Do statins slow the process of calcification of aortic tissue valves?

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Summary

A best evidence topic in cardiac surgery was written according to a structured protocol. The question addressed was whether statins slow the process of calcification of aortic tissue valves. Altogether 207 papers were found using the reported search, of which eight represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. We acknowledge the limited evidence in this very specific field of cardiac surgery. Due to their pleiotropic effects, including anti-inflammatory properties, there has been speculation that statins could reduce and delay the degeneration and calcification of aortic bioprosthetic valves. Mainly, it was extrapolation of the recently discovered molecular similarities between atherosclerosis and native aortic valve stenosis (AS), with some evidence that statins may slow the progression of native aortic valve calcific degeneration, and the potential harmful impact of atherosclerotic risk factors on the development of native AS. Several studies have been conducted to evaluate the impact of hyperlipidemia and serum cholesterol levels on structural valve deterioration (SVD). Indeed, two studies suggested hyperlipidemia was a risk factor for SVD and correlated reoperation, from which one case-control study based on first-generation biological valves without specific anti-calcification treatment, while three – more convincingly by number of patients observed and design of the study – reported contrary results. The other three studies focused on statin treatment in patients after aortic biological valve replacement. Two studies confirmed beneficial effects of statin therapy on valve hemodynamics or inflammatory damage in vivo, but another study, with significantly greater patients series, found lipid-lowering therapy futile in this clinical aspect. Currently, studies and their results are discordant, but statin therapy appears insufficient to result in better clinical outcomes. We conclude that even though the data is conflicting, statin therapy does not prevent SVD of bioprosthetic valves in the aortic position.

Keywords: Review; Aortic biological prosthetic valve; Structural degeneration/deterioration; Statin therapy

1. Introduction

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

2. Three-part question

In [patients following a bioprosthetic aortic valve replacement] is [statin therapy] effective in [preventing tissue valve deterioration]?  

3. Clinical scenario

Five days ago you replaced a severely calcified aortic valve with a bioprosthesis in a 75-year-old patient. He recovered very well and at discharge he asks you and the team if any of his tablets will stop this new valve calcifying in the same way that his old valve calcified. Your registrar confidently tells him that the statins will do this, but you are less sure and thus resolve to look up the answer before he goes home.

4. Search strategy

Medline 1950–December 2009 using OVID interface [exp Heart Valve Prosthesis/OR exp Heart Valve Prosthesis Implantation/OR aortic valve.mp. or exp Aortic Valve/] AND [exp Anticholesteremic Agents/or StatinS.mp OR atorvas-tatin.mp OR simvastatin.mp OR pravastatin.mp OR ceruvas-tatin.mp].

5. Search outcome

Two hundred and seven papers were found using the reported search, in addition, the reference lists of all relevant articles were searched. From these eight papers the best evidence to answer the question was found. These are presented in Table 1.

6. Results

David and Ivanov [2] did not confirm a role of hyperlipidemia in predicting freedom from reoperation after aortic valve replacement with bioprosthetic valves. However, the authors cautioned that the probability of valve failure in
Table 1. Best evidence papers

<table>
<thead>
<tr>
<th>Author, date, and country, Study type (level of evidence)</th>
<th>Patient group</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Comment</th>
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<tbody>
<tr>
<td>David and Ivanov, J Thorac Cardiovasc Surg, USA, [2]</td>
<td>653 patients without coronary artery disease, who underwent aortic valve replacement with the Hancock I bioprosthesis two similar age-defined cohorts</td>
<td>Reoperation</td>
<td>RR for age, 0.95; 95% CI, 0.94–0.96; P = 0.001 Hyperlipidemia was not a significant predictor (P = 0.5)</td>
<td>The only independent predictor of reoperation was young age</td>
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<tr>
<td>Farivar and Cohn, J Thorac Cardiovasc Surg, USA, [3]</td>
<td>144 patients at a single institution, who had bioprosthetic aortic or mitral valves removed</td>
<td>Prognostic factors for valve calcification</td>
<td>High serum cholesterol (P = 0.035), younger age at implantation (P = 0.014), coronary artery disease (P = 0.017) – univariate analysis Only the mean serum cholesterol level was linked to valve calcification (P = 0.02) by stepwise multiple regression analysis Sex, hypertension, smoking, diabetes, and implant position were not linked to calcification</td>
<td>Hypercholesterolemia could be considered a risk factor for bioprosthetic valve calcification and explantation</td>
</tr>
<tr>
<td>Gring et al., J Heart Valve Dis, USA, [4]</td>
<td>7150 patients (mean age 68 ± 12 years) undergoing bioprosthetic aortic valve replacement (January 1975–December 2002) The average follow-up was 3.7 years 208 had explants for SVD</td>
<td>Predictors of explant for structural valvar deterioration</td>
<td>Younger age (P &lt; 0.0001), greater body weight (P &lt; 0.0001), elevated serum creatinine level (P = 0.0004) and use of a pericardial valve (P = 0.04) predicted SVD. Neither preoperative cholesterol nor its fractions predicted valve explant for SVD (log-rank P = 0.19)</td>
<td>Preoperative cholesterol levels do not predict SVD in patients undergoing bioprosthetic AVR</td>
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Table 1. (Continued)

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<tr>
<td>Le Tourneau et al., (2007), J Heart Valve Dis, France, [5] Retrospective observational study (level llb)</td>
<td>222 patients (110 males, 112 females; mean age 73 ± 8 years) underwent surgery for severe AS between 1989 and 1993. Mean follow-up was 7.3 ± 4.7 years</td>
<td>Predictors of mortality</td>
<td>Independent predictors of mortality were age (HR 1.11; 95% CI: 1.08–1.14, P &lt; 0.0001), DM (HR 2.53; 95% CI: 1.65–3.88, P &lt; 0.0001), male gender (HR 2.17; 95% CI: 1.53–3.12, P &lt; 0.0001), and NYHA class (HR 1.66; 95% CI: 1.17–2.34, P = 0.004). Other cardiovascular risk factors had no significant effect on survival</td>
<td>No cardiovascular risk factors but renal failure predicted bioprosthesis durability</td>
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<td>Nollert et al., (2003), J Thorac Cardiovasc Surg, Germany, [6] Retrospective cohort study (level llb)</td>
<td>161 patients (74% male; mean age, 54.4 ± 1.0 years; age range, 17–76 years; median age, 56.5 years) survived isolated aortic (n = 137) or combined aortic and mitral (n = 25) valve replacement with a Hancock extracorporeal pericardial valve. Of these patients, 90 (56%) had reoperations as a result of tissue failure of the aortic valve 5.6 ± 0.25 years postoperatively</td>
<td>Factors associated with accelerated valve failure</td>
<td>Sex (female, P = 0.001), smoking (P = 0.001), DM (P = 0.020), and cholesterol levels (P = 0.011) were risk factors for reoperation</td>
<td>This study is censured for usage of Hancock pericardial valves which are already out of market as disqualified ones. Nevertheless, it shows importance of cholesterol levels in the development of SVD</td>
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<td>Antonini-Canterin et al., (2004), Ital Heart J, Italy, [7] and (2003), Am J Cardiol, Italy, [8] Retrospective cohort study (level llb)</td>
<td>167 patients – 97 men, 70 women, mean age 71 ± 9 years, follow-up 46 ± 38 months, 22 patients (13%) were treated with statins, 145 (87%) were not</td>
<td>Annual rate of increase in the peak prosthetic velocity</td>
<td>Statin-treated patients 0.038 ± 0.074 vs. controls 0.140 ± 0.228 m/s/year (P = 0.001)</td>
<td>The only factor associated with the significantly less progression of bioprosthetic aortic valve failure was statin treatment</td>
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<td>Annual rate of decrease in the prosthetic effective orifice area</td>
<td>Statin group 0.031 ± 0.052 vs. controls 0.100 ± 0.150 cm²/year (P &lt; 0.001)</td>
<td>Retrospective nature of the study</td>
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<td>Aortic regurgitation worsening</td>
<td>Controls 33.1% vs. statin treatment group 9.1% (P = 0.022)</td>
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<td>Probability of bioprosthesis dysfunction</td>
<td>Odds ratio to develop either a rate of increase in peak velocity ≥ 0.3 m/s/year or of</td>
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patients with atherosclerosis risk factors was reduced because most of them were actually taking statins. Farivar and Cohn [3] found that serum cholesterol, younger age and coronary artery disease were linked to calcification of first-generation aortic bioprosthetic valves. Case-control analysis of the explanted tissue valves showed that the mean serum cholesterol level in the explanted valve group was significantly higher (*P* < 0.0001) than that of those who did not need re-replacement (the odds ratio (OR) for valve explantation and re-replacement was 3.9-fold higher for serum cholesterol levels > 5.18 mmol/l).

Gring et al. [4] from the evaluation of 7150 patients which included 208 explants for structural valve deterioration (SVD) showed that only younger age, greater body weight, elevated serum creatinine level and use of a pericardial valve predicted SVD. Neither preoperative cholesterol nor its fractions predicted valve explant for SVD. Moreover, no cardiovascular risk factors were predictive of SVD.

Le Tourneau et al. [5] investigated 222 patients, who underwent surgery for severe aortic valve stenosis (AS). Independent predictors of mortality were age, diabetes mellitus (DM), male gender, and New York Heart Association

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<td>Kulik et al., (2010), Eur J Cardiothorac Surg, Canada, [9]</td>
<td>1193 patients who underwent aortic valve replacement with contemporary bioprostheses between 1990 and 2006 (mean follow-up 4.5 ± 3.1 years, maximum 17.3 years) 150 of them received lipid lowering therapy (statins in 144 patients)</td>
<td>Progression of peak and mean trans-prosthetic gradients during echocardiographic follow-up (mean 3.3 years)</td>
<td>Peak increase: 0.9 ± 7.7 vs. 1.1 ± 10.9 mmHg, LLT vs. no LLT, <em>P</em> = 0.87 Mean increase: 0.8 ± 4.1 vs. 0.2 ± 5.9 mmHg, LLT vs. no LLT, <em>P</em> = 0.38</td>
<td>The study demonstrated no association between early postoperative LLT and a slowing of bioprosthesis SVD</td>
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<td>Retrospective observational study (level IIb)</td>
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<td>Skowasch et al., (2006), Heart, Germany, [10]</td>
<td>Valve tissue was taken from 81 patients, 57 with non-rheumatic aortic valve stenosis and 24 with degenerative aortic valve bioprosthesis. Five non-stenosed valves and four non-implanted bioprostheses served as controls. Of the 81 patients, 26 were treated with a HMG-CoA reductase inhibitors</td>
<td>The expression of CRP</td>
<td>Valvar CRP expression (<em>P</em> = 0.02) and serum CRP concentrations (<em>P</em> = 0.04) were lower in the statin group. No significant relation was observed between CRP concentrations, different statins, or different doses of statins /The article provides no numerical data on the subject. //</td>
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<td>Single centre case study (level IV)</td>
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SVD, structural valve deterioration: DM, diabetes mellitus; LLT, lipid lowering therapy; CRP, C-reactive protein; AS, aortic valve stenosis; AVR, aortic valve replacement; RR, relative risk; HR, hazard ratio, NYHA, New York Heart Association; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-co-enzyme A.
higher than 6.21 mmol/l. Valve longevity was 2.2 years longer for cholesterol levels above 6.21 mmol/l or lower compared with cholesterol levels higher than 6.21 mmol/l. There was no relation between any of these parameters and valve dysfunction among patients older than 57 years of age. While the study suggested a relationship between hypercholesterolemia and bioprosthetic degeneration, other confounding factors limited the validity of authors’ conclusions [2].

Antonini-Canterin et al. [7, 8] retrospectively selected 167 patients with bioprosthetic aortic valves. The annual rate of increase in peak prosthetic velocity, the annual rates of decrease in prosthetic effective orifice area and indexed effective orifice area were lower in statin-treated patients. Worsening of aortic regurgitation was 3.6 times less common in the statin group vs. controls. The OR for progression of prosthetic degeneration with statin treatment was 0.13. The only factor associated with a lower progression of bioprosthetic aortic valve failure was statin treatment.

Kulik et al. [9] followed 1193 patients and 150 of them received lipid lowering therapy (LLT, including statins) early after surgery. The progression of peak and mean transprosthetic gradients during echocardiographic follow-up was equivalent between patients treated with and without LLT. The annualized linear rate of gradient progression following valve replacement was also similar between groups. The incidence of mild or greater aortic insufficiency on the most recent echocardiogram was comparable, and there was no difference in the 10-year freedom from reoperation for SVD between the two groups.

Skowasch et al. [10] analyzed the endstage degenerative aortic valve tissue from native valves, degenerated bioprostheses and tissue from non-stenosed native and non-implanted bioprosthetic control valves. They found a raised C-reactive protein (CRP) 3.7 times more frequently in bioprostheses than in native valves, also the serum CRP levels increased in patients with aortic valve bioprostheses showing a significant correlation with the valvular inflammatory process. Association of statin treatment with decreases in both valvar and serum CRP concentrations was verified suggesting possible pleiotropic and/or anti-inflammatory properties of these molecules.

7. Clinical bottom line

We acknowledge the limited evidence in this very specific field of cardiac surgery. Due to their pleiotropic effects, there has been speculation that statins could reduce and delay the degeneration and calcification of aortic bioprosthetic valves. Several studies have been conducted to evaluate the impact of hyperlipidemia and serum cholesterol levels on SVD. Indeed, two studies suggested hyperlipidemia was a risk factor for SVD and correlated reoperation, from which there was one case-control study based on first-generation biological valves without specific anti-calcification treatment, while three reported contrary results. The other three studies focused on statin treatment in patients after aortic biological valve replacement. Two studies confirmed beneficial effects of statin therapy on valve hemodynamics or inflammatory damage in vivo, but another study, with a significantly greater patients series, found LLT ineffectual in this clinical aspect. Currently, studies and their results are discordant, but statin therapy appears insufficient to provide better clinical outcomes. We conclude that even though the data is conflicting, statin therapy does not prevent SVD of bioprosthetic valves in the aortic position.

References


eComment: Simvastatin inhibits aortic valve calcification in hypercholesterolemic rabbits

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doi:10.1510/icvts.2009.230920A

Your article concerning the effect of statins in aortic tissue valve calcification [1] is an important issue of cardiac surgery which still generates...
debates. Especially, aortic valve stenosis is characterized by atherosclerosis-like lesions, consisting of activated inflammatory cells, including T lymphocytes, macrophages, and of lipid deposits, calcific nodules, and bone tissue. Active mediators of calcification and cells with osteoblast-like activity are present in diseased valves. Moreover, extracellular matrix remodeling, including collagen synthesis and elastin degradation by matrix metalloproteinases and cathepsins, contributes to leaflet stiffening [2]. Notably, several experimental studies have proved the inhibition of hypercholesterolemia-induced calcification of aortic valve in animal models. Rajamannan et al. [3] demonstrated that atorvastatin inhibits aortic valve calcification reducing bone-formation and cellular proliferation via Lrp5 receptor pathway as well as enhancing nitric oxide synthase production. Thus, Monzack et al. [4] applied multiple in vitro disease stimuli to valvular interstitial cell (VIC) cultures and examined the impact of simvastatin treatment on VIC function. Simvastatin inhibited calcific nodule formation in a dose-dependent manner on all materials (although the level of statin efficacy was highly substrate-dependent), while decreases in nodule formation were not achieved via the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase pathway, but were correlated with decreases in Rho kinase (ROCK) activity. Moreover, unpublished data from our experimental protocols are in accordance with the above evidence. Particularly, New Zealand rabbits (n=10) fed with 4% cholesterol diet and treated with simvastatin (5 mg/kg) for eight weeks revealed a statistical significant inhibition of aortic valve atherosclerosis (P<0.001) compared to cholesterol fed rabbits (n=10). Thus, similar statistical significant inhibition of atherogenesis demonstrated the histopathological examination of ascending and descending aortas of simvastatin-treated hypercholesterolemic rabbits compared to hypercholesterolemic animals. Indeed, ascending/descending aorta in hypercholesterolemic rabbits, we support the opinion, the above dose may be responsible for simvastatin treatment on VIC function. Simvastatin inhibited calcific nodule formation in a dose-dependent manner on all materials (although the level of statin efficacy was highly substrate-dependent), while decreases in nodule formation were not achieved via the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase pathway, but were correlated with decreases in Rho kinase (ROCK) activity. A key point that should be discussed is the high-dose of simvastatin (5 mg/kg) in a plethora of experimental protocols in the literature. In our opinion, the above dose — being safe and non-toxic in rabbits (according to FDA recommendations) — may be responsible for simvastatin anti-inflammatory and anti-oxidative effects contributing to inhibition of atherogenesis. In addition, Lorusso et al. [5] demonstrated that atorvastatin significantly attenuates post-mitotic structural degeneration of artificial valve bovine pericardial tissue that was subcutaneously implanted in mice. In conclusion, based on personal data concerning the aortic valve and ascending/descending aorta in hypercholesterolemic rabbits, we support the beneficial impact of simvastatin in inhibition of hypercholesterolemia-induced atherosclerosis in rabbits.

References


eComment: Statins may not prevent structural valve degeneration of aortic bioprosthetic valves, but should probably be prescribed to patients undergoing heart valve surgery nonetheless

Authors: Kosmas I. Paraskevas, Department of Vascular Surgery, Red Cross Hospital, 24 Al. Papagou Street, 14122 Athens, Greece; Dimitri P. Mikhailidis
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Based on a hypothetical clinical scenario, Gilmanov et al. [1] performed an extensive review of the literature to address the question, whether statins slow the calcification/degeneration of aortic bioprosthetic valves. The authors correctly concluded that ‘even though the data is conflicting, statin therapy does not prevent structural valve degeneration (SVD) of bioprosthetic valves in the aortic position’ [1]. Certain issues may need to be clarified to avoid any possible misunderstandings.

Even if statins do not prevent SVD of aortic bioprosthetic valves, they are not prevented in patients undergoing cardiac valve replacement [2]. Firstly, statins improve renal function [2]. Renal dysfunction is a strong predictor of mortality in patients undergoing valve surgery [2]; thus, statins may influence mortality rates following valve surgery in this indirect way. Secondly, postoperative atrial fibrillation is a common complication following cardiac surgery and is associated with considerable morbidity including stroke, ventricular arrhythmias, heart failure, myocardial infarction, prolonged hospital stay, as well as short- and long-term mortality [3]. High-dose statin administration successfully reduces the incidence of postoperative atrial fibrillation [3]. Thirdly, there is evidence suggesting that preoperative statin use is associated with a reduction in the patients’ odds of developing a postoperative infection following cardiac surgery [4]. Finally, a large (n=3829 patients; 1044 statin users; 2785 statin non-users), eight-year retrospective study on patients undergoing cardiac surgery concluded that statin use is associated with improved postoperative mortality and morbidity rates in these patients [5].

In conclusion, although the data regarding this issue is indeed conflicting, it may be misleading to conclude that statins do not prevent SVD and should therefore not be prescribed to patients undergoing aortic bioprosthetic valve replacement [1]. Due to their pleiotropic effects [2–5], statins should be prescribed to these patients, whether they prevent SVD or not. Ideally, statins should be employed preoperatively [4, 5]. However, statin treatment is associated with several beneficial actions in patients undergoing heart valve surgery even if initiated postoperatively [2]. Thus, routine statin use in patients undergoing heart valve surgery should probably be recommended.

References