Effect of Lipid Lowering With Rosuvastatin on Progression of Aortic Stenosis

Results of the Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTRONOMER) Trial

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Background—Aortic stenosis (AS) is an active process with similarities to atherosclerosis. The objective of this study was to assess the effect of cholesterol lowering with rosuvastatin on the progression of AS.

Methods and Results—This was a randomized, double-blind, placebo-controlled trial in asymptomatic patients with mild to moderate AS and no clinical indications for cholesterol lowering. The patients were randomized to receive either placebo or rosuvastatin 40 mg daily. A total of 269 patients were randomized: 134 patients to rosuvastatin 40 mg daily and 135 patients to placebo. Annual echocardiograms were performed to assess AS progression, which was the primary outcome; the median follow-up was 3.5 years. The peak AS gradient increased in patients receiving rosuvastatin from a baseline of 40.8±11.1 to 57.8±22.7 mm Hg at the end of follow-up and in patients with placebo from 41.6±10.9 mm Hg at baseline to 54.8±19.8 mm Hg at the end of follow-up. The annualized increase in the peak AS gradient was 6.3±6.9 mm Hg in the rosuvastatin group and 6.1±8.2 mm Hg in the placebo group (P=0.83). Treatment with rosuvastatin was not associated with a reduction in AS progression in any of the predefined subgroups.

Conclusion—Cholesterol lowering with rosuvastatin 40 mg did not reduce the progression of AS in patients with mild to moderate AS; thus, statins should not be used for the sole purpose of reducing the progression of AS.

Clinical Trial Registration Information—URL: http://www.controlled-trials.com/. Clinical trial registration number: ISRCTN 32424163. (Circulation. 2010;121:306-314.)

Key Words: cholesterol ■ echocardiography ■ lipids ■ trials ■ valves

Aortic stenosis (AS) is a common cardiac valvular disease, the prevalence of which increases with age. When the severity of AS is mild to moderate, it is well tolerated. When it progresses to severe, it confers significant morbidity and mortality, and valve replacement is generally required. It may be possible to improve the outcome of patients with AS if the progression from mild or moderate AS to severe AS can be prevented.

Clinical Perspective on p 314

AS has long been considered to result from a degenerative process, but recent studies have shown that its development is an active process with many similarities to atherosclerosis. The development of AS involves multiple events, including lipid deposition and oxidation, inflammation, fibrosis, calcification, and bone formation. In animal models, hypercholesterolemia has been shown to potentiate many of these events, which can be prevented by a reduction of hypercholesterolemia with atorvastatin or genetic modification. Epidemiological studies have demonstrated an association between hypercholesterolemia and AS. Furthermore, retrospective studies have shown that statin use was associated with slower progression of AS, although this finding has not been supported by recent trials. It is possible that AS in patients in these trials may be too advanced and the aortic valves too calcified to benefit from lipid-lowering therapy.

The primary objective of the Aortic Stenosis Progression Observation: Measuring the Effects of Rosuvastatin (ASTRONOMER) trial is to assess the effect of intensive lipid lowering with rosuvastatin on the progression of AS in asymptomatic patients with mild to moderate AS. The secondary objective is to assess the impact of intensive lipid lowering with rosuvastatin on adverse outcomes related to
AS, including cardiac death and aortic valve replacement surgery.

Methods

Patient Population

Details of the study design have previously been reported. Eligible patients were identified and recruited from the echocardiographic laboratories and cardiology clinics at the participating sites. We included men and women between 18 and 82 years of age with asymptomatic mild to moderate AS defined by maximum aortic valve velocity between 2.5 and 4.0 m/s. Patients with clinical indications for the use of statin as defined by Canadian guidelines such as coronary artery disease, cerebrovascular disease, peripheral vascular disease, and diabetes were excluded. The baseline lipid values of the patients had to be within the target levels for their respective risk categories according to Canadian guidelines. The study was approved by the Ethics Committee of each participating center, and all patients gave written informed consent.

Study Protocol

The study was a double-blind, randomized, placebo-controlled trial that was initiated by the investigators and received peer-reviewed funding from the Canadian Institute of Health Research. AstraZeneca Canada Inc provided additional support but had no input into the study design and data analysis. Leadership for the study was provided by the Steering Committee, which consisted of the principal investigators at each center. The Data Safety Monitoring Committee evaluated the blinded data on an annual basis, and all outcome and serious adverse events, including aortic valve replacement, death, myocardial infarction, heart failure, and stroke, were assessed by an Event Verification Committee blinded to treatment assignment and based on predefined criteria. The members of the different committees, the investigators, and the participating centers are listed in the Appendix in the online-only Data Supplement.

Randomization schedule was centralized and generated by computer program at AstraZeneca Canada Inc, which has no access to the rest of the data. When a center was ready to randomize a patient, the site coordinator obtained a randomization number from the study database via a secure Internet line. Eligible patients were randomized in a 1:1 fashion in blocks of 4 to receive either rosvastatin 40 mg daily or matching placebo. Patients, site coordinators, investigators, and statisticians were all blinded to treatment assignment. Beginning in March 2005, patients of Asian origin were excluded from the study because of concern about an increased risk of side effects resulting from potentially higher drug levels with the 40 mg daily of rosvastatin. Only 1 patient of Asian origin was enrolled before March 2005. She was free of adverse events and was allowed to remain in the study. Patients were followed up for a minimum of 3 years to a maximum of 5 years. The trial was completed when the last randomized patient had been successfully followed up for 3 years.

After the baseline assessment and randomization, the patients were followed up every 3 months to assess for adverse side effects and to ensure compliance. Lipid profiles were measured every 6 months during the first year and then annually. Immunobiochemical markers, including high-sensitivity C-reactive protein (CRP), were measured at baseline, at 1 year, and at the end of follow-up. Annual echocardiograms were performed to assess the severity of AS. The results of these echocardiograms were made available to the investigators and the patients’ primary physicians; thus, the primary physicians did not have to obtain their own echocardiograms, and decisions about valve surgery if indicated could be made without delay. However, additional echocardiograms could be obtained at any time during the study at the discretion of the primary treating physician.

Rescue Medication

Treating physicians were discouraged from measuring patients’ lipid profiles on their own to maintain blinding. The coordinating principal investigators were informed when the lipid levels during follow-up exceeded the upper limits of normal for the patients’ risk categories and remained so when measured 12 weeks later. When this occurred, the site study physicians were informed, and patients were discontinued from the study medication, without unblinding, and started on open-label rosuvastatin 40 mg daily. If the lipid levels continued to be out of the open-label range after 12 weeks of open-label treatment, the patients would be withdrawn from the study and referred back to the primary care physician for appropriate lipid-lowering therapy. Only 3 patients in the study were put on open-label treatment, and none were withdrawn for this reason.

Echocardiography

A complete Doppler echocardiogram was performed before randomization to provide hemodynamic data of AS severity. Peak and mean gradients were calculated with the modified Bernoulli equation, and the aortic valve area was obtained with the continuity equation. The severity of aortic valve calcification was semiquantified into none, mild, moderate, or severe as described by Rosenhek et al. The echocardiographers at each site received training in the acquisition and interpretation of the echocardiograms before the launch of the study. Randomly selected studies that contributed 10% of the total number of echocardiograms were reviewed to ensure that the studies and measurements were performed in accordance with the protocol.

Statistical Analysis

Data analysis was performed by the Clinical Research Unit at the Children’s Hospital of Eastern Ontario completely independently of the study sponsors, who were informed of the results after the database was locked and the analysis was completed. The primary outcome measures were hemodynamic parameters of AS severity, which were the transluminal AS gradients and aortic valve area measured by Doppler echocardiography. The secondary outcomes were a composite of aortic valve replacement and cardiac death. Depending on the recruitment date, the length of follow-up for a given subject varied from 3 to 5 years. An average follow-up of 4 years was assumed. To detect a 7-mm Hg difference in the change of AS gradient between the 2 treatment groups at the end of follow-up and assuming an SD of 14 mm Hg and a dropout rate of 20%, a total sample size of 270 was estimated to be able to achieve 90% power with a 2-tailed α of 0.05. This sample size would also achieve 85% power to detect a difference of 0.15 cm² in the change of aortic valve area from baseline to the last measurement between the 2 treatment groups with an SD of 0.3 cm² and a 2-tailed α of 0.05.

The intention-to-treat principle was used for all analyses in which the participants were analyzed regardless of withdrawal from treatment during the study. Per-protocol analyses were also performed for the primary outcomes in which the participants were excluded from the analyses if they withdrew from the treatment during the study. Analyses were performed with SAS software (version 9.1; SAS Institute Inc, Cary, NC) and R software (V2.7.2). Two-sided P values of <0.05 were considered statistically significant. Normally distributed continuous variables were summarized through the use of mean and SD. Nonnormally distributed continuous variables were summarized by the use of median and interquartile range. Categorical variables were summarized by the use of frequency and percentage. Two-sample t tests were used to compare the difference in the change in primary outcomes from baseline to the last follow-up measurement. For patients undergoing aortic valve replacement, the measurements on the last echocardiograms before surgery were used in the analysis. To account for different follow-up lengths, annualized changes in primary outcomes were calculated by dividing the total change by length of follow-up. The annualized changes were then compared between the 2 groups through the use of the 2-sample t test. Linear mixed models were also used to further investigate the effect of treatment at each follow-up time point with baseline age, gender, and aortic valve morphology as covariates. To compare changes in cholesterol and CRP levels between the 2 groups, all postbaseline cholesterol and CRP measurements were averaged and then subtracted by baseline measurement, and the changes were compared by the use of the 2-sample t test or Wilcoxon signed-rank test.
rank test, depending on the distribution of the change. In subgroup analyses, an interaction term between treatment and subgroup was included in the linear mixed models to assess whether different subgroups responded to the treatment differently. Similarly, an interaction term between follow-up time point and subgroup was used to assess whether different subgroups had different progression rates of primary outcomes over time. The effect of treatment on the secondary outcomes was assessed with Kaplan–Meier curves and log-rank tests of the time-to-event data. The adverse event rate in the 2 treatment groups was compared through the use of the Fisher exact test.

Results
Between December 2002 and December 2005, 380 patients were assessed for enrollment in 23 Canadian centers; 272 were randomized to receive either placebo or rosuvastatin 40 mg daily, and 3 of these patients who were enrolled erroneously were subsequently excluded (Figure 1). A total of 134 patients were randomized to receive rosuvastatin 40 mg daily and 135 to receive placebo, with a median follow-up of 3.5 years (interquartile range, 2.1 to 4.5 years). The baseline characteristics of the 2 groups were well balanced (Table 1). The peak aortic jet velocity at baseline was 3.18±0.42 m/s, and the peak and mean gradients were 41.2±11.0 and 22.8±7.6 mm Hg, respectively. Congenital bicuspid aortic valve, a common predisposing condition for AS, was present in 49.4% of the patients. In 51 patients (19.0%), the aortic valve morphology could not be determined with certainty. Aortic valve calcification was common at baseline, with moderate or severe calcification in 65.1% of the patients.

Cholesterol and CRP Levels
In the placebo group, the mean serum low-density lipoprotein (LDL) cholesterol was unchanged, whereas in patients receiving rosuvastatin 40 mg daily, the LDL cholesterol concentration decreased by 54.5% from 3.18 mmol/L to the postbaseline average of 1.45 mmol/L (P<0.0001). In the placebo group, the high-density lipoprotein (HDL) cholesterol concentration decreased by 1.9% from 1.55 mmol/L to the postbaseline average of 1.52 mmol/L, whereas in the treat-
ment group, the HDL cholesterol concentration increased by 1.8% from 1.59 mmol/L to the postbaseline average of 1.61 mmol/L ($P = 0.006$) (Figure 2A and 2B). The median CRP was 1.78 mg/L (interquartile range, 0.92, 3.73). The placebo group had a median increase of 0.095 mg/L in CRP concentration during follow-up, whereas the patients receiving rosuvastatin 40 mg daily had a median decrease of 0.33 mg/L in CRP concentration ($P = 0.002$).

**Progression of AS**

Progression of AS measured by the peak gradient (Figure 3A) and aortic valve area (Figure 3B) did not differ between the 2 treatment groups. In the placebo group, the baseline peak AS gradient was 40.8 ± 11.1 mm Hg; the baseline valve area was 1.56 ± 0.70 cm$^2$ at baseline and decreased to 1.51 ± 0.97 cm$^2$ at the end of follow-up with a mean change of $-0.16$ cm$^2$ (95% CI, $-0.31$ to $-0.02$). In the rosuvastatin group, the baseline peak AS gradient was 40.8 ± 11.1 mm Hg.

### Table 1. Baseline Characteristics of Patients in the 2 Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>Rosuvastatin(n = 134)</th>
<th>Placebo(n = 135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline, mean (SD), y</td>
<td>58.0 (12.9)</td>
<td>57.9 (14.3)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>81 (60.5)</td>
<td>85 (63.0)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>131 (97.8)</td>
<td>133 (98.5)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
<td>27.7 (5.05)</td>
<td>28.5 (6.21)</td>
</tr>
<tr>
<td>Blood pressure, mean (SD), mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>128.8 (15.67)</td>
<td>128.4 (15.94)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76.5 (10.04)</td>
<td>75.9 (10.92)</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>15 (11.2)</td>
<td>14 (10.4)</td>
</tr>
<tr>
<td>Former</td>
<td>54 (40.3)</td>
<td>47 (34.8)</td>
</tr>
<tr>
<td>Never</td>
<td>65 (48.5)</td>
<td>74 (54.8)</td>
</tr>
<tr>
<td>Lipids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total, mmol/L</td>
<td>5.33 (0.73)</td>
<td>5.27 (0.83)</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>3.18 (0.63)</td>
<td>3.12 (0.74)</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.59 (0.46)</td>
<td>1.55 (0.40)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.23 (0.52)</td>
<td>1.32 (0.59)</td>
</tr>
<tr>
<td>Apolipoprotein B, g/L</td>
<td>1.02 (0.18)</td>
<td>1.01 (0.20)</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>1.60 (2.17)</td>
<td>1.88 (3.62)</td>
</tr>
<tr>
<td>Echocardiographic measures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak AS velocity, m/s</td>
<td>3.16 (0.42)</td>
<td>3.19 (0.42)</td>
</tr>
<tr>
<td>Transaortic pressure gradient, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak</td>
<td>40.8 (11.1)</td>
<td>41.6 (10.9)</td>
</tr>
<tr>
<td>Mean</td>
<td>22.5 (7.6)</td>
<td>23.1 (7.6)</td>
</tr>
<tr>
<td>Aortic valve area, cm$^2$</td>
<td>1.49 (0.71)</td>
<td>1.56 (0.70)</td>
</tr>
<tr>
<td>Aortic valve morphology, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicuspid valve</td>
<td>72 (53.7)</td>
<td>61 (45.2)</td>
</tr>
<tr>
<td>Tricuspid valve</td>
<td>39 (29.1)</td>
<td>46 (34.1)</td>
</tr>
<tr>
<td>Uncertain</td>
<td>23 (17.2)</td>
<td>28 (20.7)</td>
</tr>
</tbody>
</table>

**Figure 2.** A and B, Serum LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C).

**Figure 3.** A and B, Peak AS gradient and aortic valve area in the 2 treatment groups for the duration of the study.
and increased to 57.8±22.7 mm Hg at the end of the study with a mean change of 18.3 mm Hg (95% CI, 14.0 to 22.6); the mean AS gradient was 22.5 mm Hg at baseline and increased to 32.2 mm Hg at the end of follow-up with a mean change of 10.7 mm Hg (95% CI, 8.4 to 13.0); the aortic valve area was 1.49±0.71 cm² at baseline and decreased to 1.26±0.58 cm² at the end of follow-up with a mean change of −0.19 cm² (95% CI, −0.30 to −0.08). The mean changes in the peak AS gradient, mean gradient, and aortic valve area were not statistically different between the 2 treatment groups (P=0.32, 0.49, and 0.79, respectively). The annual increase in peak AS gradient was 6.1±8.2 mm Hg in the placebo group and 6.3±6.9 mm Hg in the rosuvastatin group (P=0.83). The annual increase in the mean gradient was 3.9±4.9 mm Hg in the placebo group and 3.8±4.4 mm Hg in the rosuvastatin group (P=0.79). The annual decrease in aortic valve area was 0.08±0.21 cm² in patients receiving placebo and 0.07±0.15 cm² in patients receiving rosuvastatin (P=0.87). The linear mixed models did not show any significant differences in the primary outcomes between the placebo and rosuvastatin groups at any time point during the follow-up. The per-protocol analyses (data not shown) yielded results similar to those of the intention-to-treat analyses.

Outcome Events
There were a total of 7 cardiac deaths, 1 of which was associated with aortic valve replacement, and a total of 55 patients with aortic valve replacement (Table 2). The survival curves of the outcome events (cardiac death or aortic valve replacement) were not significantly different between the 2 groups (P=0.45; Figure 4).

Subgroup Analysis
Prespecified subgroup analyses of the primary end point data were conducted on the basis of baseline AS severity, age, and aortic valve morphology (severity of calcification and bicuspid versus tricuspid). It has been suggested that these variables may affect the rate of progression of AS.2–4,26 (Figure 5).

Table 2. Prespecified Outcome Events in the 2 Treatment Groups

<table>
<thead>
<tr>
<th>Outcome Event</th>
<th>Events (Patients), n</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rosuvastatin (n=134)</td>
<td>Placebo (n=135)</td>
</tr>
<tr>
<td>Any event</td>
<td>35 (29)</td>
<td>44 (35)</td>
</tr>
<tr>
<td>AVR</td>
<td>28 (26)</td>
<td>27 (27)</td>
</tr>
<tr>
<td>Coronary bypass surgery†</td>
<td>5 (5)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>2 (2)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0 (0)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Angina</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*P values were from the Fisher exact test based on the number of patients. Statistical tests were not done for subcategories because the numbers were too small to draw any meaningful conclusion.
†All coronary bypass surgery was performed in association with aortic valve replacement (AVR).

Increased age and moderate to severe aortic valve calcification at baseline, increased AS severity, and tricuspid aortic valve were all significantly associated with increased progression rate. After corrections for age, baseline AS severity and tricuspid aortic valve morphology were no longer associated with increased AS progression rate, but aortic valve calcification remained significant. The effects of age and baseline aortic valve calcification on AS progression rate are summarized in Table 3. We did not observe an interaction between treatment assignment and any of the predefined subgroups. Treatment with rosuvastatin was not associated with a different progression in any of the subgroups.

Adverse Events
Adverse events were common and similar between the 2 treatment groups. Among the nonserious events, the most common was muscular pain. Serious adverse events are summarized in Table 4. There were 95 serious adverse events (41 in patients receiving rosuvastatin and 48 in patients receiving placebo), and no cases of rhabdomyolysis were seen. Five patients developed cancer during the study; 3 were on placebo and 2 were on rosuvastatin.

Discussion
Recent studies have suggested that the development of AS is an active process involving multiple pathways, many of which are similar to those involved in atherosclerosis.5–10 One of the key factors in the pathogenesis of AS appears to be lipoproteins, which are intimately involved in several pathways crucial to the development of AS. Indeed, valvular AS and supravalvular AS are known complications in patients with familial hypercholesterolemia, and sclerotic changes in the aortic valve are ubiquitous in homozygotes and common in heterozygotes.27,28 It is thus a reasonable hypothesis that statins, which are effective in treating hypercholesterolemia...
and reducing coronary events, may also be effective in reducing the rate of progression of AS. Several retrospective studies have supported this notion.17–20 The results of prospective studies are somewhat conflicting.21,22,29,30 The present study is the latest prospective trial to show that statins such as rosuvastatin have a profound effect on lowering cholesterol in AS patients and yet no impact on the progression of AS.

The results of the ASTRONOMER trial confirm and extend the findings of the Scottish Aortic Stenosis and Lipid

Table 3. Subgroup Analysis of Annual Progression Rate in Peak AS Gradient

<table>
<thead>
<tr>
<th></th>
<th>Difference in the Annual Increase in Peak AS Gradient, mm Hg/y,*</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment assignment</td>
<td>Rossuvastatin (n=129) vs placebo (n=126)</td>
<td>0.66</td>
<td>-0.21–1.53</td>
</tr>
<tr>
<td>Age at baseline</td>
<td>≥58 y (n=125) vs &lt;58 y (n=130)</td>
<td>2.55</td>
<td>1.69–3.42</td>
</tr>
<tr>
<td>Calcification severity at baseline†</td>
<td>Moderate or severe (n=168) vs no or mild (n=87)</td>
<td>2.01</td>
<td>1.10–2.91</td>
</tr>
</tbody>
</table>

*Estimated from the regression coefficients of the interaction term between time and the covariate under examination in a linear mixed-effect model.
†The association between baseline calcification and AS gradient progression was corrected for age.

Table 4. Adverse Events in the 2 Treatment Groups

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Rossuvastatin (n=134)</th>
<th>Placebo (n=135)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious event</td>
<td>41 (23)</td>
<td>48 (27)</td>
<td>0.64</td>
</tr>
<tr>
<td>Incident cancer</td>
<td>2 (2)</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>3 (3)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>3 (2)</td>
<td>4 (4)</td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>29 (17)</td>
<td>37 (20)</td>
<td></td>
</tr>
<tr>
<td>Laboratory findings</td>
<td>9 (2)</td>
<td>6 (5)</td>
<td>0.45</td>
</tr>
<tr>
<td>Creatine kinase &gt;10× ULN</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>AST &gt;3× ULN</td>
<td>3 (1)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>ALT &gt;3× ULN</td>
<td>5 (2)</td>
<td>3 (3)</td>
<td></td>
</tr>
</tbody>
</table>

AST indicates aspartate aminotransferase; ALT, alanine aminotransferase; and ULN, upper limit of normal.
P*Values were from the Fisher exact test based on the number of patients. Statistical tests were not done for subcategories because the numbers were too small to draw any meaningful conclusion.
independent predictors of a more rapid progression; thus, the rate of progression was similar between patients with bicuspid aortic valve and those with tricuspid aortic valve, and cholesterol lowering with rosuvastatin did not affect the rate of progression in any of the subgroups, suggesting that cholesterol lowering may not be the appropriate treatment target even in patients with mild AS and little or no valvular calcification, and newer therapeutic strategies besides cholesterol lowering with a statin should be explored.

Adverse Events
In this study, rosuvastatin 40 mg daily was well tolerated and not associated with excessive adverse events compared with placebo. Despite the high dose of rosuvastatin used, we did not observe an excess of muscular pain, which was common in both groups of patients, and there were no cases of rhabdomyolysis. The sample size was not large enough to address the issue of excessive incident cancer observed in the SEAS study,22 which used a combination of simvastatin and ezetimibe. A recent meta-analysis showed that no excess in cancer was observed in >90 000 patients in 14 randomized trials using statins for lipid lowering.33

Clinical Implications
It is perplexing that animal studies and retrospective studies have shown statins to be effective in reducing AS progression, yet prospective trials, including the present one, have consistently demonstrated the contrary.9,17–22,30 Indeed, the development of AS is a complex process involving multiple pathways, and it is plausible that hypercholesterolemia, not normal cholesterol concentration, is required to potentiate the pathways involved in the development and progression of AS. In animal studies and retrospective clinical studies, statins were used in the setting of hypercholesterolemia, whereas in the randomized trials, patients with hypercholesterolemia were systematically excluded. This can also explain the findings of the prospective but nonrandomized Rosuvastatin Affecting Aortic Valve Endothelium (RAAVE) study, in

Subgroup Analyses
Subgroup analyses were performed to assess the effect of intensive lipid lowering in relation to predefined baseline patient characteristics that have previously been shown to affect the rate of AS progression. Of particular interest were patients with congenital bicuspid aortic valve and a propensity to develop AS at a younger age compared with those with tricuspid aortic valve.26,27 These patients can frequently be identified by echocardiography and thus represent an ideal group for preventive intervention if an effective strategy to prevent AS is available. In the present study, the rate of progression was similar between patients with bicuspid aortic valve and those with tricuspid aortic valve, and cholesterol lowering with rosuvastatin did not affect the rate of progression regardless of aortic valve morphology. We also showed that both age and severity of aortic valve calcification were independent predictors of a more rapid progression; thus, older patients and patients with more heavily calcified aortic valves need to be followed up more closely. Cholesterol lowering with rosuvastatin was not associated with a reduction in progression in any of the subgroups, suggesting that cholesterol lowering may not be the appropriate treatment target even in patients with mild AS and little or no valvular calcification, and newer therapeutic strategies besides cholesterol lowering with a statin should be explored.
which only AS patients with hypercholesterolemia were treated with rosuvastatin.\textsuperscript{26} From a practical standpoint, it may not matter whether AS patients with hypercholesterolemia have slower AS progression in response to statin therapy because these patients should receive statin anyway to reduce cardiovascular events. Taken together, the findings of SALTIRE, SEAS, and ASTRONOMER are consistent and convincing in demonstrating that lipid lowering does not affect AS progression in patients with no clinical indications for lipid lowering, that further trials of similar design are unlikely to be fruitful, and that AS per se should not be an indication for statin therapy. The last point deserves wide dissemination because we have observed that many AS patients have been and still are being treated with a statin to prevent progression largely because of the results of the retrospective and nonrandomized studies.

Conclusions

Intensive lipid lowering with rosuvastatin 40 mg daily did not reduce the rate of progression of AS in patients with mild to moderate AS. This finding is consistent with the previously published SALTIRE and SEAS studies. Thus, in patients with AS and no indications for cholesterol lowering, statins should not be used for the purpose of reducing progression of AS.

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Disclosures

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CLINICAL PERSPECTIVE

Aortic stenosis is an active process with many similarities to atherosclerosis. Animal studies and retrospective clinical studies have shown statins to be effective in reducing the progression of aortic stenosis. In a randomized, double-blind, placebo-controlled trial of 269 patients with a median follow-up of 3.5 years, we assessed the effect of rosuvastatin 40 mg daily on the progression of aortic stenosis in asymptomatic patients with mild to moderate aortic stenosis and no indication for lipid-lowering therapy. We showed that intensive lipid lowering with rosuvastatin was no better than placebo in reducing the progression of aortic stenosis. The lack of benefit was observed in predefined subgroups, including younger patients, patients with milder aortic stenosis, patients with bicuspid aortic valve, and patients with little or no aortic valve calcification. Our findings are consistent with the results of the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) and Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trials, showing that lipid lowering does not affect the progression of aortic stenosis in patients with no clinical indications for lipid lowering.
Effect of Lipid Lowering With Rosuvastatin on Progression of Aortic Stenosis. Results of the Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTRONOMER) Trial

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