Abstract

**Objective:** Bioprosthesis structural valve deterioration (SVD) is an incompletely understood process involving the accumulation of calcium and lipids. Whether this process could be delayed with lipid-lowering therapy (LLT) is currently unknown. The purpose of this observational study was to evaluate if an association exists between early LLT and a slowing of bioprosthesis SVD, with a view to designing a prospective trial. **Methods:** We followed 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). Of these patients, 150 received LLT (including statins) early after surgery. Prosthetic valve haemodynamics on echocardiography and freedom from re-operation for SVD were compared between patients who did and did not receive postoperative LLT. **Results:** After bioprosthetic implantation, the progression of peak and mean trans-prosthetic gradients during echocardiographic follow-up (mean 3.3 years) was equivalent between patients treated with and without LLT (peak increase: 0.9 ± 7.7 vs 1.1 ± 10.9 mmHg, LLT vs no LLT, \( P = 0.87 \); mean increase: 0.8 ± 4.1 vs 0.2 ± 5.9 mmHg, LLT vs no LLT, \( P = 0.38 \)). The annualised linear rate of gradient progression following valve replacement was also similar between groups (peak increase per year: 2.0 ± 12.1 vs 1.0 ± 12.9 mmHg per year, LLT vs no LLT, \( P = 0.52 \); mean increase per year: 0.5 ± 2.2 vs 0.6 ± 6.0 mmHg per year, LLT vs no LLT, \( P = 0.94 \)). The incidence of mild or greater aortic insufficiency on the most recent echocardiogram was comparable (16.3% vs 13.8%, LLT vs no LLT, \( P = 0.44 \)), and there was no difference in the 10-year freedom from re-operation for SVD between the two groups [98.9% (95% confidence interval (CI): 91.9%, 99.8%) vs 95.4% (95% CI 90.5%, 97.9%), LLT vs no LLT, \( P = 0.72 \)]. **Conclusions:** In this observational study, there was no association demonstrated between early postoperative LLT and a slowing of bioprosthesis SVD. With the excellent durability of bioprostheses in the current era, a prospective randomised trial of statin therapy to prevent bioprosthetic SVD does not appear to be justified, let alone feasible. © 2009 European Association for Cardio-Thoracic Surgery. Published by Elsevier B.V. All rights reserved.

Keywords: Aortic valve replacement; Bioprosthesis; Re-operation; Echocardiography; Lipid-lowering therapy

1. Introduction

Bioprosthesis structural valve deterioration (SVD) is an incompletely understood process involving the accumulation of calcium and lipids and the weakening of collagen within prosthesis leaflet tissue [1–3]. Thought to be inflammatory-mediated, several studies have documented the presence of lipids and monocytes in the cusps of explanted bioprosthetic valves [1–3]. Depending on the age of the patient, bioprostheses fail 10–15 years after implantation due to cuspal calcification and leaflet tearing, leading to either prosthetic valve stenosis or regurgitation [4]. Hyperlipidaemia purportedly influences the progression of native aortic stenosis [5]. Similarly, there has been a suggestion that elevated lipid levels may influence bioprosthetic valve degeneration [6–9]. It is currently unknown if the process of SVD could be delayed with lipid-lowering therapy (LLT). Intuitively, through their anti-inflammatory and pleiotropic properties, the initiation of cholesterol-reducing agents early after bioprosthetic valve implantation may lessen the inflammatory response and possibly retard leaflet accumulation of calcium and lipids. With a view to designing a randomised controlled trial, the goal of the current study was to determine the sample size and feasibility of such a study using prospectively collected observational data. We assessed whether an association existed between early LLT and a slowing of bioprosthesis SVD within a large series of patients followed with periodic echocardiography after bioprosthetic aortic valve replacement (AVR).
2. Methods

2.1. Patient population and follow-up

This study retrospectively examined a cohort of patients (N = 1193) who were followed prospectively after bioprosthetic AVR at the University of Ottawa Heart Institute between 1990 and 2006. All patients were 18 years or older and survived to hospital discharge. Patients who received prostheses that are no longer commercially available (i.e., Ionescu–Shiley valve) were excluded. Following surgery, at the discretion of their treating physicians, LLT was initiated prior to hospital discharge in 150 patients for the management of hyperlipidaemia or coronary artery disease.

Preoperative, operative and postoperative data were collected prospectively on all patients. Reported cholesterol levels reflect those measured preoperatively or the first measurement documented in the postoperative period. Following valve replacement, patients were assessed 6 months postoperatively and thereafter on an annual basis by a physician in a dedicated valve clinic. At each visit, patients underwent a medical history focussed on the determination of functional status and the occurrence of valve-related complications, a physical examination, electrocardiogram, chest radiograph, complete blood count, serum chemistries and international normalised ratio determinations when applicable. All patients were followed for at least one outpatient visit. Outcomes data, including freedom from re-operation for SVD [10], were available on all patients. The total follow-up for the entire cohort was 5306 patient years (mean 4.5 ± 3.1 years; maximum 17.3 years). The methods of the valve clinic follow-up have been reviewed and approved by the University of Ottawa Heart Institute Human Research Ethics Board. Prior to 2004, a waiver of consent was granted by the Board. Since 2004, all valve clinic patients have provided explicit, fully informed consent for enrollment.

2.2. Echocardiograms

Baseline M-mode, two-dimensional and Doppler trans-thoracic echocardiograms were performed either prior to discharge or within 3 months of surgery for 959 (80.4%) patients in this study. Echocardiography was thereafter repeated as clinically indicated. Measurements were documented from the M-mode recordings as per the recommendations of the American Society of Echocardiography [11], including peak and mean trans-prosthetic gradients. Annualised change in peak and mean gradient (mmHg per year) was calculated by dividing the difference between the first and last measurements by the time between examinations. Trans-prosthetic regurgitation was graded semi-quantitatively using colour Doppler echocardiography according to the following scale: 0, none; 1, mild; 2, moderate; and 3, severe. The incidence of mild or greater prosthetic valve regurgitation on the most recent echocardiogram was reported for each study group. Paravalvular leaks were not considered as evidence of bioprosthesis SVD and were excluded from the analysis of prosthetic valve regurgitation.

2.3. Statistical analyses

2.3.1. Clinical outcomes

Data were analysed in Intercooled Stata 9.2 (Stata, College Station, TX, USA). Prosthesis haemodynamics and clinical outcomes were compared between patients who did and did not receive early postoperative LLT following AVR. Continuous data are presented as a mean ± standard deviation and are compared between groups using unpaired two-sided Student’s t-tests for normally distributed data and Wilcoxon rank-sum tests for non-parametric data. Categorical data are presented as proportions and are compared between groups using a Fisher’s exact test. Statistical significance was set at a P value of <0.05. Non-parametric estimates of freedom from re-operation for SVD were determined using the Kaplan–Meier method and are reported as means with 95% confidence intervals (CIs).

2.3.2. Multivariate analyses

Since several factors differed between patients who did and did not receive LLT, multivariate analysis was performed to adjust for potential confounders. Predictors of re-operation for SVD were determined with multivariate Cox proportional hazards models. Predictors of trans-prosthetic gradient progression were determined with multivariate linear regression. Multivariate models were developed by incorporating variables that had a P value of 0.20 or less on univariate testing. Stepwise forward selection and backward elimination techniques were employed with P = 0.20 for entry and removal criteria. Early LLT and risk factors for SVD that have been previously identified [4,12] were considered in each model, in addition to factors that differed between study groups. Hazard ratios (HRs) are reported along with 95% CI.

2.3.3. Additional analyses

To further evaluate the potential relationship between LLT and SVD, we repeated the analyses by focussing only on the use of statin medications early after surgery. Additional analyses focussed on each type of bioprosthetic valve individually. We also evaluated the incidence of prosthetic valve dysfunction during follow-up using two previously published definitions. Applying the methods of Otto et al. [13] and Briand et al. [6], prosthetic valve deterioration was defined as either a rate of increase in mean gradient ≥3 mmHg per year or ≥1/3" worsening of valve regurgitation. Alternatively, prosthetic valve deterioration was defined as an increase in the peak velocity ≥0.3 m s$^{-1}$ per year or worsening of valve regurgitation of ≥1/3", as per Antonini-Canterin et al. [9].

3. Results

3.1. Patient characteristics

The preoperative and operative characteristics of the patients treated with and without early LLT are presented in Table 1. Patients treated with LLT had higher body mass indices (P = 0.005), had a greater incidence of diabetes mellitus (P = 0.002) and cigarette smoking (P = 0.03), and
more often required concomitant coronary artery bypass graft surgery ($P = 0.0003$). Low-density lipoprotein (LDL) cholesterol and total cholesterol levels were lower, albeit not significantly so, among patients treated with LLT. The most common medications prescribed for lipid reduction were atorvastatin (48.7%) and simvastatin (20.7%). Baseline and operative factors that differed between the groups with a $P$ value $<0.20$ were considered in each of the multivariate models to adjust for potential confounders.

3.2. Echocardiographic follow-up

Echocardiographic data were available for 126 patients treated with LLT (out of 150, 84.0%) and 833 patients not treated with LLT (out of 1043, 79.9%). The duration between the first and the most recent echocardiogram was 3.3 $\pm$ 2.6 years. After bioprosthetic valve implantation, the progression of peak trans-prosthetic gradients during follow-up was equivalent between patients treated with and without LLT (peak increase: $0.9 \pm 7.7$ vs $1.1 \pm 10.9$ mmHg, LLT vs no LLT, $P = 0.87$). The annualised linear rate of peak gradient progression after AVR was also similar between groups (peak increase per year: $2.0 \pm 12.1$ vs $1.0 \pm 12.9$ mmHg per year, LLT vs no LLT, $P = 0.52$). Similarly, the progression of mean gradients was equivalent between the two groups (mean increase: $0.8 \pm 4.1$ vs $0.2 \pm 5.9$ mmHg, LLT vs no LLT, $P = 0.38$), and the annualised linear rate of mean gradient progression was similar (mean increase per year: $0.5 \pm 2.2$ vs $0.6 \pm 6.0$ mmHg per year, LLT vs no LLT, $P = 0.94$). On multivariate linear regression, older age at surgery was associated with less progression of trans-prosthetic aortic gradients ($P = 0.01$ for mean gradient, $P = 0.1$ for peak gradient). After controlling for confounders, there was no association between LLT or cholesterol levels and aortic gradient progression. With respect to prosthetic valve regurgitation, the incidence of mild or greater aortic regurgitation on the most recent echocardiogram was comparable between the two groups (16.3% vs 13.8%, LLT vs no LLT, $P = 0.44$).

3.3. Freedom from structural valve deterioration

After AVR, freedom from re-operation for SVD amongst patients treated with LLT at 1, 5 and 10 years was 100% (95%
CI: 100—100%), 98.9% (95% CI: 91.9—99.8%) and 98.9% (95% CI: 91.9—99.8%), respectively. Freedom from SVD amongst the patients who did not receive LLT at 1, 5 and 10 years was 99.9% (95% CI: 99.3—100.0%), 99.6% (95% CI: 98.7—99.9%) and 95.4% (95% CI: 90.5—97.9%), respectively. On univariate analysis, there was no difference in the rate of SVD re-operation between the two groups (HR 1.5; 95% CI: 0.2—11.6; \( P = 0.72 \); Fig. 1). Older age at the time of surgery was associated with a lower aortic re-operation rate (HR 0.9 per year of age; 95% CI: 0.9—1.0; \( P < 0.001 \)) in the multivariate analysis. After controlling for confounders, there was no association between LLT or cholesterol levels and freedom from re-operation for SVD (\( P = \text{NS} \)).

3.4. Additional analysis

To further evaluate the potential relationship between LLT and SVD, the analyses reported above were repeated, focussing only on the use or non-use of statin medications early after surgery. This yielded nearly identical results, with no difference with regard to trans-prosthetic gradient progression between patients who did or did not receive postoperative statins (all \( P = \text{NS} \)). Comparable results were obtained when each type of prosthesis was evaluated separately. Using the methods of Otto et al. [13] and Briand et al. [6], the incidence of prosthetic valve deterioration during follow-up was similar between patients treated with or without LLT (10.6% vs 8.7%, LLT vs no LLT, \( P = 0.43 \)). Similarly, applying the definition of Antonini-Canterin et al. [9], the incidence of prosthetic valve deterioration was also similar (10.7% vs 8.7%, LLT vs no LLT, \( P = 0.43 \); Fig. 2).

4. Discussion

SVD is the most frequent indication for re-operation in patients with tissue valves [4]. Depending on the age of the patient, 30—50% of bioprostheses will fail 10—15 years after implantation. Bioprosthetic valves are known to undergo a time-dependent process of structural failure secondary to stress-related tears, perforations or dystrophic calcifications. Similar to the process of atherosclerosis, explanted bioprostheses demonstrate accumulation of lipids, inflammatory cells and calcium [1—3]. Whether the modification of atherosclerotic risk factors, such as the use of LLT, alters the natural history of bioprosthesis SVD is not currently known.

Previous studies have suggested that elevated lipid levels may be associated with faster progression of bioprosthesis SVD [6—8]. Intuitively, initiating cholesterol-lowering medications such as statins early after bioprosthetic implantation would appear to be a reasonable therapeutic option to delay the development of prosthetic valve calcification and SVD. The objective of the current study was to determine the feasibility of designing a randomised controlled trial of LLT and SVD by analysing prospectively collected observational data. We assessed whether an association existed between early LLT and a slowing of SVD within a cohort of patients followed with periodic echocardiography after the implantation of contemporary aortic bioprostheses. Our analysis revealed that: (1) LLT was not associated with a reduction in trans-prosthetic gradient progression or regurgitant deterioration after AVR, either on univariate analysis or after adjusting for confounders in multivariate analysis; (2) freedom from re-operation for SVD 10 years after bioprosthetic AVR using contemporary valves is greater than 95%; and (3) early LLT did not lower the need for SVD re-operation after bioprosthetic AVR. Thus, the initiation of early LLT after valve implantation does not appear to reduce the development of bioprosthesis SVD. Indeed, non-treated patients had a lower rate of peak gradient progression, but the difference was not statistically significant.

Statins have clearly been shown to reduce cardiovascular events and mortality in patients with coronary and cerebrovascular disease [14,15]. Recent attention, however, has focussed on the anti-inflammatory and pleiotropic effects of statins. With their ability to stabilise or reduce
atherosclerosis burden, statins have been proposed as a therapeutic modality for the treatment of native aortic valve stenosis, an active disease process similar to that of atherosclerosis [5,13]. Numerous observational studies have documented the effect of hyperlipidaemia on the progression of native aortic stenosis, resulting in lipoprotein deposition, chronic inflammation and active calcification of the valve [5]. Treating hyperlipidaemia with statins has been linked with a slowing of native aortic stenosis in retrospective observational studies [5,16], and in vitro data have suggested that statins could inhibit the calcification process of native aortic valves [17]. This led to the design of several large prospective trials to evaluate the impact of statins on the progression of native aortic stenosis. One prospective non-randomised trial demonstrated a slowing of native aortic stenosis with the use of rosuvastatin [18]. However, two randomised placebo-controlled trials using either atorvastatin or simvastatin/ezetimibe found that LLT did not slow or reverse the progression of calcific native aortic stenosis [19,20].

Similar to the interest in hyperlipidaemia and native aortic stenosis, the impact of lipids on the structural failure of bioprostheses has also been the subject of recent investigation. Nollert et al. assessed the influence of atherosclerotic risk factors on the degeneration of the aortic Hancock pericardial bioprosthesis, a valve that has since been removed from the market due to its early structural failure. Within a younger subgroup of their 161-patient cohort, independent risk factors associated with the need for re-operation included a history of smoking, diabetes mellitus and hyperlipidaemia [8]. Farivar and Cohn also evaluated the impact of hypercholesterolaemia on the risk of bioprosthetic valve calcification and the need for re-operation. They identified higher cholesterol levels to be independently associated with greater bioprosthetic calcification. In a case—control portion of their study, they found that patients who had their valves explanted had higher serum cholesterol levels compared to a control group of patients who did not require re-operation [7]. Most recently, Briand et al. showed that patients with aortic bioprostheses who had metabolic syndrome developed a faster progression of trans-prosthesis gradients and more prosthetic valve regurgitation as compared with patients who did not have metabolic syndrome [6]. In contrast to the studies listed above, those from Toronto, Stanford, and the Cleveland Clinic have reported the opposite results, with no association found between hyperlipidaemia and either SVD or the need for re-operation [21,22].

Statins have been proposed as a treatment to decrease bioprosthetic degeneration through their pleiotropic and anti-inflammatory properties and their ability to decrease C-reactive protein levels [2]. To date, only one small observational study has evaluated the impact of LLT on the structural failure of bioprostheses. Antonini-Canterin et al. compared serial echocardiograms in 22 patients treated with statin medication to 145 patients who did not receive statins after tissue AVR [9]. All patients had at least two echocardiograms more than 6 months apart between 1988 and 2002. According to the authors, patients who received statins had less progression of bioprosthetic degeneration, including a slower increase in trans-prosthetic gradients, a slower decline in effective orifice area and less worsening of aortic regurgitation. A combined parameter of prosthetic degeneration progression, defined as the existence of either an annular rate of increase in peak velocity of $>$0.3 m s$^{-1}$ per year or worsening aortic regurgitation more than 1/3, occurred in 9.1% of patients taking statins compared with 43.4% of patients not taking statins ($P = 0.002$). In contrast, when we applied the same definition in our study, we found the incidence of prosthetic valve deterioration to be similar between patients treated with or without LLT after AVR (10.7% vs 8.7%, LLT vs no LLT, $P = 0.43$) [9]. The study by Antonini-Canterin et al. was limited in its incomplete description of the types of the bioprostheses used and the duration between implantation and echocardiographic evaluation. It is possible that older prostheses that have since been withdrawn from the market (such as the Hancock or Ionescu—Shiley pericardial valves) may have been included in their study, particularly within the non-statin group that likely represented a historical control. In contrast to the findings of Antonini-Canterin et al., the current study and that of Briand et al. [6] found that statins are not associated with slowing of bioprosthesis degeneration

No significant differences between the two groups were found in the evaluation of SVD in this study. Nevertheless, we acknowledge that our data cannot confirm that no difference actually exists. Given the over-lapping confidence intervals however, and the large standard deviations for the study endpoints, if differences were apparent (with either a larger sample size or longer follow-up), we doubt that it would be of great clinical relevance. With no trend in favour of LLT, we believe that a prospective randomised trial of statin therapy to prevent bioprosthetic SVD does not appear to be justified. Bioprostheses have excellent durability in the current era, and therefore a prospective study evaluating LLT and SVD could only be possible with the collection of more than 10 years of follow-up data and the recruitment of hundreds (if not thousands) of patients. In our view, such a trial cannot practically be completed.

4.1. Limitations

This study sought to assess the feasibility of performing a randomised controlled trial of LLT and SVD by analysing prospectively collected observational data. Patients were treated with LLT at the discretion of their treating physicians, and thus bias is an inherent limitation of the analysis. Nevertheless, we did control for group differences and known confounders using multivariate analysis. Because LLT has been in use for only 15 years, and bioprostheses take 10–15 years to fail, our follow-up duration may simply have been too short to assess the impact of LLT on the outcome of re-operation. That being said, we did not find any trend in favour of LLT and a reduced need for re-operation, and we thoroughly evaluated the potential relationship between LLT and SVD using several echocardiographic outcomes. Baseline cholesterol levels were not associated with SVD in this study. However, serial cholesterol levels were not measured in this cohort of patients, impairing our ability to assess the influence of varying lipid levels on the progression of SVD. Data were also not available regarding the use of LLT prior to surgery.
Finally, our data do not allow for an evaluation of the long-term adherence to LLT or the impact of LLT administration late after hospital discharge. Nevertheless, we believe this limitation is mitigated for three reasons. First, previous research has shown that patients who initiate cholesterol-lowering medication prior to hospital discharge after a cardiovascular event have the highest adherence rates to therapy [23,24], suggesting (although we cannot confirm) a high compliance rate within the LLT group in this study. Second, we have previously documented that LLT prescription rates increase only slightly in the months that follow discharge after cardiac surgery [15,25], implying that only a few non-treated patients in this study would ultimately receive LLT late after AVR. Finally, it is our belief that if LLT were to retard the development of bioprosthetic SVD, then such a benefit would have been evident with its administration early after surgery. No such reduction in SVD was seen in this study.

5. Conclusions

In patients undergoing AVR with currently available bioprostheses, there was no association between LLT initiated in the early postoperative period and the progression of trans-prosthetic gradients or the incidence of structural failure. With the excellent durability of bioprostheses in the current era, a prospective randomised trial of statin therapy to prevent bioprosthetic SVD does not appear to be justified, let alone feasible, given the duration that such a study would require.

Acknowledgment

The authors thank Linda Morrow and Mary Thomson for their continued assistance with the organisation of the valve clinic, and Michel Asselin and Brian Asselin in the collection of data for the purpose of this study.

References