Are statins effective in preventing bioprosthetic aortic valve failure? A need for a prospective, randomized trial

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Since the first successful human valve replacements were performed more than four decades ago, a wide variety of prostheses, including mechanical, biological and human tissue prostheses, became available for clinical use. However, none of the currently available prosthetic heart valves approach the normal human valve in terms of hemodynamic function and/or freedom from valve-related complications. Mechanical valves have a greater long-term durability and provide a satisfactory hemodynamic function, but are thrombogenic and require permanent anticoagulation with the risk of hemorrhagic complications[1,2]. In contrast, bioprosthetic valves have a low thrombogenicity and usually do not require anticoagulation. This reduces the risk of bleeding; however, bioprosthetic valves have the propensity to undergo structural degeneration limiting their durability and often necessitating reoperation, with increased morbidity and mortality. For these reasons, bioprostheses are generally preferred in old patients, while mechanical valves are chosen in younger ones. The choice in the individual patient is all the same difficult.

Nowadays, aortic valve replacement is one of the most often performed cardiac surgery procedures in the developed world and the proportion of tissue valves used in the aortic position may reach 70% in patients > 70 years[3,4]. Moreover, with the aging of the general population, the number of patients requiring aortic valve replacement has rapidly increased over the last years and, given the increased age at implantation, the proportion of biological prostheses is also increasing. Therefore, a medical treatment able to significantly reduce bioprosthetic aortic valve degeneration would have an important clinical and socio-economic impact.

It has recently been suggested that statins might reduce the progression of mild and moderate aortic valve stenosis[5-7].

Farivar and Cohn[8] have recently demonstrated in a retrospective cohort study that hypercholesterolemia is a risk factor for bioprosthetic valve calcification and explantation. Similar results were found by Nollert et al.[9]. In these two studies both aortic and mitral bioprostheses were evaluated, but the role of statin treatment was not specifically addressed. On the other hand, David and Ivanov[10], analyzing two large databases from Stanford University and Toronto General Hospital, did not confirm a role of hyperlipidemia in predicting freedom from reoperation after aortic valve replacement with bioprosthetic valves. However, the authors could not exclude the hypothesis that the probability of valve failure in patients with risk factors for atherosclerosis was reduced because most of them were taking statins. Nevertheless, a direct role of statin treatment in slowing down the degeneration of bioprosthetic valves has not been previously demonstrated.

Our group has recently suggested, for the first time, a possible positive effect of statin treatment on the progression of bioprosthetic aortic valve degeneration[11]. In order to assess whether statins play a role in slowing down the degeneration of bioprosthetic aortic valves, we have retrospectively selected, from our 15-year database

(1988-2002), all the patients with bioprosthetic aortic valves having at least two echocardiographic examinations at least 6 months apart. There were 167 patients (97 men, 70 women, mean age 71 ± 9 years at the first examination), followed-up for 46 ± 38 months. During follow-up, 22 patients (13%) were treated with statins, while 145 (87%) were not. There were no differences between the two groups regarding age, gender, follow-up duration, baseline peak aortic velocity, mean gradient, effective orifice area, degree of aortic regurgitation, and left ventricular ejection fraction. The prevalence of systemic hypertension and diabetes was also similar in both groups. As expected, statin-treated patients had a significantly higher prevalence of documented hypercholesterolemia, proven coronary artery disease, and associated coronary artery bypass surgery ($p < 0.001$ for each). There were no significant differences between the two groups in prosthetic size, or prosthetic type (stented vs stentless, or porcine vs pericardial valves). Three different statins were used in the statin group. The agents used, the number of patients and the mean daily dosage were: simvastatin, 11 patients, 11 ± 5 mg; pravastatin, 7 patients, 19 ± 4 mg; atorvastatin, 4 patients, 14 ± 5 mg. The annual rate of increase in the peak prosthetic velocity (0.038 ± 0.074 vs 0.140 ± 0.228 m/s/year, $p < 0.001$) was lower in statin-treated patients. The annual rates of decrease in the prosthetic effective orifice area (0.031 ± 0.052 vs 0.100 ± 0.150 cm^2/year) and indexed effective orifice area (0.019 ± 0.031 vs 0.056 ± 0.086 cm^2/m^2/year) were also lower in statin-treated patients ($p < 0.001$ for both). Worsening of aortic regurgitation was found in 2/22 patients (9.1%) in the statin group and in 48/145 (33.1%) of controls ($p = 0.022$). The existence of either a rate of increase in peak velocity ≥ 0.3 m/s/year or of a worsening in aortic regurgitation ≥ 1/3 degree was found in 2/22 (9.1%) of statin-treated and in 63/145 (43.4%) of non-treated patients ($p = 0.002$) (odds ratio with statin treatment 0.13; 95% confidence interval 0.03-0.58). The overall annual rate of progression of the peak prosthetic velocity was similar between porcine and pericardial valves and between stented and stentless valves. The only factor associated with the progression of bioprosthetic aortic valve failure was statin treatment. During follow-up, there was no difference in major clinical event occurrence between the two groups. There were 25 deaths and 3 aortic reoperations for bioprosthetic degeneration in the non-statin group (19%), compared to 3 deaths and no reoperations in the statin group (14%) ($p = 0.73$). No significant adverse effects of statin treatment were recorded during follow-up. Our study is the first one to provide evidence that statin treatment is associated with significantly less bioprosthetic aortic valve failure, opening a new field for clinical research.

The major limitations related to bioprostheses are, indeed, the increased incidences of structural valve deterioration and of reoperation with their related consequences, including mortality. Factors responsible for calcification and degeneration of valvular bioprostheses may be valve-related and patient-related. The two large randomized trials with a long-term follow-up comparing patient outcomes with the use of a mechanical valve (Bjork-Shiley tilting disk) and a porcine valve (Hancock or Carpentier-Edwards) showed a significantly higher reoperation rate with the porcine valve vs the mechanical valve[1,2]. Importantly, the rate of structural valve deterioration of bioprosthetic aortic valves is related to the age of patient at the time of implantation. Younger patients were more likely to require reoperation: the relative risk of reoperation increased by 55% for each decade[1]. Recently, Puvimanasinghe et al.[12], estimated, using a mathematical microsimulation model, the lifetime risk of a reoperation or of a valve-related event after aortic valve replacement and found an inverse correlation with age at the time of implantation. Of all the valve-related events, changes in structural valve deterioration had the largest influence on the event-free life expectancy. In our study, the two groups were similar regarding age at the time of implantation.

The mechanism of the early formation of calcific deposits in heart valves is not known, but most likely, the formation of calcific deposits proceeds through the nucleation and growth of precursors. Tomazic et al.[13] compared the physicochemical properties of calcific deposits on natural diseased heart valves with those formed on or in bioprosthetic heart valves and showed that natural valve calcific deposits have a higher crystallinity and a lower solubility. The authors propose that the formation of calcific deposits proceeds through a similar mechanism regardless of site. The main strategy for preventing the calcific deterioration of bioprosthetic heart valves would be the development of locally applied inhibitors that suppress the nucleation and growth of soluble precursors and inhibit augmentation of less soluble calcific deposits. Two other studies performed in rat models[14,15] underscored the potential role of the pre-implantation methods of fixation and treatment of the bioprosthetic valve in achieving better long-term results in terms of bioprosthetic degeneration.

Current data show that pericardial valves are probably superior to porcine valves for aortic valve replacement[16,17]. Except for this difference, there is no hard evidence that, in patients with similar characteristics at baseline, outcomes are better with newer than with older bioprosthetic aortic valves. At present, all porcine valves have substantially similar rates of structural valve deterioration[18]. In our study, the majority of patients had a porcine aortic valve, and there were more stented than stentless valves. On the other hand, there were no differences regarding the proportion of porcine vs pericardial prostheses, or that of stented vs stentless valves in the two groups.

In the last years some studies, conducted both in animal models and in humans, addressed the question re-

garding the role of lipid-lowering treatment in the progression of aortic valve stenosis. Several studies suggested that atherosclerosis and aortic valve stenosis could be different manifestations of the same disease[19-22]. In a cholesterol-fed rabbit model, hypercholesterolemia induced atherosclerotic-like lesions in the aortic valve, and atorvastatin reduced the degree of structural changes in the aortic valve[23]. Furthermore, over the last years, a number of retrospective, non-randomized studies reported a reduced rate of progression of mild or moderate aortic stenosis in human native valves with statin therapy[5-7]. Other studies[24,25], using electron beam computed tomography, demonstrated a significantly decreased rate of aortic valve calcium accumulation in patients treated with statins. These results are remarkably similar in suggesting that statin treatment could slow the rate of progression of native aortic valve stenosis. The possible mechanism of the benefit of statin treatment in slowing down this degenerative process has not yet been clarified. The correlation between lipid levels and the progression of aortic stenosis is very controversial. Two studies[5,24] found a significant correlation, while other studies[6,7] showed a lack of any correlation between lipid levels and the progression of this process. The intriguing hypothesis that the benefit of statin treatment in slowing the progression of aortic stenosis could be due to their anti-inflammatory properties remains speculative. The mechanism of the benefit of statin treatment in biological prostheses is not clear, but we may speculate that it could be similar to that responsible for the beneficial effect of these drugs in slowing down the progression of native aortic valve stenosis.

Martinez-Gonzalez and Badimon[26] showed that human and porcine smooth muscle cells share a similar proliferation dependence on the mevalonate pathway, inhibited by statin treatment. They concluded that the porcine model closely resembles the human model and that it is suitable for testing *in vivo* new treatment strategies. More recently, the same authors showed a positive effect of statin treatment on the vessel wall expression of a protein involved in the progression of atherosclerosis in a hypercholesterolemic porcine model[27]. This could explain, in part, a similar positive effect of statins in human and porcine valves.

As aortic valve prostheses most often behave hemodynamically like a mildly stenotic native valve, the pattern of flow through the valve is similar in these two situations. This mechanistic similarity of the hydrodynamic patterns could provide another explanation for a similar benefit of statin treatment in both native and bioprosthetic aortic valves. On the other hand, statins exhibit pleiotropic effects over and above lipid lowering, including anti-inflammatory, effects[28] with a reduction of C-reactive protein independent of lipid changes[29]. They retard extraosseous calcifications, as for coronary vessels[30], and decrease native aortic valve calcium accumulation[24,25]. Of note, the doses used in statin-treated patients in our study were relatively low compared to the currently used dosages, reflecting the prescribing habits at the time of enrollment. Because of the submaximal doses, the actual effect of statins may have been underestimated. It is also noteworthy that statin-treated patients had a reduced progression of bioprosthetic degeneration despite a higher risk profile for progression (hypercholesterolemia, coronary artery disease and associated coronary artery bypass surgery were significantly more prevalent in the statin-treated group).

Our recent study, which showed a positive effect of statins in slowing down bioprosthetic degeneration has, however, several limitations: it is a retrospective, non-randomized study in a limited number of patients. The number of patients on statins is small, and this is explained by the study period starting back in 1988 and reflects the prescription habits during the tested time-interval. Given the small number of patients with different types of bioprostheses on statins, a meaningful subgroup analysis of the differences in outcome between different types of biological prostheses was not possible. Because of the retrospective nature of the study and because of the inclusion period, complete information regarding the patients' lipid profile was not available. Therefore, we could not test for a relation between the changes in lipid profile and bioprosthetic aortic valve degeneration, and so the mechanism of the benefit of statin treatment in this setting remains speculative.

In conclusion, our study suggests, for the first time, that treatment with statins is associated with significantly less degeneration of bioprosthetic aortic valves. This is concordant with the recent observations on a possible effect of hypercholesterolemia in the degenerative process of bioprosthetic valves[8,9]. On the other hand, statins may also be effective because of their anti-inflammatory or pleiotropic properties. The large number of patients carrying an aortic valve bioprosthesis and the inherent high morbidity of these valves, accounted for mainly by structural degeneration, underscore the importance of a possible medical therapy aimed at slowing down the degenerative process. This could influence the type of aortic valve prosthesis chosen in patients requiring aortic valve replacement and could ultimately have important socio-economic and clinical consequences, allowing implantation of biological prostheses in younger patients. Further studies and in particular a large prospective, randomized trial are needed to ultimately assess whether statins prevent bioprosthetic valve failure.

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