Best evidence topic - Valves

Do statins slow the progression of aortic valve stenosis?

Christos E. Tournousoglou*, Spiros Lalos, Themistokles Psarros

Department of Cardiothoracic Surgery, Hippocratio General Hospital, Athens, Greece

Received 15 February 2008; received in revised form 30 March 2008; accepted 1 April 2008

Summary

A best evidence topic in cardiac surgery was written according to a structured protocol. The question addressed was whether therapy with statins significantly slows the progression of aortic valve stenosis. Altogether 226 papers were found using the reported search, of which twelve represented the best evidence to answer the clinical question. The authors, journal, date, country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. The results of the reported studies provided conflicting results. There are twelve studies. Ten retrospective studies and one prospective had been promising with a slower rate of hemodynamic progression in patients taking statins. One retrospective and one randomized controlled trial did not halt the progression of calcific aortic stenosis or induce its regression. The data are discrepant as to whether this effect is related to serum lipid levels or to other effects of statins. While the data are not yet strong enough to change clinical practice, two large randomized controlled trials (ASTRONOMER and SEAS) which have recruited 272 and 1873 patients, respectively, will provide important new evidence in this area in the near future.

Keywords: Statins; Aortic valve stenosis; Thoracic surgery

1. Introduction

A best evidence topic was constructed according to a structured protocol. This is fully described in the ICVTS [1].

2. Three-part question

In [patients with calcific aortic valve stenosis] do [statins] significantly [slow the progression of the disease]?

3. Clinical scenario

You are seeing a 61-year-old patient with calcific aortic valve stenosis and an aortic valve peak gradient of 69 mmHg who is completely asymptomatic on an exercise test and has a normal left ventricle. Cholesterol > 230 mg/dl, HDL < 35 mg/dl, LDL > 135 mg/dl. Other parameters are normal. You say to him that there is no indication for aortic valve replacement now, although he may need a valve replacement in the future. The patient asks if there is something he can do to stop the progression of stenosis. You wonder whether statins reduce significantly or not the hemodynamic progression of aortic valve stenosis.

4. Search strategy

Medline 1950 to February 2008 using OVID interface. [exp Anticholesteremic Agents/OR exp Simvastatin/OR statins.mp OR Simvastatin.mp OR rosuvastatin.mp OR Atorvastatin.mp OR ceruvastatin.mp OR pravastatin.mp OR mevastatin.mp OR lovastatin.mp OR fluvastatin.mp] AND [exp aortic valve/OR aortic valve.mp].

5. Search outcome

Using the reported search, 226 papers were identified of which 12 papers provided the best evidence to answer the question. These papers are summarized in Table 1.

6. Results

The search was wide but the range and quality of relevant papers was poor. There were ten retrospective studies, one prospective non-randomized and one randomized controlled trial.

Aronow et al. [2] performed a retrospective analysis of older patients with mild valvular aortic stenosis (AS) and showed that independent predictors of the progression of AS were male gender, smoking, diabetes mellitus, LDL, HDL and statins (inverse association). Novaro et al. [3] in their study excluded patients who had greater than moderate aortic regurgitation, depressed ventricular function, severe aortic stenosis or if <2 echo cardiograms failed to generalize the findings to patients. The statin-treated patients were taking low doses of medication. The authors found that statins slowed the disease.

Pohle et al. [4] observed that there was a strong influence of LDL cholesterol level on the progression of aortic valve calcification, suggesting that lipid-lowering therapy might decrease the progression of aortic valve calcification.
Table 1

<table>
<thead>
<tr>
<th>Author, date and country</th>
<th>Study type (level 2b)</th>
<th>Patient group</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aronow et al., 2001, Am J Cardiol, USA, [2]</td>
<td>Cohort study (level 2b)</td>
<td>180 patients ≥60 years old with mild valvular AS (peak systolic gradient across aortic valve of 10–25 mmHg). Initial serum LDL ≥125 mg/dl not treated with statins (n = 69). Initial serum LDL ≥125 mg/dl treated with statins (n = 62). Initial serum LDL &lt;125 mg/dl not treated with statins (n = 49). Mean duration of follow-up: 33 months. Mean age: 82 ± 5 years</td>
<td>Progression of AS with follow-up Doppler at ≥2 years with measurement of peak systolic gradient across the aortic valve/year</td>
<td>– Increase in peak systolic gradient across aortic valve/year (mmHg)</td>
<td>Retrospective. More patients did not take statins</td>
</tr>
<tr>
<td>Novaro et al., 2001, Circulation, USA, [3]</td>
<td>Cohort study (level 2b)</td>
<td>174 patients with mild to moderate calcific aortic stenosis. Patients with normal left ventricular function, ≤2+ aortic regurgitation and ≥2 echocardiograms performed at least 12 months apart were included. 33% of patients received statins. Mean duration of follow-up: 21 months. Mean age: 68 ± 12 years</td>
<td>– Peak gradient aortic valve pressure</td>
<td>– Peak gradient aortic valve pressure</td>
<td>Retrospective. Five different statins were given</td>
</tr>
<tr>
<td>Pohle et al., 2001, Circulation, Germany, [4]</td>
<td>Cohort study (level 2b)</td>
<td>104 patients with an EBT scan positive for aortic valve calcification and coronary calcification. EBT was repeated at a mean interval of 15 months. – Group 1 (57 patients): LDL ≤130 mg/dl – Group 2 (47 patients): LDL ≥130 mg/dl – 54 patients were treated with statins (39 in group 1 and 15 in group 2)</td>
<td>Aortic valve calcification</td>
<td>Annualized aortic valve calcium progression in 54 patients treated with statins</td>
<td>Retrospective. Small sample size. No measurements about the functional status of aortic valve</td>
</tr>
<tr>
<td>Shavelle et al., 2002, Lancet, USA, [5]</td>
<td>Cohort study (level 2b)</td>
<td>65 patients with calcific aortic valvular stenosis. Patients underwent two electron-beam computed tomography scans at a mean interval of 2.5 years. 43% of patients received statins. Mean age: 67 ± 10 years</td>
<td>Aortic valve calcification score with EBT scan (Agatson score and volumetric score)</td>
<td>In statin group 62–63% lower rate of AVC accumulation in Agatson and volumetric score</td>
<td>Retrospective. Small number of patients</td>
</tr>
</tbody>
</table>

(Continued on next page)
Table 1 (Continued)

<table>
<thead>
<tr>
<th>Author, date and country</th>
<th>Patient group</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bellamy et al., 2002, J Am Coll Cardiol, USA, [6]</td>
<td>156 patients with calcific aortic stenosis. Progression of AS with Doppler echocardiography at baseline and at least six months later.</td>
<td>Mean gradient of aortic valve pressure (mmHg)</td>
<td>– Aortic mean gradient Statin group Baseline: 18 ± 7 mmHg Follow-up: 27 ± 12 mmHg</td>
<td>– Annualized change in AAV</td>
</tr>
<tr>
<td>Cohort study (level 2b)</td>
<td>38 patients received statins. Mean interval between echocardiograms was 3.7 ± 2.3 years, Mean age: 77 ± 12 years</td>
<td>– Aortic valve area (cm²)</td>
<td>– Aortic valve area Statin group Baseline: 22 ± 12 mmHg Follow-up: 39 ± 19 mmHg (P &lt; 0.01)</td>
<td></td>
</tr>
<tr>
<td>Rosenhek et al., 2004, Circulation, Austria, [7]</td>
<td>211 patients with native AS defined by a peak velocity 2.5 m/s, valve area 0.84 ± 0.23 cm². Mean gradient 42 ± 19 mmHg, with normal left ventricular function and had 2 echocardiograms separated by at least 6 months were included. 50 patients received statins and 32 patients received statins and ACEIs. Mean interval between the first and last echo was 24 ± 18 months. Mean age: 70 ± 10 years</td>
<td>Annualized change in peak aortic jet velocity</td>
<td>– Annualized increase in peak aortic jet velocity: Statin group: 0.10 ± 0.41 m/s/year No statin group: 0.39 ± 0.42 m/s/year (P &lt; 0.0001)</td>
<td></td>
</tr>
<tr>
<td>Antonini-Canterin et al., 2005, Ital Heart J, Italy, [8]</td>
<td>242 patients, 121 patients age- gender-matched, not treated with statins with similar initial Vmax were included. Follow-up with echocardiographic studies ≥ 6 months apart. Mean duration of follow-up: 54 ± 34 months in statin group and 50 ± 33 months in control group. Mean age: 67 ± 9 years</td>
<td>Rate of increase in peak aortic-jet velocity</td>
<td>– Statin group 0.13 ± 0.24 m/s/year – Control group 0.14 ± 0.19 m/s/year (P = 0.72)</td>
<td></td>
</tr>
<tr>
<td>Cohort study (level 2b)</td>
<td>155 patients with calcific aortic stenosis with an aortic jet velocity over 2.5 m/s (range 2.5–5.0 m/s, not yet with an indication for aortic valve surgery. 65 patients received statins, patients were randomized to atorvastatin 80 mg daily or placebo. Median follow-up 25 months (range, 7 to 36), Mean age: 68 ± 11 years</td>
<td>Change in aortic jet velocity on ECHO (m/s/year)</td>
<td>– Atorvastatin group: 0.199 ± 0.210 m/s/year – Placebo group: 0.203 ± 0.208 m/s/year (P = 0.95)</td>
<td></td>
</tr>
<tr>
<td>Cowell et al., 2005, N Engl J Med, UK, [9]</td>
<td>48 rabbits were treated for 3 months.</td>
<td>Aortic valve calcification with micro-computed</td>
<td>– Control group: Aortic valves and aortas had no mineralization.</td>
<td></td>
</tr>
<tr>
<td>Rajamannan et al., 2005, Heart, USA, [10]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued on next page)
Patients with symptoms suggestive of severe aortic valve stenosis were excluded. Shavelle et al. [5] found that statins slowed the disease. But no information was available about the doses of statins and lipid concentrations were restricted to total cholesterol levels. The patients might not be representative of most patients with calcific aortic valvular disease as they were referred by their primary physicians. Bellamy et al. [6] in their study with the longest follow-up showed that AS progression was unrelated to cholesterol...
levels, total or fractions. The degree of obstruction qualifying as AS was not well defined. Statins were associated with slower progression of the disease.

Rosenhek et al. [7] included patients with severe AS and demonstrated that statins slowed the hemodynamic progression in mild-to-moderate and severe AS. Besides this effect was independent of cholesterol levels.

Antonini-Canterin et al. [8] showed that statins could be beneficial in retarding the progression of valvular aortic sclerosis to aortic stenosis. Patients with more than mild aortic regurgitation were excluded from the study.

Rajamannan et al. [9] in their experimental study with rabbits provided the evidence that chronic hypercholesterolemia produced bone mineralization in the aortic valve which was inhibited by atorvastatin.

Rajamannan et al. [10] in another experimental study supported the hypothesis that degenerative valvular aortic stenosis was the result of active bone formation in the aortic valve, which might be mediated through a process of osteoblast differentiation and that statins inhibited this calcification process.

Cowell et al. [11] performed the 1st RCT evaluating this issue and showed that intensive lipid-lowering therapy did not halt the progression of calcific aortic stenosis. There was no relationship between LDL and the progression of AS. They also excluded patients with an aortic-jet velocity of <2.5 m/s even though knowing that intervening at this earlier stage might be more beneficial. In this way they might have missed a modest treatment benefit especially for younger patients with mild disease.

Moura et al. [12] showed that statin therapy was associated with slowing of the hemodynamic progression of aortic stenosis and reduction of CPR levels, IL-6, sCD40L and serum LDL levels. This was a non-randomized, prospective, open-label observational study that suggested that the earlier treatment with statins was more efficacious in the prevention of progression of AS than late treatment.

Mohler et al. [13] did not demonstrate any statistically significant reduction in the accumulation of calcium in the aortic valve for the statin group compared to the non-statin group, although there was a trend towards a lesser progression of calcification in the former case.

The results of two RCTs (SEAS and ASTRONOMER) are pending. The ASTRONOMER (The Aortic Stenosis Progression Observation: Measuring Effects of Rovustatin) trial is a double-blind placebo-controlled trial. Patients with mild to moderate AS are randomized to receive 40 mg/day of rovustatin or placebo. Patients with any clinical indication for the use of cholesterol-lowering agents according to the 2000 Canadian guidelines are excluded. The recruitment of 272 patients was completed in December 2005. The patients are younger (58.1 ± 13.6 years) and 48.9% of them have a bicuspid aortic valve. The mean aortic jet velocity is 3.2 ± 0.4 m/s. The results will be available at the end of 2008.

The SEAS (The Simvastatin and Ezetimibe in Aortic Stenosis) study is a randomized double-blind, placebo-controlled, multicenter study of a minimum four years’ duration that will investigate the effect of lipid lowering with ezetimibe/simvastatin 10/40 mg/day in patients with asymptomatic AS with peak transvalvar jet velocity 2.5–4.0 m/s. Primary efficacy variables include aortic valve surgery and ischemic vascular events such as cardiovascular mortality and the effect on echocardiographically evaluation of progression of AS. From January 2003 to March 2004, a total of 1873 patients from 173 hospitals and outpatient clinics in Europe have been randomly assigned in the study. Some baseline characteristics are: age 68 ± 10 years and mean transaortic maximum velocity 3.1 ± 0.5 m/s. The SEAS study is the largest randomized trial in patients with AS.

7. Clinical bottom line

The results of the reported studies provided conflicting results. There are twelve studies. Ten retrospective studies and one prospective had been promising with a slower rate of hemodynamic progression in patients taking statins. One retrospective and one randomized controlled trial did not halt the progression of calcific aortic stenosis or induce its regression. The data are discrepant as to whether this effect is related to serum lipid levels or to other effects of statins.

While the data are not yet strong enough to change clinical practice, two large randomized controlled trials (ASTRONOMER and SEAS) which have recruited 272 and 1873 patients, respectively, will provide important new evidence in this area in the near future.

References


ARTICLE IN PRESS


eComment: Statins decelerate the sclerosis progression of senile aortic valves in only selected cases

Authors: Efstratios Apostolakis, Cardiothoracic Surgery Department, University Hospital of Patras, 22500 Rion Patras, Greece; Ioanna Koniari doi:10.1510/icvts.2008.178038A

There is no doubt that despite the controversial conclusions of your review [1], statins contribute to the deceleration of atherosclerosis of the stenotic aortic valve; fact that has been proved by various experimental studies [2]. Besides, early results of experimental trials in our department support the beneficial effect of statins, while we strongly believe that additional future randomized trials will confirm the above findings. However, future studies in order to be reliable should primarily examine the comparative deceleration of atherosclerosis in different subgroups, based on the patient lipid profile before the therapy initiation. Secondly, an ‘objective’ method should be applied concerning the ‘quantitative measurement’ of this deceleration. It is notable that the anti-inflammatory action of statins – as it is reported by the reduction of IL – 6 and CRP levels respectively – contributes to the deceleration of valve sclerosis, independently of their corresponding impact on serum lipids [3]. On the other side, it has been demonstrated that statins induce the angiogenesis, and as a consequence, statins contribute to the increase of the atherosclerotic plaque [4]. But if this beneficial action of statins will be supported by a great number of randomized trials in the future, what should we do? Could we administer a statin as an agent that slows the progression of a stenotic aortic valve in elderly people? Such an indication would be meaningful in selective cases, such as patients with type II hypercholesterolemia or with coronary artery disease; while in patients with normal cholesterol and LDL levels there is no significant difference concerning the velocity of valvular aortic sclerosis progression. However, the limitation of several studies is that their results are not being evaluated according to the hypercholesterolemic subgroups of the whole number of patients [1].

In conclusion, taking into consideration the low incidence of reported complications as well as the great cost concerning the prevention of CAD – that fluctuates from €6700 up to €11,400 [5] – we should give the green light concerning the administration of statins only in selective cases of aortic valve stenosis.

References


