Statins and Progression of Calcified Aortic Stenosis

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**OBJECTIVE:** To review the evidence evaluating the efficacy of statins in reducing the progression of calcified aortic stenosis (AS).

**DATA SOURCES:** MEDLINE, EMBASE, and PubMed were searched (all up to November 2006) for studies evaluating the use of statins to reduce the progression of calcified AS. Search terms included statin, HMG CoA reductase inhibitor, calcified AS, valve stenosis, and calcified stenosis. Additional primary trials were located by searching references noted in review articles.

**STUDY SELECTION AND DATA EXTRACTION:** Clinical trials published in the English language were selected for review. Primary efficacy outcomes evaluated were changes in aortic valve measurements, hemodynamic measures of AS, and change in measures of AS severity.

**DATA SYNTHESIS:** Two prospective clinical trials and 5 retrospective studies were included in this review. All of the retrospective studies demonstrated that statin use was associated with a statistically significant delay in the progression of AS. One prospective observation trial showed benefit of statin use; however, a large, randomized, double-blind, prospective trial showed no benefit of statin use in decreasing the progression of AS.

**CONCLUSIONS:** An association between statin use and a delay in AS progression has been observed in retrospective studies; however, prospective trials showed conflicting results. Currently, statins cannot be recommended for medical treatment of AS until larger trials are conducted.

**KEY WORDS:** aortic stenosis, HMG-CoA reductase inhibitors, statins.


Published Online, 28 Nov 2006, [www.theannals.com](http://www.theannals.com), DOI 10.1345/aph.1H206

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**REQUEST**

Does the use of statins reduce the progression of calcified aortic stenosis (AS)?

**RESPONSE**

**BACKGROUND**

AS is the most common valve lesion requiring surgical intervention in the US and the third most common cardiovascular disorder after hypertension and coronary artery disease. The morbidity associated with valvular surgery is high, and there is currently no approved medical therapy to treat AS. In AS, there is a fixed obstruction of the functional area of the aortic valve, resulting in impaired cardiac outflow from the left ventricle. This obstruction can cause progressive pressure overload on the left ventricle, leading to ventricular hypertrophy and ultimately to ventricular dysfunction and symptoms of heart failure. The prognosis is poor once symptoms of AS become evident, with estimated survival of 2–3 years; however, the prognosis is excellent with aortic valve replacement.

The pathophysiology of calcified AS was previously thought to be a degenerative change secondary to longstanding mechanical stress and passive calcium deposition. Recent studies have found pathophysiological changes and risk factors similar to those present in coronary artery disease and hypercholesterolemia. AS starts with thickening and calcification of the valve cusps, ultimately progressing to heavily calcified stiff cusps, which causes impaired valve movement. Eventually, the functional valve...
area is reduced, leading to impaired hemodynamic flow across the aortic valve. Histopathologic studies have shown that the progression of AS is an active process involving inflammation, lipid infiltration, dystrophic calcification, platelet deposition, and endothelial dysfunction. Similar to atherosclerosis, lipids that are deposited on the aortic leaflets are oxidized and accompanied by subsequent sclerosis and calcified deposits. This accumulation of lipids, inflammatory cells, and subsequent calcification on the aortic leaflets initiate the pathology of AS.

This association between lipid deposition and progression of AS has led to the proposed theory that the use of statins may delay the progression of AS. Several studies have been published investigating the role of statins in delaying AS progression.

**Literature Review**

A thorough search of the available literature yielded 8 potential studies. One study was excluded, as the outcome measured was a laboratory measure of inflammation with cellular adhesion molecules, which is not a clinically useful marker of AS. Thus, 5 retrospective studies, 1 open-label prospective trial, and 1 randomized controlled trial were included in this review (Table 1).

Novaro et al. conducted a retrospective study of patients with an aortic valve area (AVA) of 1.0–1.8 cm² or mild-to-moderate AS. The patients in the statin group tended to be older (71 vs 67 y) and have a higher prevalence of coronary artery disease (89% vs 44%). Through multivariate analysis, statin use was found to be a significant independent predictor of a smaller reduction in AVA. There was no significant association found between change in low-density lipoprotein cholesterol (LDL-C) and change in AVA. The authors suggested that the use of statins is associated with significantly less progression of AS. However, the small sample size and low percentage of patients receiving statin therapy in this retrospective study weaken its conclusion.

Another retrospective study evaluated patients who received computed tomography to assess coronary artery calcification. The patients on statin therapy had a higher incidence of hyperlipidemia (100% vs 45%) compared with the non-statin patients. Patients not on statins had a greater

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**Table 1. Studies of Statin Use and Progression of AS**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Treatment</th>
<th>Results</th>
<th>Association of AS Progression and LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novaro (2001)</td>
<td>retrospective</td>
<td>non-statin (n = 117) statin (n = 57)</td>
<td>annual decrease in AVA: non-statin = 0.11 cm² statin = 0.06 cm² p = 0.003</td>
<td>no</td>
</tr>
<tr>
<td>Shavelle (2002)</td>
<td>retrospective</td>
<td>non-statin (n = 37) statin (n = 28)</td>
<td>AVC change/y: non-statin = 32% statin = 12.1% p = 0.0006</td>
<td>no</td>
</tr>
<tr>
<td>Rosenhek (2004)</td>
<td>retrospective</td>
<td>non-statin (n = 161) statin (n = 50)</td>
<td>increase in peak aortic jet velocity: non-statin = 0.39 m/sec/y statin = 0.10 m/sec/y p = 0.0001</td>
<td>no</td>
</tr>
<tr>
<td>Antonini-Canterin (2003)</td>
<td>retrospective</td>
<td>non-statin (n = 145) statin (n = 22)</td>
<td>increase in peak aortic jet velocity: non-statin = 0.140 m/sec/y statin = 0.038 m/sec/y p &lt; 0.001</td>
<td>no</td>
</tr>
<tr>
<td>Antonini-Canterin (2005)</td>
<td>retrospective</td>
<td>non-statin (n = 121) statin (n = 121)</td>
<td>increase in peak aortic jet velocity: non-statin = 0.14 m/sec/y statin = 0.13 m/sec/y p = 0.72</td>
<td>no</td>
</tr>
<tr>
<td>Bellamy (2002)</td>
<td>prospective</td>
<td>non-statin (n = 118) statin (n = 38)</td>
<td>annual AVA decrease: non-statin = 0.09 cm²/y statin = 0.04 cm²/y p = 0.04</td>
<td>no</td>
</tr>
<tr>
<td>Cowel (2005)</td>
<td>randomized, double-blind, placebo-controlled</td>
<td>placebo (n = 78) atorvastatin 80 mg/day (n = 77)</td>
<td>increase in peak aortic jet velocity: non-statin = 0.203 m/sec/y atorvastatin = 0.199 m/sec/y p = 0.95 absolute change in AVC score: placebo = 1648 AU/y atorvastatin = 1564 AU/y p = 0.80</td>
<td>no</td>
</tr>
</tbody>
</table>

AS = aortic stenosis; AU/y = arbitrary units per year; AVA = aortic valve area; AVC = aortic valve calcium; LDL-C = low-density lipoprotein cholesterol; NR = not reported.
change in aortic valve calcification (AVC) scores per year compared with those on statin therapy. The authors concluded that statin therapy may alter the natural history of aortic calcification based on AVC scores. The small number of patients in this study limits the robustness of its results and the role of AVC scores in relation to other measures of AS severity remains unclear and is not used routinely as a clinical measure.

Rosenhek et al. performed a retrospective cohort study in patients who had aortic valve stenosis, defined as a peak aortic jet velocity greater than 2.5 m/sec. The statin-treated patients had a higher incidence of coronary artery disease (60% vs 29%) and hyperlipidemia (100% vs 40%) than patients not treated with statins. Hemodynamic progression of AS was significantly lower in the statin group compared with the non-statin group. This benefit in the statin group was seen across the subgroups of patients with mild, moderate, and severe AS. Multivariate linear regression showed that statin therapy was independently correlated to a delayed progression of AS; however, cholesterol levels did not show such a correlation. The authors concluded that the use of statins can delay hemodynamic progression of AS due to their pleiotropic effects rather than their cholesterol-lowering effects. The small number of subjects in this study is the main weakness, and several potential confounding factors, such as comorbidities and concomitant medications, were not taken into account.

A retrospective study investigated the effect of statin treatment on the progression of bioprosthetic aortic valve degeneration. The clinical characteristics of the 2 study groups were similar, except that the statin group had a higher incidence of hypercholesterolemia (95% vs 13%) and coronary artery disease (77% vs 28%). At the end of the study, the rate of increase of peak jet velocity per year across the bioprosthetic valve was higher in the non-statin group compared with the statin group. Through univariate analysis, the authors determined that only statin use influenced the annual rate of increase in peak velocity and change in prosthetic valve area, while hypercholesterolemia and coronary artery disease did not appear to have an influence. The results of this study suggest that statin use is associated with significantly less bioprosthetic aortic valve degeneration. However, this study involved patients with bioprosthetic valves; the results cannot be extrapolated to native valve stenosis without further study.

The same investigators performed a similar retrospective study investigating the role of statin treatment in the progression of AS. Patients with aortic valve sclerosis or aortic valve stenosis (peak aortic jet velocity of 1.5–3.9 m/sec) were selected. At baseline, the statin group had a higher incidence of hypercholesterolemia (92% vs 14%) and coronary artery disease (72% vs 21%) compared with the control group. At the end of the study, there was no difference in the rate of increase of peak aortic jet velocity between the control group and the statin-treated group. However, in a subgroup of patients with aortic valve sclerosis, statin use was associated with a lower increase in peak velocity compared with the control group (annual increase in peak aortic jet velocity 0.04 vs 0.08 m/sec/y, respectively; \( p = 0.007 \)). Hypercholesterolemia was not shown to influence the progression of aortic sclerosis or stenosis. The authors concluded that the use of statins may be beneficial in retarding the progression of aortic sclerosis to AS; although, there was no benefit seen with statin use in AS. However, one must be cautious in interpreting the results of such subgroup analysis in a trial with a small number of patients.

One prospective study investigated the effect of statins on AS progression in 165 patients with an AVA less than 2 cm². At baseline, the statin group had higher levels of LDL-C (164 vs 137 mg/dL), history of coronary artery disease (63% vs 23%), and higher AVA (1.32 vs 1.20 cm²) compared with the non-statin group. The statin group had a smaller annualized decrease in AVA versus the non-statin group. There was no correlation seen between change in AVA and LDL-C levels. The authors concluded that AS progression is unaffected by hyperlipidemia, cholesterol levels, or other atherosclerosis risk factors, but that the pleiotropic effects of statins may play a role in slowing AS progression. However, the small size of this study and the differences in baseline characteristics between the 2 groups may have influenced the results.

Cowell et al. conducted the only randomized, double-blind, placebo-controlled trial studying the association between statin use and calcified AS. Patients meeting the entry criteria of having calcified AS (defined as an aortic jet velocity of at least 2.5 m/sec) and aortic valve calcification on echocardiography were randomized to receive either atorvastatin 80 mg/day or matching placebo. The primary endpoints were progression of AS (determined by changes in aortic jet velocity) and progression of valvular calcification at 25 months. At baseline, there were no significant differences in characteristics between the study groups. The differences in the endpoints (the change in aortic jet velocity and absolute change in AVC score) between the placebo and atorvastatin groups were not significant. The atorvastatin group achieved a lower LDL-C at the end of the study compared with the control group (63 vs 130 mg/dL respectively, \( p < 0.001 \)); however, serum LDL-C levels did not correlate with disease progression. The authors concluded that intensive lipid lowering with atorvastatin did not halt the progression of calcified AS or induce its regression. Therefore, they did not recommend statin treatment for patients with AS in the absence of coexisting vascular disease. This trial was well designed and was the only one to have matched patient characteristics at baseline, thus adding to the validity of its results.
DISCUSSION

The initial studies of statin use to delay progression of AS did show benefit, but many of these studies were retrospective. These studies only showed an association between statin use and delay in progression of AS, and confounding factors such as underlying comorbidities and concomitant drug therapy may have biased the results. The statin-treated groups also had a higher incidence of coronary artery disease and dyslipidemia, thus potentially comparing higher cardiovascular risk patients to lower risk control patients. The inclusion and exclusion criteria for the retrospective studies also differed considerably; thus, it would be difficult to determine which patients would most likely benefit from statin use. The only large, randomized trial also showed no benefit of statin use in delaying the progression of AS; however, it may have been underpowered, and treatment duration may not have been adequate. The weak designs of the majority of these studies make it difficult to draw firm conclusions regarding the benefit of statins in AS. Several larger trials, such as the ASTRONOMER (Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin) and SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) studies, are underway to further investigate the use of statin therapy in delaying AS.17

The heterogeneity of the various studies makes it difficult to draw any firm conclusions. The different studies investigated patients at various stages of AS, from aortic atherosclerosis to severe AS, and one study investigated bioprosthetic aortic valves. Some investigators concluded that statin use was beneficial only in the early stages of AS, while others showed benefit across the spectrum of AS severity. The types and doses of statins used and the use of concomitant medications in many of the retrospective studies were not described. Cowell et al.16 evaluated high-intensity statin therapy with atorvastatin 80 mg, while many of the other retrospective studies involved statin therapy only at usual doses. Thus, it is hard to elucidate whether statin dose played a factor in the results of these studies. In addition, the duration of treatment may influence outcome of the study, as it may not have been sufficient to influence the natural history of AS. Several of the trials used different outcome measures of AS (eg, change in AVA, change in aortic jet velocity), which makes comparisons between trials difficult. While the AVA is used to define the severity of AS and aortic jet velocity has been shown to predict progression of AS, these are not validated surrogate outcome measures and may not reflect clinical outcomes. Ultimately, studies must show that statin use would delay progression of AS, leading to a reduction in heart failure symptoms or prolonged time to cardiac valve surgery.

Interestingly, the association between the lowering of cholesterol levels and the progression of AS was inconsistent among the various trials. This suggests that any benefit of statin use in the retardation of AS progression is independent of the lipid-lowering actions of these drugs. Some of the authors postulated that the benefit seen in AS is due to the pleiotropic effect of statins.4 However, the optimal dose, statin, and duration for this pleiotropic effect remains elusive and is still an unclear and controversial property of statins.18,19

SUMMARY

Studies have shown a consistent positive association between statin use and delay in AS progression. However, the poor nature and design of most of these studies make it difficult to definitively conclude that statin use can delay the progression of AS. The only randomized trial to date did not show a benefit of statin use in reducing AS progression. Currently, statin use cannot be recommended as a therapy to reduce the progression of AS until further results from well-designed trials are available.

REFERENCES

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EXTRACTO

OBJETIVO: Revisión sistemática de las evidencias mediante la evaluación de la eficacia de las estatinas en la reducción de la progresión de la estenosis aórtica calcificada.

FUENTES DE INFORMACIÓN: Se realizó una búsqueda en inglés en las bases de datos MEDLINE, EMBASE, y PubMed (hasta noviembre de 2006) de autores y ensayos clínicos que evaluaran el uso de las estatinas para reducir la progresión de la estenosis aórtica calcificada. Los términos de búsqueda incluyeron estatina, inhibidores de la HMG CoA reductasa, estenosis aórtica calcificada, estenosis valvular, y estenosis calcificada. Además se localizaron ensayos primarios mediante las notas de referencia en los artículos de revisión.

SELECCIÓN DE FUENTES DE INFORMACIÓN Y MÉTODO DE EXTRACCIÓN DE INFORMACIÓN: Sólo se incluyeron ensayos clínicos realizados en humanos, publicados en revistas en inglés, que evaluaran la eficacia de la terapia con estatinas en la reducción de la progresión de la estenosis aórtica. Los resultados de la eficacia primaria fueron cambios en las medidas de la válvula aórtica, mediciones hemodinámicas de la estenosis aórtica, y cambios en las mediciones de la gravedad de la estenosis aórtica.

SÍNTESIS: En esta revisión se incluyeron 2 ensayos clínicos prospectivos y 5 retrospectivos. Todos los estudios retrospectivos demostraron que el uso de las estatinas se asociaba con un retraso estadísticamente significativo en la progresión de la estenosis aórtica. Un ensayo prospectivo observacional demostró beneficios del uso de las estatinas, sin embargo, un ensayo clínico prospectivo, a doble ciego, aleatorio, de gran tamaño no demostró beneficios del uso de las estatinas en la reducción de la progresión de la estenosis aórtica.

CONCLUSIONES: Existe una asociación entre el uso de las estatinas y un retraso en la progresión de la estenosis aórtica que se basa en estudios retrospectivos, sin embargo, los ensayos prospectivos muestran resultado contrario. En la actualidad no se puede recomendar el uso de estatinas para el tratamiento médico de la estenosis aórtica hasta que se lleven a cabo ensayos clínicos de mayor tamaño.

Alain Marcotte