

Preoperative Cholesterol Levels do not Predict Explant for Structural Valve Deterioration in Patients Undergoing Bioprosthetic Aortic Valve Replacement

Christian N. Gring¹, Penny Houghtaling², Gian M. Novaro³, Eric Roselli², Nicholas Smedira², Michael Banbury², Eugene Blackstone², Brian P. Griffin¹

Departments of ¹Cardiovascular Medicine and ²Cardio-Thoracic Surgery, Cleveland Clinic Foundation, Cleveland, Ohio, ³Department of Cardiology, Cleveland Clinic Florida, Weston, Florida, USA

Background and aim of the study: Structural valve deterioration (SVD) is the most common cause of bioprosthetic valve failure. Coronary disease risk factors, including hypercholesterolemia, might predict SVD. Here, the relationship was examined between preoperative cholesterol levels and SVD in patients undergoing bioprosthetic aortic valve replacement (AVR).

Methods: A total of 7,150 patients (mean age 68 ± 12 years) was identified who underwent bioprosthetic AVR at the Cleveland Clinic Foundation, between January 1975 and December 2002. Preoperative and postoperative variables were retrieved from a prospective, computerized database. A parametric method was used to estimate the distribution of valve explants; a multivariable risk factor model was then developed to include patient demographics, cardiac and non-cardiac comorbidities, valve type and interactions. The primary end-point was explant for SVD. All explants were examined, and observations were censored at the time of any explant or death.

Bioprosthetic valves have been used with great success for mitral and aortic valve replacements since the early 1970s. Long-term follow up has shown that bioprosthetic valves compare favorably with mechanical valves in terms of endocarditis risk, thromboembolic events and valve thrombosis (1). The main drawback of bioprostheses has been structural valve deterioration (SVD), which results in calcification, leaflet perforation and dehiscence from struts, and ultimately valve failure with stenosis or regurgitation.

Despite over 30 years of experience with biopros-

thetic valves, very little is known about modifiable risk factors for SVD. Large patient series have consistently shown that valve position and patient age have a profound effect on valve survival. Bioprostheses in younger patients have markedly shorter lifespans, and 15-year freedom from SVD ranges from 37 to 76% for aortic valves, whilst that for mitral valves ranges from 30 to 47% (2-5).

Results: Among 7,150 patients, 208 had explants for SVD. Mean preoperative total cholesterol (TC) was 203 ± 48 mg/dl, HDL-cholesterol 45 ± 15 mg/dl, and LDL-cholesterol 121 ± 41 mg/dl. The average follow up was 3.7 years, and 1,169 patients (16%) were followed for more than eight years. In multivariable analysis, only younger age ($p < 0.0001$), greater body weight ($p < 0.0001$), 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 $p = 0.19$). Moreover, no cardiovascular risk factors were predictive of SVD.

Conclusion: Preoperative cholesterol levels do not predict SVD in patients undergoing bioprosthetic AVR. Whether long-term hypercholesterolemia or statin therapy impacts SVD requires further investigation.

The Journal of Heart Valve Disease 2006;15:261-268

Presented as an abstract at the American Heart Association Scientific Sessions, November 6th-11th, New Orleans, 2004

Address for correspondence:
Brian P. Griffin, Department of Cardiology, Cleveland Clinic Foundation, Desk F15, 9500 Euclid Avenue, Cleveland, OH 44195, USA
e-mail: griffib@ccf.org

The pathology of SVD has been examined in detail, and has led to speculation that it might share risk factors with atherosclerosis. The basis for this hypothesis stems from common histopathologic features of SVD, native valve aortic stenosis (AS) and coronary artery disease (CAD). The hallmark of SVD is leaflet calcification, which correlates with duration of implant (6). Histologically, SVD is characterized by an inflammatory cellular infiltrate, as well as amyloid and cholesterol deposits. The calcification ultimately disrupts the collagen matrix of the valve, and phagocytic destruction

of the collagen fibrils has been described (7). Deteriorated valves have also been found to have a high content of collagenase, matrix metalloprotease and glucuronidase enzymes - all of which are secreted by macrophages - and this reinforces the potential role of inflammatory cell-mediated degeneration (8). Interestingly, the features of lipid deposition, collagen fiber disruption, inflammatory cellular infiltrates and tissue mineralization parallel native valve AS, which in turn, has been linked with CAD (9).

The results of several clinical studies have suggested that coronary risk factors, including hypercholesterolemia, accelerate the progression of AS (10-12). Additional investigations, using serial echocardiography, have indicated that statins attenuate AS progression (13,14). In light of the parallels between SVD and native valve AS, recent studies have focused on potential links between SVD and atherosclerotic risk factors, and in particular on hypercholesterolemia (15-17). The results of these investigations have varied: two studies reported that hypercholesterolemia increased the risk of SVD (16,17), whilst study one refuted these findings (15). The present authors' institution performs a high volume of bioprosthetic aortic valve replacements (AVR). Thus, the study aim was to identify risk factors for SVD; specifically, it was hypothesized that preoperative cholesterol levels might be associated with an increased occurrence of SVD.

Clinical material and methods

Patient population

Patients who underwent primary or redo cardiac valve surgery and received a bioprosthetic aortic valve between January 1975 and December 2002 at the Cleveland Clinic Foundation were identified using the institution's computerized, prospective cardiovascular surgery database. This database has been approved for research by the institutional review board. Patients having concomitant bioprosthetic mitral valve replacement surgery were excluded. In total, 7,150 AVRs were performed during this time period; of these, 4,833 were stented bovine pericardial valves, 1,456 were stented porcine xenografts, and 853 were homografts (eight valves had unknown serial numbers, and therefore were of unknown type).

The database incorporated systematic follow up on all valve operations at two-year intervals. All cases of valve explant were carefully reviewed through examination of the operative records, intraoperative echocardiographic data and, when necessary, pathologic data. Follow up data were available on all but 16 patients. The mean follow up period was 3.7 years (range: 1 day to 24 years); 16% of the patients (n = 1,169) were followed for more than eight years.

Clinical data

Preoperative, operative and postoperative variables were retrieved from the database, and are listed in Table I. Demographic variables included age, gender and body mass of patients. The mean patient age at valve implant was 68 ± 12 years, and 69% of the patients were male. Additionally, data were collected on concomitant cardiovascular disease, including CAD, valvular dysfunction and left ventricular ejection fraction. Non-cardiac variables included tobacco use, peripheral vascular disease, diabetes, hypertension and renal dysfunction (see Appendix I).

Preoperative cholesterol data

Preoperative cholesterol data were available for 5,063 patients. High-density lipoprotein (HDL)-cholesterol values were available in 3,740 patients and low-density lipoprotein (LDL)-cholesterol was recorded for 3,354. The total cholesterol (TC) data were analyzed both as a continuous measure and by tertiles (<180, 180-220 and >220 mg/dl). Additionally, the TC:HDL-cholesterol ratio was examined, because this variable has been associated with native valve AS progression (18).

End-points

The primary end-point of the study was explant for SVD.

Statistical analysis

For all valves, unadjusted bioprosthetic valve survival (freedom from explant for SVD) was estimated using the non-parametric Kaplan-Meier method. Observations were censored at the time of explant for any reason other than SVD or patient death. A parametric method was used to obtain the number of phases for the instantaneous risk of explant (hazard function) and to estimate its shaping parameters (19). To identify factors associated with SVD, a multivariable risk factor model was developed using a directed stepwise technique. Variables included in this analysis are detailed in Appendix I. Bootstrap random resampling was used to validate the model (20).

A rigorous investigation for possible interactions between variables was performed. Interactions with age and preoperative cholesterol level were investigated because it is known that SVD is linked to younger age, and younger persons may tend to have higher lipids. The impact of valve type on the time course of events was also closely scrutinized. Additionally, interactions between preoperative cholesterol and gender, age, type of valve, coronary disease, and other factors were investigated, as were the effects of valve type and age.

For patients with missing values of TC, HDL- and LDL-cholesterol, mean value imputation was used.

Missing value flags were constructed and retained in the final model. To ensure proper calibration of variables with time to event, possible transformations of scale were considered for ordinal and continuous variables.

All statistical analyses were performed using SAS® version 8.2.

Results

Risk factors for SVD

Baseline patient characteristics are listed in Table I. During the study period, 319 valves were explanted, with 208 valve explants for SVD. A total of 1,748 patient deaths was recorded prior to valve explant,

Table I: Baseline characteristics for aortic bioprosthesis patients and for patients undergoing explant for structural valve deterioration.

Characteristic	All patients* (n = 7150)	Explants for SVD* (n = 208)
Demography		
Age (years)*	68.0 ± 12.4	54.9 ± 12.7
Height (cm)*	169.6 ± 10.6 (n = 6813)	172.6 ± 8.8 (n = 170)
Bodyweight (kg)*	79.0 ± 16.4 (n = 6807)	82.3 ± 13.9 (n = 168)
Male gender	4828 (69)	165 (79)
Non-cardiac characteristics		
Diabetes	1059/6769 (16)	10/180 (6)
Peripheral vascular disease	2561/7148 (36)	19/207 (9)
Smoking history	3552/6891 (63)	71/187 (38)
Hypertension	4201/6688 (63)	77/168 (46)
Preop. serum creatinine (mg/dl)*	1.24 ± 1.0	1.7 ± 2.2
Emergency surgery	105 (1.5)	1 (0.5)
NYHA functional class		
I	1092 (15)	41 (20)
II	3796 (53)	126 (61)
III	1599 (22)	30 (14)
IV	658 (9)	10 (5)
History of myocardial infarction	1889 (26)	29 (14)
Left ventricular dysfunction		
Normal/none	2274 (53)	105 (53)
Mild	775 (18)	39 (20)
Moderate	778 (18)	38 (19)
Severe	466 (11)	17 (8)
Not recorded	2857	9
Coronary artery disease (≥50%)		
Left main trunk	648 (9)	3 (1.5)
LAD coronary artery	2961 (43)	44 (21)
Left circumflex coronary artery	2476 (36)	38 (18)
Right coronary artery	2725 (40)	42 (20)
Number of diseased vessels		
0	2999 (44)	140 (68)
1	1128 (16)	25 (12)
2	1186 (17)	21 (10)
3	1554 (23)	19 (9)
Operative procedure		
CABG	3381 (47)	65 (31)
Mitral valve repair	682 (9)	13 (6)
Bovine pericardial bioprosthesis	4833 (68)	64 (31)
Porcine bioprosthesis	1456 (20)	121 (58)
Homograft bioprosthesis	853 (12)	23 (11)

*Values are mean ± SD.

*Values in parentheses are percentages of respective column totals.

CABG: Coronary artery bypass graft; LAD: Left anterior descending.

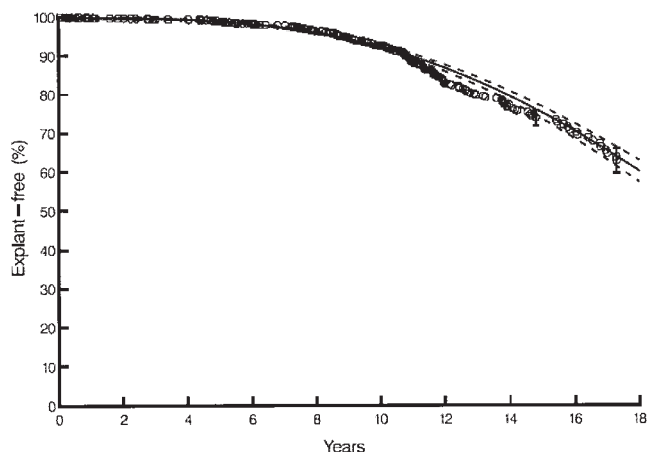


Figure 1: Unadjusted freedom from structural valve deterioration (SVD). Each circle represents one event, and is positioned according to the Kaplan-Meier estimate. Vertical bars are asymmetric 68% confidence intervals (± 1 SE). The solid line is the parametric estimate enclosed within the dashed 68% confidence limits. Numbers of patients at risk at five, 10 and 15 years were 1952, 748 and 261, respectively.

whilst there were 1,864 deaths over the entire study period. Freedom from explant for SVD at five, 10 and 15 years was 99%, 93% and 74%, respectively (Fig. 1). The hazard function for SVD explant resolved to two phases; an early phase, which accounted for 16 events, was observed during the first two years after valve implant, while a late phase contained the other 192 events (Fig. 2). Multivariable model results show that there were no significant risk factors for explant during the early phase. In the later phase, only younger patient age ($p < 0.0001$), preoperative serum creatinine

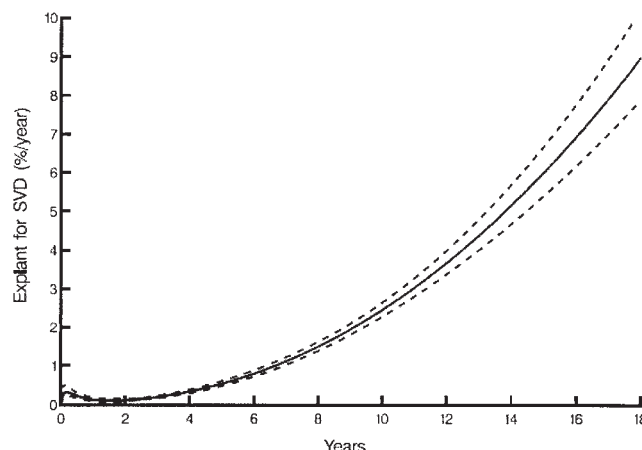


Figure 2: Hazard function for valve explant for structural valve deterioration (SVD). The solid line is the parametric estimate enclosed within the dashed 68% confidence limits.

level ($p = 0.0005$), body weight (elevated weight-to-height ratio, $p < 0.0001$) and the use of bovine pericardial valves ($p = 0.04$) were risk factors for SVD (Table III).

Effects of lipids on SVD

Preoperative TC values were recorded for 5,063 patients, and 90% of these were measured within six months of surgery. The mean preoperative TC level was 203 ± 48 mg/dl. HDL-cholesterol values were available for 3,740 patients (mean 45 ± 15 mg/dl), and LDL-cholesterol values were recorded in 3,354 patients (mean 121 ± 41 mg/dl). Selected patient characteristics by preoperative TC tertile are listed in Table II.

Table II: Baseline patient characteristics by preoperative total cholesterol tertile.

Characteristic	Cholesterol (mg/dl)		
	<180 (n = 1651)	180-220 (n = 1696)	>220 (n = 1716)
Demography			
Age (years)			
Mean*	68 \pm 13	68 \pm 12	67 \pm 11
Median	71.7	70	69
Height (cm)*	171 \pm 10	170 \pm 10	168 \pm 10
Weight (kg)*	80 \pm 16	80 \pm 16	78 \pm 16
Operative procedure			
Coronary artery bypass graft	780 (47)	773 (46)	828 (48)
Mitral valve repair	229 (14)	127 (7)	107 (6)
Bovine pericardial bioprosthesis	1225 (74)	1101 (65)	1024 (60)
Porcine bioprosthesis	216 (13)	405 (24)	549 (32)
Homograft bioprosthesis	209 (13)	188 (11)	140 (8)

*Values are mean \pm SD.

+Values in parentheses are percentages.

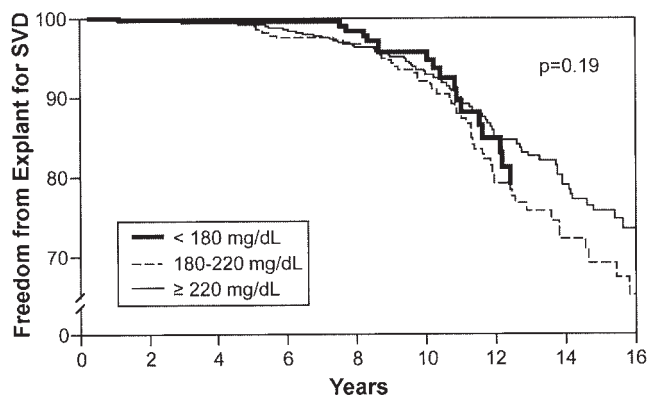


Figure 3: Freedom from structural valve deterioration (SVD) by total cholesterol tertile.

No lipid variable significantly impacted upon the development of SVD in any type of bioprosthetic valve. Preoperative TC, whether analyzed as a continuous variable or by tertile, did not predict explant for SVD (Fig. 3). Similarly, neither HDL- nor LDL-cholesterol, nor the TC:HDL-cholesterol ratio impacted upon freedom from SVD. No interactions were found between preoperative cholesterol level and any bioprosthetic valve type, including homografts; neither were there any interactions between cholesterol and age or other atherosclerotic risk factors.

Effects of CAD and CAD risk factors on SVD

Coronary artery disease and CAD risk factors were prevalent in this patient population. Coronary disease (>50% stenosis) was found in 56% of patients, and 23% had three-vessel disease. At the time of valve surgery, 47% of patients underwent concomitant coronary artery bypass surgery. Additionally, 26% had a history of myocardial infarction. With respect to coronary risk factors, 16% of patients had diabetes, 36% had peripheral vascular disease, 63% were current or past smokers, and 63% were hypertensive.

Neither CAD nor the need for bypass surgery conferred any additional risk for SVD. Likewise, no ather-

osclerotic disease risk factor increased the likelihood of SVD. These findings were true, regardless of prosthetic valve type.

The effect of statins on SVD

The present database did not contain information on patient medication use, and particularly on hexamethyl-glutaryl co-enzyme A (HMG-CoA) reductase inhibitors (statins). Nevertheless, an attempt was made to infer indirectly data on the impact of statin therapy on SVD. The results of the Scandinavian Simvastatin Survival Study (4S) were published in 1994, after which time statin use became the standard of care for patients with CAD. As previously noted, neither the presence of CAD nor the need for coronary bypass surgery altered a patient's risk of SVD. These data were re-analyzed in two groups - pre- and post-1994 - with the assumption being made that patients who received bypass surgery after the release of 4S data would have a higher likelihood of receiving statin therapy. However, no effect of preoperative cholesterol level, concomitant CAD or bypass surgery, regardless of the time period examined, could be demonstrated.

Discussion

In the present study, preoperative cholesterol levels did not impact upon valve failure due to SVD. Only an elevated body weight:height ratio, elevated serum creatinine level, use of pericardial valves and age were predictive of SVD. The impact of age on SVD has been very well described in almost all studies that have examined the long-term durability of bioprostheses. Similarly, the association between renal insufficiency and valve degeneration has been well described previously (21,22). The present authors are not aware of any prior studies that have associated an increased body mass with valve degeneration. Nonetheless, such an association is plausible on a pathophysiologic basis, because increased body mass correlates with increased cardiac output, and this may lead to accelerated valvular deterioration.

In the present study, neither the need for coronary bypass surgery at the time of valve implant nor any conventional atherosclerotic risk factor was associated

Table III: Incremental risk factors for explant for structural valve deterioration.

Risk factor (Late phase)	Estimate	SE	p-value
Younger age ⁺	-0.52	0.06	<0.0001
Preop serum creatinine	0.24	0.07	0.0005
Weight/height ratio	4.8	1.1	<0.0001
Bovine pericardial valve	0.33	0.16	0.04

⁺Exponential transformation of age, (age/50)⁴.

with a higher risk of SVD. Prior studies have shown that bypass surgery at the time of valve replacement is associated with higher late mortality (23), but that concomitant coronary artery bypass grafting is also protective against SVD and extends the life of bioprosthetic valves (24). No association was found between hyperlipidemia, hypertension, tobacco abuse or diabetes and SVD.

Three recently reported smaller studies have examined hyperlipidemia and other CAD risk factors in the setting of bioprosthetic valve deterioration, although the results of these investigations have varied. Farivar and Cohn (16) retrospectively examined the relationship between hypercholesterolemia and SVD in a cohort of 144 patients, and found that cholesterol correlated with prosthetic valve calcification levels. In a separate case-control analysis of 66 explanted valves, a high preoperative cholesterol level was predictive of explantation for SVD, irrespective of statin use (16). Hypertension, diabetes and tobacco abuse were not predictive of explant. Nollert et al. (17) examined 90 patients without significant CAD who underwent reoperation for SVD. Among younger patients (aged <57 years), diabetes, female gender, tobacco use and elevated preoperative TC level were all associated with SVD in a multivariable analysis. In patients aged over 57 years, none of these risk factors was associated with SVD. Finally, Antonini-Canterin et al. (15) conducted an echocardiographic study of patients with aortic valve bioprostheses, and found that statin use was protective against SVD; preoperative cholesterol levels, however, were not associated with valve deterioration.

There are several key differences between the present findings and those of prior studies. First, both Farivar and Cohn (16) and Nollert et al. (17) linked cholesterol levels to SVD. Although Nollert et al. also used preoperative cholesterol levels, Farivar and Cohn averaged TC values monitored after the valve had been implanted. Second, in the analysis by Nollert et al., there was an interaction between age and lipids, and thus the data analysis was stratified by patient age. Only in the younger group (aged <57 years) was SVD associated with lipids and other atherosclerotic risk factors. In the present study, no evidence was found of any interaction between age and lipids on SVD. The mean age of the present patient group was 68 years, and there was no influence of CAD risk factors on the need for subsequent AVR. In addition, there were no data available to evaluate directly the impact of statin use on SVD. However, when time was analyzed as a continuous variable no association was found between year of implant, preoperative cholesterol and SVD. Additionally, the data from pre- and post-1994 groups were evaluated, with the assumption

being made that statin use should have been much more prevalent after the publication of the 4S Trial in 1994, especially in patients with CAD. However, no difference could be shown in SVD between the two groups, irrespective of any CAD history, need for bypass surgery or preoperative cholesterol level.

Study limitations

Among study limitations, the primary drawback was that the data, although prospectively collected, were extracted from a large clinical database. As with any database research, there are inherent limitations on data availability and analysis. A second limitation was that the cholesterol data were restricted to preoperative values only. Clearly, a single preoperative value cannot be equated with steady-state postoperative lipid levels, and thus it is possible that long-term hyperlipidemia during the postoperative period might have some effect on SVD. In addition, a substantial minority of patients had missing preoperative cholesterol values, though attempts were made statistically to compensate for missing values. A third limitation was that data on medication use were not available. For the purpose of this study, data on statin therapy would have been valuable. The most important limitation was that SVD is a time-related process, not an event. However, few data were available on the development of SVD; thus, explant for SVD was used as a hard end-point. Such an end-point is, however, subject to physician and surgeon bias, to patient tolerance of gradually diminishing valve function, and to the probability of death with or from unrecognized SVD. Few autopsies were available to investigate the latter possibility.

Nonetheless, the present study had several notable strengths. First, an unselected cohort of patients was studied who received a bioprosthetic AVR, and observations at the time of patient death or valve explant were censored for reasons other than SVD. This provided a more clinically relevant evaluation of the impact of lipids on SVD. In addition, it avoided any biases associated with the establishment of a cohort of patients who had already experienced the end-point of interest. A second strength was that, with the inclusion of 7,150 patients in total and 208 cases of explant for SVD, the study was substantially larger than any prior research in this area. Third, a rigorous multivariable analysis was carried out and multiple potential interactions examined between lipid levels and age, valve type, gender and atherosclerotic risk factors.

In conclusion, these data provide compelling evidence that argues against a link between preoperative cholesterol and bioprosthetic SVD. In this respect, the data differ from the findings of Farivar, Nollert and col-

leagues. Moreover, the data also run counter to recent data linking native valve AS and atherosclerotic disease. As noted above, these differences in data could be related to methodologic disparities - for example the use of preoperative versus postoperative cholesterol values. However, consideration must also be given that the pathological effect of preoperative cholesterol on native valves and bioprosthetic valves may differ. Although native valve AS and bioprosthetic SVD share several histologic features, these may be two distinct pathophysiologic processes. AS, like CAD, occurs in live, cellular and dynamic tissue. In contrast, implanted valves are, at baseline, acellular; even homografts, which structurally should be most like native valves, lose their normal structure and cellularity after implantation (25). Because of the fundamental difference between native and bioprosthetic valves, it is quite possible that the factors which precipitate native valve calcific AS are different from those that lead to inflammatory infiltrates and dystrophic calcification in prosthetic valves.

References

1. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: Final report of the Veterans Affairs randomized trial. *J Am Coll Cardiol* 2000;36:1152-1158
2. Cohn LH, Collins JJ, Jr., DiSesa VJ, et al. Fifteen-year experience with 1678 Hancock porcine bioprosthetic heart valve replacements. *Ann Surg* 1989;210:435-442; discussion 442-443
3. Magilligan DJ, Jr., Lewis JW, Jr., Stein P, Alam M. The porcine bioprosthetic heart valve: Experience at 15 years. *Ann Thorac Surg* 1989;48:324-329; discussion 330
4. Edwards TJ, Livesey SA, Simpson IA, Monro JL, Ross JK. Biological valves beyond fifteen years: The Wessex experience. *Ann Thorac Surg* 1995;60:S211-S215
5. Jones EL, Weintraub WS, Craver JM, et al. Ten-year experience with the porcine bioprosthetic valve: Interrelationship of valve survival and patient survival in 1,050 valve replacements. *Ann Thorac Surg* 1990;49:370-383; discussion 383-384
6. Schoen FJ, Hobson CE. Anatomic analysis of removed prosthetic heart valves: Causes of failure of 33 mechanical valves and 58 bioprostheses, 1980 to 1983. *Hum Pathol* 1985;16:549-559
7. Grabenwoger M, Grimm M, Eybl E, et al. New aspects of the degeneration of bioprosthetic heart valves after long-term implantation. *J Thorac Cardiovasc Surg* 1992;104:14-21
8. Simionescu A, Simionescu D, Deac R. Biochemical pathways of tissue degeneration in bioprosthetic cardiac valves. The role of matrix metalloproteinases. *Am Soc Artif Intern Organs J* 1996;42:M561-M567
9. Otto CM, Kuusisto J, Reichenbach DD, Gown AM, O'Brien KD. Characterization of the early lesion of 'degenerative' valvular aortic stenosis. Histological and immunohistochemical studies. *Circulation* 1994;90:844-853
10. Aronow WS, Ahn C, Kronzon I, Goldman ME. Association of coronary risk factors and use of statins with progression of mild valvular aortic stenosis in older persons. *Am J Cardiol* 2001;88:693-695
11. Ngo MV, Gottdiener JS, Fletcher RD, Fernicola DJ, Gersh BJ. Smoking and obesity are associated with the progression of aortic stenosis. *Am J Geriatr Cardiol* 2001;10:86-90
12. Pohle K, Maffert R, Ropers D, et al. Progression of aortic valve calcification: Association with coronary atherosclerosis and cardiovascular risk factors. *Circulation* 2001;104:1927-1932
13. Bellamy MF, Pellikka PA, Klarich KW, Tajik AJ, Enriquez-Sarano M. Association of cholesterol levels, hydroxymethylglutaryl coenzyme-A reductase inhibitor treatment, and progression of aortic stenosis in the community. *J Am Coll Cardiol* 2002;40:1723-1730
14. Novaro GM, Tiong IY, Pearce GL, Lauer MS, Sprecher DL, Griffin BP. Effect of hydroxymethylglutaryl coenzyme a reductase inhibitors on the progression of calcific aortic stenosis. *Circulation* 2001;104:2205-2209
15. Antonini-Canterin F, Zuppiroli A, Popescu BA, et al. Effect of statins on the progression of bioprosthetic aortic valve degeneration. *Am J Cardiol* 2003;92:1479-1482
16. Farivar RS, Cohn LH. Hypercholesterolemia is a risk factor for bioprosthetic valve calcification and explantation. *J Thorac Cardiovasc Surg* 2003;126:969-975
17. Nollert G, Miksch J, Kreuzer E, Reichart B. Risk factors for atherosclerosis and the degeneration of pericardial valves after aortic valve replacement. *J Thorac Cardiovasc Surg* 2003;126:965-968
18. Yilmaz MB, Guray U, Guray Y, et al. Lipid profile of patients with aortic stenosis might be predictive of rate of progression. *Am Heart J* 2004;147:915-918
19. Blackstone EH, Naftel DC, Turner MEJ. The decomposition of time-varying hazard into phases, each incorporating a separate stream of concomitant information. *J Am Statist Assoc* 1986;81:615-624
20. Breiman L. Bagging predictors. *Machine Learning* 1996;24:123-140
21. Fann JJ, Miller DC, Moore KA, et al. Twenty-year

- clinical experience with porcine bioprostheses. *Ann Thorac Surg* 1996;62:1301-1311; discussion 1311-1312
22. Akins CW, Hilgenberg AD, Vlahakes GJ, MacGillivray TE, Torchiana DF, Madsen JC. Results of bioprosthetic versus mechanical aortic valve replacement performed with concomitant coronary artery bypass grafting. *Ann Thorac Surg* 2002;74:1098-1106
23. Cohen G, David TE, Ivanov J, Armstrong S, Feindel CM. The impact of age, coronary artery disease, and cardiac comorbidity on late survival after bioprosthetic aortic valve replacement. *J Thorac Cardiovasc Surg* 1999;117:273-284
24. Angell WW, Pupello DF, Bessone LN, et al. Influence of coronary artery disease on structural deterioration of porcine bioprostheses. *Ann Thorac Surg* 1995;60:S276-S281
25. Schoen FJ, Levy RJ. Pathology of substitute heart valves: New concepts and developments. *J Card Surg* 1994;9:222-227

*Appendix I: Variables considered in analyses.**

Demography: gender, age (years), weight (kg), height (cm), body surface area (m²), body mass index
Symptoms: NYHA class, Canadian angina class, emergency surgery
Left ventricular (LV) function: grade of LV dysfunction, history of myocardial infarction, LV ejection fraction from catheterization
Valve pathology: aortic valve regurgitation, aortic valve stenosis, mitral valve regurgitation, mitral valve stenosis, pulmonary valve regurgitation, pulmonary valve stenosis, tricuspid valve regurgitation, tricuspid valve stenosis
Cardiac comorbidity: family history of CAD, preoperative atrial fibrillation, ventricular arrhythmia, complete heart block/pacer, history of endocarditis, history of cardiac surgery
Non-cardiac comorbidity: history of smoking, peripheral vascular disease, chronic pulmonary disease, carotid disease, popliteal disease, pharmacologically treated diabetes, insulin-dependent diabetes, hypertension, renal disease, creatinine, cholesterol, HDL, LDL, triglycerides, blood urea nitrogen, bilirubin, hematocrit
Coronary anatomy: left main trunk, left anterior descending coronary artery, right coronary artery, and left circumflex coronary artery coronary system disease (% maximal diameter reduction, presence of >50% and >70% stenosis), number of diseased systems (>50% criteria)
Operative procedure: coronary artery bypass grafting, concomitant mitral valve repair or replacement, tricuspid valve repair or replacement, type of bioprosthesis inserted (homograft, stented porcine valve, stented bovine pericardial)
Experience: date of operation (number of years since January 1975)
Interactions: age with diabetes and valve type; preoperative cholesterol with age, CAD, smoking, diabetes, gender, date of surgery, valve type, preoperative atrial fibrillation

*These are the primary variables that were considered; however several derived variables were also investigated and used in the analyses (i.e. transformations and groupings of these primary variables for main effects and interaction terms).