Performance of bioprostheses and mechanical prostheses assessed by composites of valve-related complications to 15 years after aortic valve replacement

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Objective: This study was conducted to compare the composites of valve-related complications, namely reoperation, morbidity (defined as permanent neurologic or other functional impairment), and mortality, between bioprostheses and mechanical prostheses for aortic valve replacement.

Methods: Between 1982 and 1998, 2195 bioprostheses were implanted in 2179 patients and 980 mechanical prostheses were implanted in 883 patients. Total follow-up was 16,442 years and 5740 years for bioprostheses and mechanical prostheses, respectively. Eight variables were considered as predictors of risk for the composites of valve-related complications.

Results: Linearized rates for valve-related reoperation were 1.3%/patient-year and 0.3%/patient-year for bioprostheses and mechanical prostheses ($P < .001$), respectively. All age groups were differentiated, except >70 years. Valve-related morbidity was differentiated for all age groups and overall, for bioprostheses and mechanical prostheses, was 0.4 %/patient-year and 2.1%/patient-year, respectively ($P < .001$). Overall valve-related mortality was 1.0%/patient-year for bioprostheses and 0.7%/patient-year for mechanical prostheses ($P = .018$). Age and valve-type were predictive risk factors for reoperation and morbidity, whereas age alone was predictive of mortality. Actual freedom from valve-related reoperation favored mechanical prostheses for all age groups, except 61-70 years and >70 years. Actual freedom from valve-related morbidity favored bioprostheses in all age groups, except ≤ 40 years. Actual freedom from valve-related mortality was undifferentiated in patients 51-60, 61-70, and >70 years.

Conclusion: No differences were observed in valve-related reoperation and mortality in patients >60 years. Comparative evaluation gives high priority for bioprostheses in patients >60 years based on improved morbidity profile. This evaluation extends this center's recommendation for bioprostheses in aortic valve replacement to include patients >60 years.

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The long-term performance of bioprostheses and mechanical prostheses for aortic and mitral valve replacement has been evaluated by two large randomized control studies.¹⁻⁴ These studies evaluated survival and valve-related complications. Little is known regarding the performance of biologic and mechanical valves in terms of composites of complications, namely valve-related reoperation, valve-related morbidity, and valve-related mortality, which are important to the patient. Only one study in the literature thus far has used actual and actuarial methods to evaluate composites of valve-related complications in bioprostheses and mechanical prostheses. Jamieson and colleagues⁵ recently published their results concerning mitral valve replacement. This study will evaluate valve-related

Abbreviations and Acronyms

BP group = bioprosthesis group

MP group = mechanical prosthesis group

reoperation, valve-related morbidity (defined as permanent neurologic or other functional impairment), and valve-related mortality for aortic valve replacement.

Methods

Between 1982 and 1998, a total of 2195 bioprostheses were implanted in 2179 patients and a total of 980 mechanical prostheses were implanted in 883 patients. Patients considered for this study had not undergone previous cardiac surgery procedures. Cumulative follow-ups for the bioprosthesis (BP) and mechanical prosthesis (MP) groups were 16,442.1 years and 5740.3 years, respectively. Average follow-ups in years for the BP and MP groups were $7.5\% \pm 4.7\%$ and $5.9\% \pm 3.3\%$ ($P < .001$), respectively. Concomitant coronary revascularization was performed in 43.5% of the initial operations of BP patients and 26.0% of MP patients. The male/female proportions for the BP and MP groups were 64.5:35.5 and 70.2:29.8, respectively. Mean patient age was greater in the biological group than in the mechanical group (BP $69.7\% \pm 10.6\%$ vs MP $58.2\% \pm 12.4\%$, $P < .001$).

During the 16-year period of this study, the following bioprostheses were used: Carpentier-Edwards SAV (Edwards Lifesciences, Irvine, Calif; $n = 1728$), Carpentier-Edwards Pericardial ($n = 299$), Medtronic Mosaic (Medtronic, Inc, Minneapolis, Minn; $n = 164$), and other ($n = 4$). The mechanical prostheses used during the study period were St Jude Medical (St Jude Medical Inc, Minneapolis, Minn; $n = 514$), CarboMedics (Sorin CarboMedics Inc, Austin, Tex, $n = 463$), and other ($n = 3$).

Follow-up Procedure

The patients in this study were followed up regularly through the University of British Columbia Cardiac Valve Database, with the closing interval in the year 2000-2001. Information was received through direct telephone interviews with patients and through review of medical records, including operative and consultation reports. Vital statistics death registry was also used to ensure completeness of mortality data.

Study End Points

The three study end points were valve-related mortality, valve-related morbidity, and valve-related reoperation. These composites of complications, including valve-related complications, were defined according to the "Guidelines for Reporting Morbidity and Mortality After Cardiac Valvular Operations."⁶ Valve-related mortality included death caused by structural valve deterioration, nonstructural dysfunction, thrombosis, thromboembolism, hemorrhage, or prosthetic valve endocarditis, and death related to reoperation for a valve-related complication. Valve-related mortality included sudden unexplained, unexpected deaths. Valve-related reoperation was reoperation for any valve-related complication. Valve-related morbidity was defined in this study as permanent valve-related impairment as a result of permanent neurologic or other functional

deficit caused by structural valve deterioration, nonstructural dysfunction, valve thrombosis, thromboembolism, hemorrhage, prosthetic valve endocarditis, or reoperation.

When a patient with a bioprosthetic valve underwent reoperation with a mechanical prosthesis, or vice versa, the patient was censored from the former group after 30 days and entered in the latter group. If the valve type did not change, the patient was kept in his or her original group. Operative mortality (30-day mortality) was attributed to the explanted valve and was subsequently used to calculate valve-related mortality. Patient survival was therefore not determined in this study, because a small portion of the patients were included in both study arms. Variables considered as predictors of risk for the composites of valve-related complications were prosthesis type, age (continuous and categorical variables), gender, prostheses size, and concomitant coronary revascularization. All patients undergoing initial cardiac operations between 1982 and 1998, as well as reoperation in 1999 to 2001, were included in this analysis.

Statistical Analysis

The baseline characteristics of the BP and MP groups were assessed by *t* tests for continuous variables and χ^2 for categorical variables. The freedom from the composites of valve-related complications, namely valve-related morbidity, valve-related mortality, and valve-related reoperation, was calculated by Kaplan-Meier actuarial methods and compared with the log-rank statistic. The actual freedom or cumulative incidence was determined by the modified Kaplan-Meier method described by Grunkemeier and colleagues.⁷⁻¹⁰ Composites of valve-related complications were also described with the use of linearized rates, which describe the number of events per 100 patient-years or percent per patient-year. Comparisons between linearized rates were made with the log-likelihood ratio. Linearized occurrence rates are not recommended for evaluation of structural valve deterioration and reoperation resulting from structural valve deterioration owing to an accelerating, rather than constant, hazard with time. The Weibull distribution curve is the appropriate statistic to describe structural valve deterioration and reoperation secondary to reoperation.⁷ Linearized rates were used to describe valve-related reoperation as it was inclusive of reoperation secondary to all causes, namely prosthetic valve endocarditis, nonstructural dysfunction, and prosthesis thrombosis in addition to structural valve deterioration. Predictors of risk of the composites of complications were determined by univariate and multivariate Cox hazard analysis.

Results

The linearized occurrence rates of the composites of valve-related complications are described in Table 1. Overall valve-related reoperation occurred at a rate of 1.3 events/100 patient-years and 0.3 events/100 patient-years for patients receiving bioprostheses (BP group) and mechanical prostheses (MP group), respectively ($P < .001$). The BP and MP groups were also differentiated for all age groups, except >70 years. In contrast to valve-related reoperation, overall valve-related morbidity favored the BP versus the MP group ($P < .001$). This was also significant for all age categories. Overall valve-related mortality for the BP and

TABLE 1. Linearized occurrence rates of composites of valve-related complications by age group

Age groups	VR reop (% censored)			VR morbidity (% censored)			VR mortality (% censored)		
	BP (%/pt-y)	MP (%/pt-y)	P value	BP (%/pt-y)	MP (%/pt-y)	P value	BP (%/pt-y)	MP (%/pt-y)	P value
≤40	5.5	0.3	<.001	0.0	0.8	.011	1.1	0.0	.003
41-50	4.3	0.6	<.001	0.0	1.3	<.001	0.8	0.5	.516
51-60	3.5	0.2	<.001	0.3	2.2	<.001	0.6	0.5	.646
61-70	1.0	0.3	<.001	0.4	2.7	<.001	1.0	1.1	.738
>70	0.2	0.0	.091	0.5	2.9	<.001	1.3	1.1	.712
Total	1.3	0.3	<.001	0.4	2.1	<.001	1.0	0.7	.018

VR, Valve-related; BP, bioprosthesis group; MP, mechanical prosthesis group; pt-y, patient-year.

MP groups were 1.0 events/100 patient-years and 0.7 events/100 patient-years, respectively ($P = .018$).

Predictors of risk for composites of valve-related complications are described in Table 2. Age and valve type were predictive of valve-related reoperation and morbidity, whereas age alone was predictive of valve-related mortality.

The freedom ($\pm$ SD) from composites of valve-related complications are detailed for actual and actuarial freedom to 15 years from valve-related reoperation, valve-related morbidity, and valve-related mortality in Figures 1 through 9 for age groups 51-60 years, 61-70 years, and >70 years. The actual freedom from valve-related reoperation in patients 51-60 years were $98.3\% \pm 0.9\%$ and $59.7\% \pm 3.7\%$ for the MP and BP groups, respectively (actuarial freedom, $98.1\% \pm 1.0\%$ for MP and $45.2\% \pm 4.9\%$ for BP, $P < .001$) (Figure 1). Fifteen-year actual freedom from reoperation in the 61-70-year age group was $89.4\% \pm 8.7\%$ for the MP group and $87.9\% \pm 1.8\%$ for the BP group, whereas actual freedom in the >70-year age group was 100 at 12 years for the MP group and $97.4\% \pm 0.7\%$ at 15 years for the BP group (Figures 2 and 3). Figures 2 and 3 also show that no significant difference was observed between the two valve groups in the 61-70-year age group and the >70-year age group by actuarial analysis.

The actual freedom from valve-related morbidity in patients 51-60, 61-70, and >70 years is described in Figures 4 to 6. Actual freedom from valve-related morbidity in patients 51-60 years was $97.8\% \pm 1.0\%$ for the BP group and $86.4\% \pm 2.3\%$ for the MP group (actuarial $85.4\% \pm 2.5\%$

for MP and $97.6\% \pm 1.1\%$ for BP, $P < .001$) (Figure 4). Actual freedom from morbidity also favored bioprostheses in the 61-70-year age group and the >70-year age group (Figures 5 and 6). Actual freedom for patients 61-70 years in the MP group was $84.4\% \pm 2.8\%$ at 15 years and $96.6\% \pm 0.8\%$ at 15 years for those in the BP group (Figure 5). Actual freedom from morbidity in patients >70 years was $86.9\% \pm 3.4\%$ for the MP group at 12 years and $95.9\% \pm 0.8\%$ for the BP group at 15 years (Figure 6).

Freedom from valve-related mortality for patients 51-60 years of age is described in Figure 7. Actual freedom to 15 years for the MP and BP groups were $94.9\% \pm 2.2\%$ and $93.2\% \pm 1.9\%$, respectively. Figure 7 also shows that no difference was observed between either valve type based on actuarial analysis. Figure 8 describes the freedom from valve-related mortality for patients 61-70 years. Fifteen-year actual freedom was $91.1\% \pm 2.4\%$ for the MP group and $88.3\% \pm 1.7\%$ for the BP group. Figure 9 shows that the 15-year actual freedom from valve-related mortality in patients >70 years was $96.0\% \pm 2.0\%$ at 12 years for the MP group and $87.9\% \pm 1.3\%$ at 15 years for the BP group. No difference in valve-related mortality was observed between valve types (Figures 8 and 9).

In total, this study describes 3175 cardiac valve replacements that were conducted on 3062 patients. There were 234 valve-related operations: 218 reoperations in the BP group and 16 in the MP group. The distributions by cause of first events for the BP group were nonstructural dysfunction, 40; prosthetic valve endocarditis, 28; structural valve dete-

TABLE 2. Predictive risk factors for composites of valve-related complications

	Reoperation		Morbidity		Mortality	
	HR*	P value	HR*	P value	HR*	P value
Age	0.95 (0.94-0.96)	<.001	1.03 (1.01-1.05)	<.001	1.04 (1.03-1.06)	<.001
Gender	1.04 (0.75-1.44)	.812	1.17 (0.80-1.70)	.438	0.91 (0.65-1.29)	.607
Valve type	0.22 (0.13-0.38)	<.001	6.57 (4.58-9.44)	<.001	1.00 (0.68-1.48)	.992
Size	1.04 (0.98-1.10)	.142	1.06 (0.98-1.14)	.151	1.01 (0.95-1.08)	.750
Concomitant CABG	0.87 (0.63-1.20)	.390	1.06 (0.80-1.50)	.727	1.13 (0.85-1.51)	.398

Baseline assumptions for dichotomous variables: gender, valve type, bioprostheses; concomitant coronary artery bypass graft (CABG). HR, Hazard ratio.

*The 95% confidence intervals for the hazard ratio are given in parentheses.

Figure 1. Freedom from valve-related reoperation in patients 51-60 years. BP, Bioprosthesis group; MP, mechanical prosthesis group.

rioration, 145; and thrombosis, 5. In the MP group, the distributions of first events were nonstructural dysfunction, 9; prosthetic valve endocarditis, 6; and thrombosis, 1.

There were 211 valve-related deaths in this study, 171 of which were observed in the BP group. Hemorrhage was described in 42 of these deaths: BP 27 and MP 15. In patients >70 years, 17 bleeding events occurred in the BP group whereas none were observed in the MP group. In patients 61-70 years, 7 bleeding events occurred in the BP group and 11 events occurred in the MP group. The distribution of first events also included nonstructural dysfunction (BP 3; MP 1), prosthetic valve endocarditis (BP 28; MP 2), structural valve deterioration (BP 29; MP 3), sudden unexpected death (BP 15; MP 7), and thromboembolism (BP 69; MP 12).

Discussion

There is little documentation comparing the long-term performances of bioprostheses versus mechanical prostheses to 15 years. Further, the literature comparing biologic and mechanical valves has largely focused on individual valve-related complications. There has been little documentation of composites of valve-related complications that are also clinically relevant. This study tracked the performance of

Figure 2. Freedom from valve-related reoperation in patients 61-70 years. BP, Bioprosthesis group; MP, mechanical prosthesis group.

Figure 3. Freedom from valve-related reoperation in patients >70 years. BP, Bioprosthesis group; MP, mechanical prosthesis group.

biologic and mechanical valves for use in aortic valve replacement to 15 years.

To summarize, this study found that linearized occurrence rates for valve-related reoperation favored mechanical valves, except in patients >70 years. Valve-related morbidity, defined as permanent neurologic or other functional impairment, favored bioprostheses for all age categories and overall valve-related mortality favored mechanical prostheses. Actual/actuarial freedom from these composites of valve-related complications revealed results similar to the linearized rates. Freedom from valve-related reoperation favored mechanical valves for all age groups to 15 years, except 61-70 years and >70 years. Fifteen-year freedom from valve-related morbidity favored biologic valves for all age groups, except in patients ≤40 years of age at operation. Freedom from valve-related mortality was undifferentiated between valve types to 15 years for patients 51-60, 61-70, and >70 years. Age and valve type were found to be predictive risk factors for valve-related reoperation and morbidity, whereas age alone was predictive of valve-related mortality.

The interpretation of these results is that biologic valves appear to be favorable in patients on the basis of the lower incidence of valve-related morbidity. Of course, biologic valves were associated with increased overall valve-related reoperation. Since no significant difference in reoperation was observed between the MP and BP groups in patients

Figure 4. Freedom from valve-related morbidity in patients 51-60 years. BP, Bioprosthesis group; MP, mechanical prosthesis group.

Figure 5. Freedom from valve-related morbidity in patients 61-70 years. BP, Bioprosthesis group; MP, mechanical prosthesis group.

61-70 years, biologic valves appear the clear preference for patients in this age group; they offer an improved morbidity profile while not sacrificing durability. Valve-related mortality was also undifferentiated between valve types in patients 61-70 years. In the 51-60-year age group, reoperation favored mechanical prostheses, yet no difference in valve-related mortality was observed between valve types. This is an important finding because patients in the sixth decade receiving biologic valves that are prone to valve-related reoperation did not have any increased risk of dying from that reoperation. In fact, patients receiving bioprostheses benefited from fewer valve-related morbid events that were defined as permanent neurologic or other functional impairment in this study.

The findings of this study are also consistent with work conducted by other researchers. There have been two large randomized trials to date comparing biologic and mechanical heart valves. Hammermeister and colleagues^{1,2} United States Veterans Affairs Study reported on 575 patients undergoing isolated aortic valve replacement or mitral valve replacement at 13 Veterans Affairs medical centers. Survival analysis at 15 years showed that all-cause mortality was lower with mechanical prostheses in the context of aortic valve replacement, but not mitral valve replacement. Biologic valves, whether implanted in the aortic or mitral position, were associated with significantly lower bleeding

Figure 6. Freedom from valve-related morbidity in patients >70 years. BP, Bioprosthesis group; MP, mechanical prosthesis group.

Figure 7. Freedom from valve-related mortality in patients 51-60 years. BP, Bioprosthesis group; MP, mechanical prosthesis group.

rates, but also more frequent cases of structural valve deterioration. The Edinburgh Trial^{3,4} evaluated over 530 patients receiving either a Björk-Shiley tilting disc valve or a porcine bioprosthesis. This study concluded that mechanical prostheses had improved survival over bioprostheses at 12 years, but not at 20 years after cardiac valve replacement. This was true for both aortic and mitral valve replacement. Mechanical prostheses were also found to be associated with a higher bleeding rate for both aortic and mitral valve replacement. Beyond these randomized trials, the consensus in the literature is that biologic valves tend to be associated with increased structural valve deterioration and reoperation, but lower bleeding and thromboembolic rates.¹¹⁻¹³

Prasongsukarn, Jamieson, and Lichtenstein¹⁴ recently compared mechanical and bioprosthetic valves in patients 61-70 years in terms of combined major thromboembolism and hemorrhage and valve-related reoperation. That study revealed no difference between biologic and mechanical valves in terms of valve-related reoperation and mortality. The 15-year actuarial freedom from reoperation of 85.8 for bioprostheses and 82.2 for mechanical prostheses were comparable with freedoms from reoperation of 77.5% ± 3.7% and 82.3% ± 15.0% for the BP and MP groups, respectively, in this study. Further, similar to this study, valve-related morbidity was significantly different between biologic and mechanical groups. Fifteen-year actuarial free-

Figure 8. Freedom from valve-related mortality in patients 61-70 years. BP, Bioprosthesis group; MP, mechanical prosthesis group.

Figure 9. Freedom from valve-related mortality in patients >70 years. BP, Bioprostheses group; MP, mechanical prostheses group.

dom from valve-related morbidity of 95.4% and 79.9% for bioprostheses and mechanical prostheses groups were also comparable with freedoms of $95.6\% \pm 1.1\%$ and $81.5\% \pm 3.7\%$ in this study.

Jamieson's group has also provided extensive documentation in regard to the indications for implantation of bioprostheses and mechanical prostheses. In separate studies, Tyers and colleagues¹⁵ have noted that patients with bioprostheses were more likely to require valve-related reoperation than were those with mechanical prostheses. But mortality from reoperation secondary to bioprosthetic aortic structural failure can be lowered by reoperation in patients with low, rather than medium to high, New York Heart Association functional class.¹⁶ The relevance of these observations to this study is that patients with biologic valves may have an increased risk of reoperation, but may not necessarily have any increased risk of mortality from that reoperation if closely monitored through a vigilant surveillance program. Concomitant revascularization procedures negatively influence survival in patients undergoing cardiac valve replacement.^{17,18} However, Jamieson's group¹⁹ has found that this is actually protective against structural valve deterioration since patients are more likely to die than to have structural failure. This study considered all causes leading to reoperation rather than simply reoperation resulting from structural valve deterioration alone.

Most recently, Jamieson and colleagues⁵ compared composites of valve-related complications in biologic and mechanical heart valves in terms of mitral valve replacement. In that report, 15-year freedom from valve-related reoperation differentiated bioprostheses and mechanical prostheses in patients 61-70 years, but not >70 years. Further, no difference was observed between valve types in terms of 15-year freedom from valve-related morbidity, whereas freedom from valve-related mortality was differentiated in patients 61-70 years. When compared with this study, clear differences exist in the rationale for biologic and mechanical valves in the setting of aortic and mitral replacement beyond age alone. In the case of mitral replacement, mor-

bidity was undifferentiated; thus reoperation and mortality were the major influences in determining >70 years as the recommended age. In the case of aortic valve replacement, no differences were observed in terms of mortality in patients 61-70 years whereas differences were observed in the morbidity profile; therefore morbidity was the most influential variable.

The main limitation of this study was that patient survival for the BP and MP groups was not calculated. The design of this study was such that patients undergoing reoperation with a different prosthesis were censored from the former group and entered into the latter group after 31 days. This precluded the calculation of survival because patients were included into both study arms. Further, the mean follow-up period for patients undergoing aortic valve replacement with a biologic valve was 7.5 years. Although this ranks among the longest series reported in the literature, some instances of structural valve deterioration may be missed, which may affect the incidence of reoperation and valve-related mortality.

Notwithstanding, this study compares the performance of biologic and mechanical valves to 15 years in terms of composites of valve-related complications. Biologic valves are favorable in patients in their seventh decade because they provide a superior morbidity profile, defined as permanent neurologic or other functional impairment, relative to mechanical valves. For the same age group, bioprostheses were undifferentiated in terms of valve-related reoperation and mortality, meaning that no compromise in durability or survival was observed with bioprostheses. Survival from reoperation can also be improved through early re-referral for operation when patients are in New York Heart Association class I/II. These findings not only affirm this center's previous recommendation for biologic valves for aortic valve replacement¹⁹⁻²¹ but extends this recommendation to possibly include patients >60 years of age.

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