (87.3% in Cambodia and 98.4% in Mozambique). On the other hand, rheumatic etiology is still the most frequent cause of MS worldwide. The pathogenic mechanisms leading to rheumatic valve disease consist initially of antigenic mimicity of the M protein antigen found in both heart structures and group A hemolytic Streptococcus, which results in an autoimmune reaction of the heart in response to streptococcal infection. The rheumatic process leads to inflammation in all layers of the heart. However, the disease primarily affects the endocardium, leading to inflammation, valvulitis, and scarring of the cardiac valves. After a rheumatic attack, the alterations of the valve progress slowly, driven by hemodynamic stress on the injured valve and by repeated acute episodes of rheumatic fever. MS develops and progresses in time from leaflet thickening, commissural fusion, and chordal shortening and fusion to ultimately form calcification of the valve and subvalvular apparatus. The factors that determine the rate of MS progression could be related to a continuing rheumatic process with either repetitive rheumatic insults or an ongoing inflammatory process but also to trauma caused by the continuing turbulence of the blood flow through a deformed valve orifice, analogous to the mechanism suggested for calcific aortic stenosis. The progression of rheumatic MS over long periods of time is generally slow but extremely variable. The rate of rheumatic MS progression in different studies assessing the natural history of rheumatic MS was 0.09±0.13 cm²/y, 0.09±0.21 cm²/y, or 0.06±0.04 cm²/y. In our study, we found a rate of rheumatic MS progression of 0.062±0.079 cm²/y in the entire study sample and a significantly slower progression rate (0.027±0.056 cm²/y) in patients treated with statins compared with those untreated. The individual or cutoff parameters that may predict the rate of decline in MVA in the individual patient are controversial. One study describes a higher initial MV score and transmural gradient as predictors of more rapid progression, but another study showed that no single value for initial MVA, echocardiographic score, gradient, or combination of such values could separate the groups with and without progression or allow confident prediction of changes in valve area in any individual patient. In addition, we found a significant difference between the 2 groups regarding the proportions of patients with fast MS progression, with fewer patients experiencing a fast MS progression pattern in the statin group.

Valve calcification is an important determinant of disease progression and patients’ outcome, orienting the therapeutic approach (eg, the feasibility of percutaneous balloon dilatation). Recent studies have tried to elucidate the cellular mechanisms responsible for calcification in the cardiac valves, with either nonrheumatic or rheumatic etiology. It has been suggested that the mechanism for valvular calcification is similar to skeletal bone formation and that calcification occurs in areas of neoangiogenesis, which is stimulated by an active inflammatory process. The cellular differences between the rheumatic and degenerative lesions are the intense inflammatory infiltrate and the demonstration of vascular endothelial growth factor in areas of neoangiogenesis found in the rheumatic valves compared with the degenerative valves. There is an increasing body of evidence that inflammation is an ongoing process in patients with chronic rheumatic valve disease. Elevated CRP levels, circulating adhesion molecules, and different proinflammatory cytokines as well as oxidative stress have been demonstrated in these patients. Moreover, there is some evidence that increased levels of CRP could be associated with rheumatic MS progression.

In view of all of this evidence, the idea of a therapy that could target some of the mechanisms of the calcification process and the ongoing inflammation has emerged. Therefore, a number of experimental studies as well as retrospective and prospective clinical trials have tested the role of statins in influencing the valvular calcification process in calcific aortic stenosis. Some of the experimental studies have shown a reduction in the atherosclerotic bone-forming
lesions, whereas the clinical studies have had conflicting results, influenced by the characteristics of populations studied and by the stage of valvular disease at which the therapeutic intervention was applied. In the first prospective randomized study (Scottish Aortic Stenosis and Lipid Lowering Trial [SALTIRE]) testing the effects of statins in aortic valve disease, the intensive lipid-lowering therapy did not halt the progression of calcific aortic stenosis or induce its regression; a potential reason is the fact that patients received the therapy late in the course of the disease process. Experimental data show that the earlier in the disease process that the statin therapy is initiated, the greater is the potential for slowing the progression of this disease. The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial initiated therapy earlier in the disease process, but the progression of aortic stenosis was not influenced. In the Rosuvastatin Affecting Aortic Valve Endothelium (RAAVE) study, prospective treatment of moderate aortic stenosis with rosuvastatin targeting serum low-density lipoprotein slowed progression of echocardiographic measures of aortic stenosis severity and improved inflammatory biomarkers, providing the first clinical evidence for targeted therapy in asymptomatic patients with moderate to severe aortic stenosis.

The only study that tested the role of statins in rheumatic valve disease showed that statin treatment could reduce the progression of rheumatic aortic stenosis. In the present study, we analyzed the effects of statin treatment in slowing the progression of rheumatic MS, targeting these pathophysiological mechanisms involved in the development of rheumatic valve involvement. We found a significantly slower progression of rheumatic MS in patients treated with statins compared with untreated patients. In addition, there was also a significant effect in preventing the worsening of mitral regurgitation, indicating a positive effect of statin treatment on slowing the progression of rheumatic MV disease. The hemodynamic consequences of MS on pulmonary circulation are well known, and some studies have described the progression of right heart disease associated with MS: progression of pulmonary hypertension and tricuspid regurgitation, gradual increase in right heart size, and slight decrease in right ventricular function over time. In our study, the slower progression of MV disease in the statin group was associated with a slower progression of pulmonary hypertension.

These results confirm the potentially beneficial effects of statin treatment in slowing the progression of rheumatic valve disease. This positive effect could be related to both their lipid- and nonlipid-lowering effects, including anti-inflammatory properties, especially through CRP lowering, improvement in endothelial function, and reduction of oxidative processes. In addition, impacts on the lipid effects of activation of the low-density lipoprotein receptor-related protein 5–mediated bone formation and cellular proliferation may play a role. Most of the additional nonlipid effects, referred to as pleiotropic effects, are a direct result of the downstream effect of inhibiting 3-hydroxy-3-methylglutaryl coenzyme A, the rate-limiting enzyme in the synthesis of cholesterol. Future prospective clinical trials are necessary to understand the role of statins in the treatment of RHD.

Study Limitations
The main limitation of our study is the fact that it is a retrospective, observational, nonrandomized study with its inherent limitations. Patients were not randomly assigned to the statin or nonstatin group; this classification was done on the basis of the treatment patients were receiving according to their medical records. One reason for the patients in the statin group to receive statin treatment is the greater prevalence of hypercholesterolemia, hypertension, and CAD, which made the 2 groups somewhat dissimilar. This stems from the retrospective nature of this study. For the lack of complete MVA measurements (also a consequence of the retrospective nature of the study), we analyzed only MVA and mean transmitral gradient to assess MS progression. The severity of mitral regurgitation was not always assessed with all of the established criteria during the long period of >20 years, but for each moment of time a semiquantitative assessment validated in our laboratory was used. LA size was assessed only with the use of the anteroposterior diameter from the parasternal long-axis view because at the time of the first echocardiographic studies, little was known about the value of measuring its area or volume.

Even if a patient was considered to be statin-treated provided that the information about statin treatment was present in serial medical records during the entire follow-up period, we cannot ascertain perfect compliance with the statin treatment.

Lacking information about the number of rheumatic fever attacks/rheumatic carditis events, the time interval between the acute rheumatic fever diagnosis and the first echocardiographic examination and the previous antibiotic prophylaxis treatment and duration is another limitation of this retrospective study. Although data about recurrences of rheumatic fever and prophylaxis are important factors in analyzing the progression of rheumatic MV disease, their significance in our study sample may be less important because this is a cohort of relatively old patients (mean age, 61 ± 12 years) living in a nonendemic area for rheumatic fever. Future studies addressing the effect of medical therapy such as statins in slowing the progression of rheumatic valve disease should assess this effect in addition to that of antibiotic prophylaxis.

Another limitation is the lack of low-density lipoprotein and CRP levels (these data were not available at a time when such parameters were not assessed routinely). However, this only limits further pathophysiological insights into the possible mechanisms of statin benefit in patients with MS but does not influence the main study finding.

Conclusions
The effect of statin treatment in slowing the progression of rheumatic MV disease is assessed for the first time in the present study. The results show a significantly slower progression of rheumatic MV disease in patients treated with statins. If confirmed by prospective randomized studies, these findings could have an important impact on the early medical therapy of patients with RHD.
Disclosures

Dr Rajamanman is an inventor on a patent owned by the Mayo Clinic entitled “Method for Slowing Heart Valve Degeneration.” Dr Rajamanman does not receive any royalties from this patent. The other authors have no potential conflicts of interest to disclose.

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**CLINICAL PERSPECTIVE**

This is the first study to assess the role of statin treatment in slowing the progression of rheumatic mitral stenosis (MS). Three hundred fifteen patients with rheumatic MS, either statin treated (35 patients, 11.1%) or untreated (280 patients, 88.9%), were followed for 6.1±4.0 years in this retrospective study. We found a significantly slower progression of MS, as assessed by decrease in mitral valve area, in patients treated with statins compared with untreated patients (0.027±0.056 versus 0.067±0.082 cm²/y; P=0.005). The increase in mean transmitral gradient was also lower in statin-treated patients (0.20±0.59 versus 0.58±0.96 mm Hg/y; P=0.023). The prevalence of fast MS progression (annual change in mitral valve area >0.08 cm²) was significantly lower in the statin group (P=0.008). In addition, there was a significant effect of statin treatment in reducing progression of mitral regurgitation during follow-up (P=0.038). These results indicate a possible benefit of statin treatment in slowing the progression of rheumatic mitral valve disease. Although the global prevalence of rheumatic valve disease seems to be decreasing, this condition remains an important cause of morbidity and mortality in many areas of the world. A medical treatment effective in slowing the progression of rheumatic mitral valve disease would have a critical role in delaying mitral valve interventions (eg, percutaneous or surgical). This could be particularly important in areas where access to such interventions is inadequate. If confirmed by prospective randomized controlled trials, these results may have important therapeutic, social, and economic implications.
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