Effect of Hydroxymethylglutaryl Coenzyme A Reductase Inhibitors on the Progression of Calcific Aortic Stenosis

Gian M. Novaro, MD; Irving Y. Tiong, MD; Gregory L. Pearce, MS; Michael S. Lauer, MD; Dennis L. Sprecher, MD; Brian P. Griffin, MD

Background—Recent studies have supported the hypothesis that calcific aortic stenosis is the product of an active inflammatory process, with similarities to atherosclerosis. We sought to determine whether therapy with hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) might slow the progression of aortic stenosis.

Methods and Results—A retrospective study of 174 patients (mean age 68 ± 12 years) with mild to moderate calcific aortic stenosis was conducted. Patients required normal left ventricular function, ≥2+ aortic regurgitation, and ≥2 echocardiograms performed at least 12 months apart. Fifty-seven patients (33%) received treatment with a statin; the remaining 117 (67%) did not. The statin group was older and had a higher prevalence of hypertension, diabetes mellitus, and coronary disease. During a mean follow-up of 21 months, patients treated with statin had a smaller increase in peak and mean gradient and a smaller decrease in aortic valve area. When annualized, the decrease in aortic valve area for the nonstatin group was 0.11 ± 0.18 cm² compared with 0.06 ± 0.16 cm² for those treated with a statin (P = 0.03). In multivariate analysis, statin usage was a significant independent predictor of a smaller decrease in valve area (P = 0.01) and a lesser increase in peak gradient (P = 0.02).

Conclusions—Statin-treated patients, despite a higher risk profile for progression, had reduced aortic stenosis progression compared with those not treated with a statin. These data provide justification for a prospective randomized trial to substantiate whether statin therapy slows the progression of aortic stenosis. (Circulation. 2001;104:2205-2209.)

Key Words: stenosis ■ cholesterol ■ statins

Despite the excellent outcomes of aortic valve replacement,1-3 calcific aortic stenosis remains a significant cause of morbidity and mortality. Although once thought to be a degenerative age-related condition, there is increasing evidence that calcific aortic stenosis is the product of an active inflammatory process. The aortic valve lesion simulates atheroma, and its progression is related to known atherosclerotic risk factors, such as hyperlipidemia.4 The role of lipids and inflammation in the development of this valvular lesion is illustrated histologically by the presence of lipoproteins, foam-cell macrophages, and T lymphocytes in the early lesion of aortic stenosis.5,6 To date, no medical therapy has been proven to alter the natural history of patients with aortic stenosis. Therapy with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) has been shown to slow the progression of coronary atherosclerotic disease.7,8 Given the similarities between the lesions of aortic stenosis and coronary disease, we hypothesized that these agents might also reduce the progression of aortic stenosis. A medical therapy that could effectively slow the progression of aortic stenosis is of considerable potential importance and might delay or obviate the need for valve replacement in this patient population. To address this hypothesis, we studied patients with mild to moderate calcific nonrheumatic aortic stenosis and assessed the effect of HMG-CoA reductase inhibitors on the progression of this obstructive valvular lesion. We confined our study to patients who did not have severe aortic stenosis, because we postulated that more severe degrees of calcific stenosis might be less amenable to the effects of these lipid-lowering agents.

Study Patients
All patients who were studied in our echocardiographic laboratory between January 1, 1996, and December 31, 1999, and who were found to have an aortic valve area of 1.0 to 1.8 cm² were screened for inclusion in the study. Patients were required to have at least two transthoracic echocardiograms 12 or more months apart and were excluded if they had an ejection fraction <50% or >2+ aortic regurgitation. Patients with echocardiographic evidence of rheumatic mitral valve disease (ie, leaflet doming with or without mitral stenosis or commissural fusion) were also excluded. Demographic, clinical, and laboratory data were obtained by review of the patients’
medical records. Specifically, use of an HMG-CoA reductase inhibitor was identified from the patient charts. Initiation of a lipid-lowering agent was done at the discretion of the patient’s primary physician.

An initial 3391 patients with mild to moderate aortic stenosis were screened for inclusion in the study. Of this group, although not exclusively, 1366 had only a single transthoracic echocardiogram, 1262 had an ejection fraction of <50% or ≥2+ aortic regurgitation, and 686 had two studies within 12 months of one another. After exclusion of these patient subgroups, 174 patients were identified who met study criteria. Mean age (±SD) was 68±12 years, with 77 males and 97 females. Median aortic valve area (with interquartile ranges) was 1.2 cm² (1.0 to 1.4 cm²), with a median peak gradient of 29 mm Hg (21 to 38) and mean gradient of 15 mm Hg (12 to 22).

Clinical and Laboratory Data

Clinical data recorded from the patients’ charts included the following: prior evidence of coronary artery disease (history of myocardial infarction, angioplasty, coronary artery bypass grafting, or coronary artery disease by angiography [epicardial coronary stenosis ≥50%]); history of hypertension; present smoking; history of diabetes mellitus; and endstage renal disease requiring dialysis. Lipid profiles recorded were those within 6 months of the baseline and follow-up echocardiograms. All lipid profiles were collected in the fasting state and included total cholesterol, LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), and triglyceride levels. Additional laboratory data included serum creatinine levels.

Transthoracic Echocardiography

All echocardiographic data were obtained by an experienced sonographer, interpreted by an experienced staff echocardiographer, and entered into the institutional database. Study interpretations by staff echocardiographers were conducted without knowledge of the present study. Comprehensive examinations were performed on all study patients, including M-mode, two-dimensional, conventional Doppler, and color Doppler echocardiography. Aortic valve area was calculated by the continuity equation and defined as mild if the valve area was 1.5 to 1.8 cm² and moderate if it was 1.0 to 1.4 cm². By conventional and color Doppler, aortic regurgitation was graded semiquantitatively, and patients with >2+ regurgitation were excluded to avoid a confounding increase in forward-flow hemodynamics. The annualized average change in peak and mean gradient for the two groups was calculated by dividing the difference between gradients measured at the first and last study by the time between echocardiograms. A similar calculation was conducted for annualized change in aortic valve area.

Statistical Analysis

Progression of aortic stenosis was measured with changes in peak gradient, mean gradient, and aortic valve area. Rates were calculated in absolute terms and on an annualized basis (by dividing the gradient, mean gradient, and aortic valve area. Rates were calculated in absolute terms and on an annualized basis (by dividing the

### TABLE 1. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>No Statin (n=117)</th>
<th>Statin (n=57)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (±SD)</td>
<td>67±13</td>
<td>71±9</td>
<td>0.01</td>
</tr>
<tr>
<td>Female, %</td>
<td>55</td>
<td>58</td>
<td>0.69</td>
</tr>
<tr>
<td>CAD, %</td>
<td>44</td>
<td>89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HTN, %</td>
<td>63</td>
<td>81</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>20</td>
<td>35</td>
<td>0.03</td>
</tr>
<tr>
<td>Present smoker, %</td>
<td>15</td>
<td>16</td>
<td>0.83</td>
</tr>
<tr>
<td>ESRD on CD, %</td>
<td>6</td>
<td>0</td>
<td>0.10</td>
</tr>
<tr>
<td>Bicuspid valve, %</td>
<td>18</td>
<td>12</td>
<td>0.34</td>
</tr>
<tr>
<td>Creatinine, mg/dL*</td>
<td>0.97±0.26</td>
<td>0.99±0.32</td>
<td>0.71</td>
</tr>
<tr>
<td>TC, mg/dL†</td>
<td>208 (186–227)</td>
<td>210 (193–241)</td>
<td>0.41</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>131 (112–143)</td>
<td>128 (94–146)</td>
<td>0.49</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>46 (35–55)</td>
<td>46 (37–55)</td>
<td>0.71</td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>130 (93–188)</td>
<td>165 (110–264)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Values are shown as mean±SD when variables are normally distributed and as medians (interquartile range) when non-Gaussian. CAD indicates coronary artery disease; ESRD on CD, endstage renal disease on chronic dialysis; HTN, hypertension; TC, total cholesterol; and TG, triglycerides.

*Values are available for 95 no-statin patients and 55 statin patients.
†Values are available for 75 no-statin patients and 48 statin patients.

The remaining 117 (67%) did not. Baseline characteristics of the two groups are shown in Table 1. The mean time interval between echocardiograms was 21±7 months for both groups (range, 12 to 40 months). Patients taking a statin, on average, were older and had a higher prevalence of hypertension, diabetes mellitus, and coronary artery disease. Baseline levels of LDL-C were similar between the groups, as were levels of total cholesterol, HDL-C, and serum creatinine. Triglyceride levels, however, were higher in the statin group. The percentage of patients with congenitally bicuspid aortic valves, as well as those with endstage renal disease requiring dialysis, a known risk factor for disease progression, was low and similar in both groups.

The baseline echocardiographic parameters were similar for the two groups. The nonstatin- and statin-treated groups had the same degree of aortic stenosis at the time of first study, with a median aortic valve area of 1.2 cm² (1.0 to 1.4 cm²; P=0.71). Mean gradient for both groups was also similar (15 mm Hg [12 to 22 mm Hg]; P=0.47), as was peak gradient (29 mm Hg [21 to 38 mm Hg] versus 28 mm Hg [22 to 37 mm Hg], respectively; P=0.80). Both cohorts had the same left ventricular systolic function with ejection fractions of 0.57±0.4 (P=0.63).

Five different statins were used during the study period in the treatment group. The various agents used, number of patients, and mean daily dose were as follows: simvastatin, 21 patients; pravastatin, 20±12 mg; lovastatin, 18 patients, 25±12 mg; atorvastatin, 8 patients, 23±10 mg; and fluvastatin, 2 patients, 25±21 mg.

Overall and Annualized Progression of Aortic Stenosis

Table 2 shows the baseline and follow-up echocardiographic parameters of both groups. During the mean follow-up
TABLE 2. Changes in Echocardiographic Characteristics Over Study Period (Mean, 21 Months)

<table>
<thead>
<tr>
<th></th>
<th>No Statin (n=117)</th>
<th>Statin (n=57)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>0.57±0.04</td>
<td>0.57±0.04</td>
<td>0.63</td>
</tr>
<tr>
<td>End</td>
<td>0.57±0.05</td>
<td>0.57±0.04</td>
<td>0.34</td>
</tr>
<tr>
<td>Peak gradient*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>29 (21–38)</td>
<td>28 (22–37)</td>
<td>0.80</td>
</tr>
<tr>
<td>End</td>
<td>37 (27–52)</td>
<td>32 (23–48)</td>
<td>0.03,0.02†</td>
</tr>
<tr>
<td>Mean gradient*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>15 (12–22)</td>
<td>15 (12–22)</td>
<td>0.47</td>
</tr>
<tr>
<td>End</td>
<td>21 (14–29)</td>
<td>18 (13–28)</td>
<td>0.19,0.10†</td>
</tr>
<tr>
<td>AVA, cm²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>1.2 (1.0–1.4)</td>
<td>1.2 (1.0–1.4)</td>
<td>0.71</td>
</tr>
<tr>
<td>End</td>
<td>1.0 (0.8–1.2)</td>
<td>1.1 (0.9–1.2)</td>
<td>0.03,0.01†</td>
</tr>
</tbody>
</table>

Values are mean±SD when variables are normally distributed and medians (interquartile range) when non-Gaussian. AVA indicates aortic valve area; EF, ejection fraction.

*Gradients shown in mm Hg.
†P values for univariate and multivariable analyses.

interval of 21 months, univariate analysis showed that patients treated with a statin had a smaller increase in peak and mean gradient, although the difference in mean gradient did not achieve statistical significance (Figure 1). The average decrease in aortic valve area over the follow-up period for the nonstatin group was 0.19±0.25 cm², whereas the statin-treated patients had an average decrease in valve area of 0.12±0.22 cm² (P=0.03). The annualized decrease in aortic valve area for the nonstatin group was 0.11±0.18 cm², a rate similar to that of previous studies.12,16,17 The annualized decrease in area for the statin-treated patients was 0.06±0.16 cm², representing 45% less progression in valve area stenosis per year.

Predictors of Progression

In univariate analysis, other than not being on a statin, only advancing age was associated with stenosis progression, specifically with mean gradient (r=0.17, P=0.02). No significant association was found between gender, hypertension, diabetes mellitus, or tobacco use and progression of stenosis.

The multivariate association between statin use and aortic stenosis progression was reflected as the annualized change in peak and mean gradient and aortic valve area (to control for possible differences attributable to follow-up duration). Parameter estimates (β) and probability value associated with statin use were derived from multivariate linear regression models. Other variables entered into the model included age, hypertension, diabetes mellitus, coronary artery disease, and baseline severity of stenosis. After adjusting for these covariables, statin use was still found to be a significant and independent predictor of a smaller increase in peak gradient (β=−2.99 mm Hg; P=0.02) and a lesser reduction in aortic valve area (β=−0.07 cm²; P=0.01). Because of the link between end-stage renal disease and the potential rapid progression of aortic stenosis, we reanalyzed the groups after exclusion of these patients (7 patients in the nonstatin group). After their exclusion, the association between statin use and a lesser reduction in aortic valve area (P=0.03), as well as a smaller increase in peak gradient (P=0.03), was still present in multivariate analysis.

Age, coronary artery disease status, and baseline triglyceride levels were identified as significant predictors (P<0.05) of statin use through logistic regression modeling. These parameters were used to calculate propensity scores for statin use. This derived parameter, included as a covariate in the multivariable models, did not significantly contribute to the explanation of variation in the change in peak gradient (P=0.67), mean gradient (P=0.19), or aortic valve area (P=0.71). Moreover, the inclusion of the propensity score did not affect conclusions regarding the effect of statin use on peak gradient (P=0.03), mean gradient (P=0.19), or aortic valve area (P=0.01).

Relation Between LDL-C and Stenosis Progression

Statin-treated patients had a significant reduction in LDL-C (P<0.001), a nonsignificant reduction in triglycerides (P=0.36), and a significant increase in HDL-C (P=0.03), changes that were not seen in the nonstatin group (Figure 2). In the statin group, we looked at the association between change in LDL-C and stenosis progression. There was evidence of a modest relationship between percent LDL-C change and changes in peak (r=0.29, P=0.02) and mean (r=0.23, P=0.06) gradient, whereas the association with change in aortic valve area was not significant (r=0.07, P=0.63). When analyzing the annualized change in aortic valve area between patients whose end of study LDL-C was >100 mg/dL versus <100 mg/dL, patients with LDL-C <100 mg/dL had less reduction in aortic valve area, albeit nonsignificant, compared with those with levels >100 mg/dL (0.065 versus 0.080 cm²/yr; P=0.72). Additionally, within the statin group, progression of aortic valve area stenosis showed a nonsignificant inverse relationship to both statin dose (r=−0.10, P=0.57) and duration (r=−0.05, P=0.75).

Discussion

Calcific aortic stenosis remains a problematic condition in the developed world. Once the condition is established, no
known medical therapy exists that reduces the progression of stenosis and helps delay the need for aortic valve replacement. This study is consistent with a hypothesis that the use of an HMG-CoA reductase inhibitor may be associated with a significant reduction in the progression of calcific aortic stenosis as assessed by both valve area and pressure gradient.

Previous studies have indicated that the average rate of progression of calcific aortic stenosis is a reduction in valve area of ≈0.1 cm² per year.12,16–18 The nonstatin group in our study (ie, those not treated with an HMG-CoA reductase inhibitor) showed an annual reduction in valve area of 0.11 cm², a rate similar to that of previous studies. This suggests that this group is representative of the average patient with calcific aortic stenosis. The statin-treated group, however, had a significant 45% reduction in the rate of stenosis progression with an annual stenosis rate of 0.06 cm². This reduction remained significant even after adjusting for differences in baseline characteristics.

There has been increasing awareness surrounding the association between modifiable risk factors, such as hyperlipidemia and tobacco use, and aortic stenosis over the last decade. Several studies have found total cholesterol as well as elevated LDL-C and lipoprotein (a) levels to be independent predictors of calcific aortic stenosis.19–22 Consistent with these observations, we recently analyzed 2356 patients undergoing aortic valve replacement and found that patients in whom aortic stenosis was the predominant lesion had significantly more abnormal lipid profiles than those with aortic regurgitation.23 These studies coupled with the histologic characterization of the degenerative aortic valve lesion by Otto et al24 have paved the way for investigation into the effect of risk factor modification on disease progression.

In addition to its development, previous studies have identified risk factors associated with stenosis progression.5,18 Specifically, age, hypercholesterolemia, elevated serum creatinine, tobacco use, and milder degrees of aortic stenosis have all been linked to more rapid progression. Our study, however, identified only advancing age and lack of statin use as predictors of progression. Peter et al18 also confirmed the correlation between rapid progression and age. Although this finding has not been supported by all studies on the hemodynamic progression of aortic stenosis, the significantly older age of statin-treated patients in our study can only bolster the detected effects of these agents. Notably, baseline factors such as presence of mild aortic stenosis, tobacco use, LDL-C level, and serum creatinine were similar in both groups.

A modest relationship existed in our study between change in LDL-C and change in valve gradients. Additionally, final LDL-C <100 mg/dL was associated with a slower progression than a final LDL-C of >100 mg/dL. These findings support the hypothesis that oxidized LDL-C plays a role in the pathogenesis and progression of calcific aortic stenosis. However, alternative effects of statin therapy may also be important in modulating the progression of aortic stenosis. These agents are known to reduce monocyte adhesiveness24 and plaque calcification,25 important histologic characteristics of calcific aortic valve disease. Furthermore, a chronic inflammatory infiltrate has been demonstrated on diseased aortic valve leaflets. Chlamydia pneumoniae has been detected with a high prevalence in degenerative aortic valves but with significantly less frequency in normal valves.26 It is possible, therefore, that the anti-inflammatory effects of statins, independent of their well-known lipid-lowering effects, may play a role in modifying the active subendothelial process that occurs on diseased aortic valves.

Based on these mechanisms, one might expect statins to be effective in modifying the histologic architecture of the leaflets mainly during the early stages of the disease and before the late-stage morphological features predominate, namely gross nodular calcification. According to previous studies, higher aortic-jet velocities12,27 and greater degrees of valvular calcification28 have been associated with subsequent cardiac events in patients with asymptomatic aortic stenosis. The possibility of altering these valvular characteristics and purported predictors of adverse outcome presents an attractive benefit from statins, even in the absence of surgery.

Study Limitations
This was a nonrandomized, retrospective, observational study. As such, it should be considered only hypothesis-generating and thus requires external confirmation, ultimately with a randomized trial. Although our two patient cohorts were similar at baseline, it was not possible to adjust for all potential confounders, known or unknown, that could have affected the detected benefits of therapy. Exclusion of patients with greater than moderate aortic regurgitation, depressed ventricular function, severe aortic stenosis, or <2 echocardiograms fails to generalize the findings to patients with such characteristics. Because of the observational analysis, all of these factors are sources of potential selection bias. Although propensity analysis failed to detect a significant bias in favor of the statin group in terms of predicting less progression in gradient or valve area, we cannot be sure that important unmeasured variables may have differed in the two groups and therefore may have explained our findings rather than the use of statins per se.

It should be noted that statin-treated patients were taking relatively low doses of medication. It is possible that the
effects of statin treatment are underestimated because of the submaximal doses and variable duration of treatment. Additionally, given the inclusion criteria used and duration of follow-up, knowing whether therapy with a statin can actually delay the need for valve replacement cannot be determined.

Conclusions

Our study provides initial observational evidence to suggest that treatment with HMG-CoA reductase inhibitors is associated with significantly less progression of aortic stenosis. The prevalence of aortic stenosis combined with the increasing age of the general population underscores the importance of a possible alternative therapy in the management of this condition. A large randomized controlled trial of HMG-CoA reductase inhibitors in patients with calcific aortic valve disease seems warranted to help demonstrate the potential benefits of these agents in a disease whose mainstay of therapy remains surgical.

Acknowledgments

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References

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