

Medtronic Mosaic Porcine Bioprosthesis: Investigational Center Experience to Six Years

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Background and aim of the study: The findings of this single-center experience with the Medtronic Mosaic porcine bioprosthesis were evaluated to determine the clinical performance of the valve.

Methods: Between 1994 and 2000, a total of 657 patients was implanted with the prosthesis. Aortic valve replacement (AVR) was performed in 415 patients (mean age 70.5 ± 10.7 years; range: 26-89 years) and mitral valve replacement (MVR) in 242 patients (mean age 70.5 ± 9.5 years; range: 19-86 years). Concomitant coronary artery bypass (CAB) was performed in 51.1% and 46.7% of AVR and MVR patients, respectively. The majority of patients were aged over 70 years (59.8% AVR, 58.7% MVR).

Results: Survival at six years was $73.0 \pm 2.4\%$ after AVR, and $74.0 \pm 5\%$ after MVR ($p = \text{NS}$). Actual freedom from valve-related mortality at six years was $98 \pm 1\%$ for AVR and $96 \pm 1\%$ for MVR; freedom from overall thromboembolism (TE) was $86 \pm 3\%$ for AVR and $89 \pm 2\%$ for MVR. After AVR, 42 thromboembolic events occurred in 39 patients (23 minor; 14 major; three reversible ischemic neurologic deficits (RIND); two thrombosis). After AVR, the late TE rate was

2.1% per pt-yr, and the major rate 0.6% per pt-yr (exclusive of thrombosis). The overall TE rate after AVR was 2.9% per pt-yr (major rate 1% per pt-yr). After MVR, 25 events occurred in 24 patients (10 minor; eight major; five RIND; two thrombosis). After MVR, the late TE rate was 2.6% per pt-yr, and the major rate 0.7% per pt-yr (exclusive of thrombosis). The overall TE rate after MVR was 3.5% per pt-yr (major rate 1.1% per pt-yr). There were four cases of structural valve deterioration (SVD) (two each after AVR and MVR). Reoperation was performed in three of four cases of thrombosis, and in two of four cases of SVD.

Conclusion: The Medtronic Mosaic porcine bioprosthesis is safe and effective. The rate of SVD after six years was low, being zero in the aortic position of patients aged >60 years, and zero also in the mitral position of patients aged <60 years. The incidence of early and late thromboembolism was contributed to by the advanced age of the patient population.

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The Medtronic Mosaic porcine bioprosthesis is a third-generation biological prosthesis which was introduced in 1994 and uses advanced technology to address the altered durability of first- and second-generation porcine and pericardial bioprostheses. In the Medtronic Mosaic supra-annular porcine bioprosthesis, the tissue is fixed with glutaraldehyde whilst in a physiological state, thereby incorporating predilatation of the aortic root, and is mounted on a low-profile

polymer stent, which was used previously in the second-generation Hancock II porcine bioprosthesis. The tissue is treated with the long-chain fatty acid alpha-amino oleic acid (AOA) to bind to the aldehyde residual moieties of glutaraldehyde in order to mitigate calcification.

The University of British Columbia was a contributing center to the US Food and Drug Administration (FDA) multi-center prospective non-randomized trial, which completed accrual in late 2000 (1-3). This contributing center enrolled 188 patients, 122 of whom were part of the post-approval longitudinal study. There were 17 centers in the original trial, including nine from Canada; the experiences of these centers have been reported previously (2,3). Six centers formed part of the longitudinal study, and three of these were in Canada (4). The European experience

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with the prosthesis has also been documented (5).

The anti-mineralization properties of AOA were recently documented by Duarte et al. (6), who identified a significant reduction in leaflet calcification in the juvenile sheep mitral replacement model with the AOA-treated Mosaic compared with the non-AOA-treated Mosaic and the Hancock I porcine bioprosthesis, which served as controls.

The aim of the present study was to evaluate the clinical performance of the total experience with the Medtronic Mosaic porcine bioprosthesis at the University of British Columbia-affiliated teaching hospitals, St. Paul's Hospital, Vancouver General Hospital, and the Royal Columbian Hospital.

Clinical material and methods

Patient population

The total study population incorporated 657 patients who received the Medtronic Mosaic porcine bioprosthesis between 1994 and 2000. Aortic valve replacement (AVR) was performed in 415 patients (mean age 70.5 ± 10.7 years; range: 26 to 89 years), and mitral valve replacement (MVR) in 242 patients (mean age 70.5 ± 9.5 years; range: 19 to 86 years). Completeness of follow up was 99.5% and 97.9% for the AVR and MVR patient populations, respectively. Details of patients with regard to age distribution, gender, previous coronary artery bypass (CAB), previous valve procedure and concomitant CAB for both AVR and MVR are listed in Table I. The majority of implants for both AVR and MVR were performed in patients aged >70 years.

Preoperatively, among the AVR patients 6.7, 20.7, 54.5 and 18.1% were in NYHA classes I, II, III and IV, respectively; among the MVR patients, 1.7, 11.6, 49.6 and 37.2% were in NYHA classes I, II, III and IV, respectively.

Table I: Details of the patient population undergoing aortic valve replacement (AVR) or mitral valve replacement (MVR).

Parameter	AVR	MVR
Gender		
Male	311 (74.9)	130 (53.7)
Female	104 (25.1)	112 (46.3)
Previous CAB	19 (4.6)	13 (5.4)
Previous valve	25 (6.0)	19 (7.9)
Concomitant CAB	212 (51.1)	113 (46.7)
Age (years)		
<60	58 (14.0)	32 (13.2)
60-70	109 (26.2)	68 (28.1)
>70	248 (59.8)	142 (58.7)

Values in parentheses are percentages.
CAB: Coronary artery bypass.

Follow up

The cumulative follow up for AVR was 1,463.3 patient-years (pt-yr) (mean 3.5 years), and for MVR was 720.4 pt-yr (mean 3.0 years). The follow up at the University of British Columbia incorporated telephone interviews, consultative reports, requests from primary physicians, echocardiographic reports, reoperation and pathology reports, hospital records, autopsy reports and vital statistics death registry certificates. Complete follow up was performed, except for patients in the longitudinal evaluation between October 2002 and January 2003.

Statistical analysis

Patient survival by valve position, and concomitant CAB and age groups by valve position were determined using actuarial Kaplan-Meier methodology. The definitions of thromboembolism (major, reversible ischemic neurological deficit (RIND), and minor) and thrombosis form part of the document on 'Guidelines for Reporting Morbidity and Mortality after Cardiac Valvular Operations' (7). The early thromboembolic event rates (≤ 30 days) were presented as crude rates (%) for each category of thromboembolic phenomena.

The late event rates for each category were presented as linearized occurrence rates (% per pt-yr). Late thromboembolism was reported as linearized occurrence rates to capture multiple events in the same individual. The concept of overall thromboembolism (inclusive of early and late events) was introduced in reporting on the performance of mechanical prostheses (8,9). This was done in recognition of the finding that early postoperative events were not necessarily a constant hazard, but that overall rates provided an approximation of overall morbidity and mortality related to thromboembolic phenomena. The incorporation of reporting overall rates enabled a better comparison to be made of the clinical performance of mechanical prostheses and bioprostheses. The reporting of only late events must be considered deficient without, at least, documentation of early events. RIND are often reported with minor events because the neurologic deficit has resolved by less than three weeks. By contrast, the pathogenesis of major events (stroke or permanent neurologic events lasting more than three weeks or causing death), RIND, and thrombosis must be considered similar and different from minor transient events lasting less than 24 hours.

The other valve-related complications, namely structural valve deterioration (SVD), non-structural dysfunction and prosthetic valve endocarditis, were considered by overall rates. Antithrombotic hemorrhage must be reported as early and late events, even if the overall rate events concept is reported. Freedom from thromboembolism and valve-related mortality

were determined by both actuarial and actual or cumulative incidence methodologies.

The following variables were considered as predictors of thromboembolism: age (continuous), age groups (≤ 65 , >65 years), prior and concomitant CAB, prior documented cerebrovascular disease, preoperative rhythm, postoperative rhythm, diabetes mellitus, chronic obstructive pulmonary disease, and anticoagulant therapy for both AVR and MVR. Numbers of AVR and MVR were combined to determine if the prosthetic position was predictive of thromboembolism.

Results

Aortic valve replacement

The early mortality after AVR was 3.1% ($n = 13$). At the recent follow up, 335 patients (80.7%) were alive, and 80 (19.3%) had died. The late mortality was 4.5% per pt-yr ($n = 67$; 16.2% of the total group). Overall survival at six years for the AVR population was $73.0 \pm 4.0\%$. Survival for AVR with and without concomitant CAB is shown graphically in Figure 1, while survival by age group for AVR is shown in Figure 2.

The actuarial and actual freedom from overall

thromboembolism for AVR is shown in Figure 3. The actuarial freedom from major thromboembolism for AVR at six years was $95 \pm 1\%$, and the actual freedom was $96 \pm 1\%$. The actuarial and actual freedom from SVD for AVR is illustrated in Figure 4. The actual freedom from SVD for the ≤ 60 -year age group was $98.3 \pm 1.7\%$, and 100% for the 61- to 70-year and >70 -year age groups. The actuarial and actual freedom from valve-related mortality is presented in Figure 5.

The early thromboembolism rate for AVR was 2.9% ($n = 12$) (Table II). There were six major events and two RIND. The late thromboembolism rate for AVR patients was 2.1% per pt-yr ($n = 30$), and for major events was 0.7% per pt-yr ($n = 10$) inclusive of thrombosis, and 0.6% per pt-yr ($n = 8$) exclusive of thrombosis (Table II). There was only one late RIND.

The overall valve-related thromboembolic complications (overall inclusive of early and late events) for AVR by linearized occurrence rates and events are detailed in Table II. A total of 42 thromboembolic events occurred in 39 patients (23 minor; 14 major; three RIND; two thrombosis). The descriptive variables, percentages and number of events for AVR are detailed in Appendix I. There were no independent

Table II: Valve-related complications (linearized occurrence rates) after aortic valve replacement (AVR) or mitral valve replacement (MVR).

Complication	No. of events	
	AVR	MVR
Early events (%)		
Early TE	12 (2.89)	6 (2.48)
TE minor	4 (0.96)	-
TE major	8 (1.93)	6 (2.48)
Major	6 (1.45)**	3 (1.24)*
RIND	2 (0.48)	3 (1.24)
Thrombosis	-	-
Late events (% per pt-yr)		
Late TE	30 (2.05)	19 (2.64)
TE minor	19 (1.30)	10 (1.39)
TE major	11 (0.75)	9 (1.25)
Major	8 (0.55)*	5 (0.69)**
RIND	1 (0.07)	2 (0.28)
Thrombosis	2 (0.14)	2 (0.28)
Overall events (% per pt-yr)		
TE overall	42 (2.87)	25 (3.47)
TE minor	23 (1.57)	10 (1.39)
TE major	19 (1.30)	15 (2.08)
Major	14 (0.96)***	8 (1.11)***
RIND	3 (0.21)	5 (0.69)
Thrombosis	2 (0.14)	2 (0.29)

*, one fatality; **, two fatalities; ***, three fatalities.
 RIND: Reversible ischemic neurological deficit.

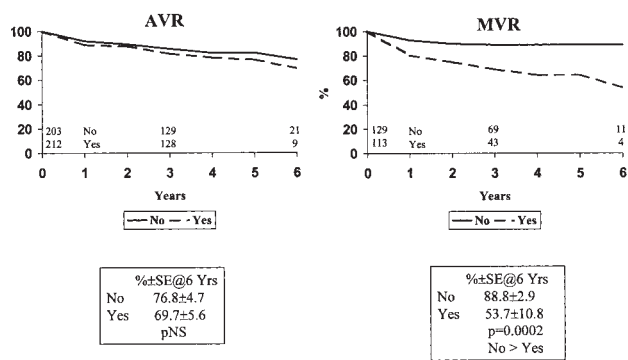


Figure 1: Survival: Concomitant coronary artery bypass after aortic valve replacement (AVR) or mitral valve replacement (MVR).

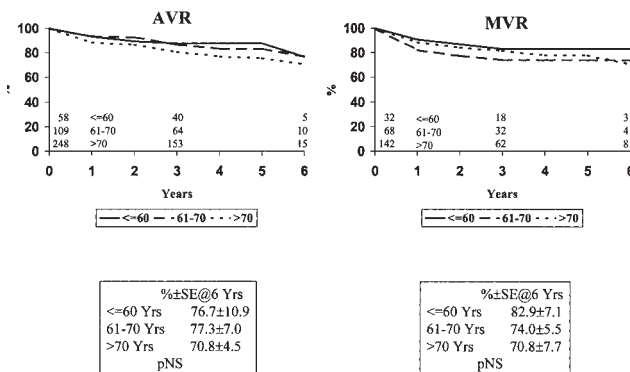


Figure 2: Survival in relation to age groups after aortic valve replacement (AVR) or mitral valve replacement (MVR).

predictors of thromboembolism by multivariate analysis for aortic prostheses. Only age was predictive by univariate analysis (>65 years greater than ≤65 years; HR 2.9, CL 1.0-8.2, p = 0.0431), although it is clear from the details provided in Appendix I that there were apparent differences in the thromboembolism rate according to the existence of patient-related risk factors, which did not reach statistical significance.

Among 11 patients, there were 11 events of hemorrhage contributed to by anticoagulant/antiplatelet therapy. There were four late fatalities. The early mortality rate was 0.7% (n = 3), and late mortality was 0.6% per pt-yr (n = 8); thus, the overall mortality rate was 0.8% per pt-yr (n = 11). There were two cases of SVD. After AVR the rate of valve-related mortality was 0.8% per pt-yr (11 events).

Numbers of valve-related mortality events, both

overall and by age category, inclusive of early mortality, are listed in Table III for AVR by valve-related complications. Numbers of valve-related reoperation events, both overall and by age category, inclusive of mortality for AVR by valve-related complications, are listed in Table IV.

At the last follow up, the distribution of NYHA classes after AVR was 66.5% in class I, 14.0% in class II, 4.6% in class III, 1.2% in class IV. The NYHA class was unavailable for 13.7% of the patients.

Mitral valve replacement

The early mortality among MVR patients was 6.6% (n = 16). At the recent follow up, 192 patients (79.3%) were alive, and 50 (20.7%) had died. The late mortality was 4.7% per pt-yr (14.4%; n = 34). Overall survival for the MVR population was 74 ± 5% at six years. Survival

Table III: Valve-related mortality: Overall and by age category after aortic valve replacement (AVR) or mitral valve replacement (MVR).

Complication	Total	Age category (years)		
		≤60	61-70	>70
After AVR				
ATH	3	1	0	2
PVE	4	1	1	2
SVD	1	1	0	0
TE	3 (2)	0	1	2 (2)
After MVR				
ATH	2	0	0	2
PVE	1	0	1 (1)	0
NSD	1 (1)	0	1	0
SVD	1	0	0	1
TE	2 (1)	1	0	1 (1)

Values in parentheses are early mortalities.

ATH: Antithrombotic hemorrhage; NSD: Non-structural dysfunction; PVE: Prosthetic valve endocarditis; SVD: Structural valve deterioration; TE: Thromboembolism.

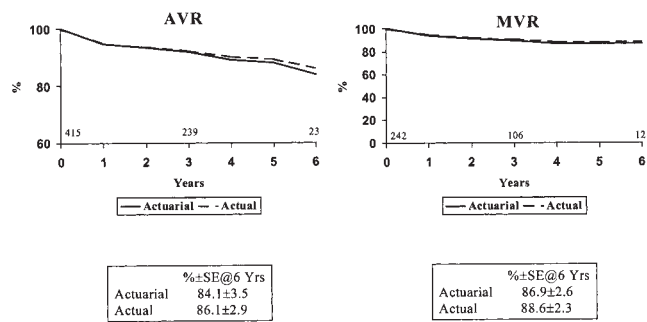


Figure 3: Freedom from overall thromboembolism after aortic valve replacement (AVR) or mitral valve replacement (MVR).

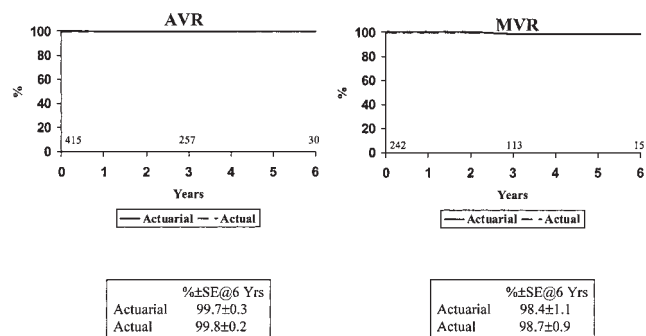


Figure 4: Freedom from structural valve deterioration after aortic valve replacement (AVR) or mitral valve replacement (MVR).

for MVR with and without concomitant CAB is illustrated graphically in Figure 1. Survival by age group for MVR is presented in Figure 2.

The actuarial and actual freedom from overall thromboembolism after MVR is shown in Figure 3. The actuarial freedom from major thromboembolism at six years after MVR was $92 \pm 2\%$, and actual freedom was $93 \pm 2\%$. The actuarial and actual freedom from SVD after MVR is shown in Figure 4. The actual freedom from SVD for the ≤ 60 -year age group was 100%, while that for the 61-to 70-year and >70 -year age groups was $98.0 \pm 2.0\%$ and $98.7 \pm 1.3\%$, respectively. The actuarial and actual freedom from valve-related mortality is shown in Figure 5.

The early thromboembolism rate after MVR was 2.5% ($n = 6$; three major events and three RIND) (Table II). The late thromboembolism rate after MVR was 2.6% per pt-yr ($n = 19$), and for major events was 1% per pt-yr ($n = 7$) inclusive of thrombosis, and 0.7% per pt-yr ($n = 5$) exclusive of thrombosis (Table II). There

were two cases of late RIND.

The overall valve-related thromboembolic complications (overall inclusive of early and late events) after MVR by linearized occurrence rates and events are listed in Table II. A total of 25 events occurred in 24 patients (10 minor; eight major; five RIND; two thrombosis). The descriptive variables, percentages and number of thromboembolic events after MVR are detailed in Appendix II. The only independent predictor of thromboembolism was prior cerebrovascular disease (multivariate analysis HR 2.8, CL 1.1-7.1, $p = 0.0370$; univariate analysis HR 3.0, CL 1.2-7.5, $p = 0.0204$). For the combined AVR and MVR populations, valve position was not predictive; only age (>65 years greater than ≤ 65 years) by multivariate analysis (HR 2.6, CL 1.2-5.7, $p = 0.0184$) and by univariate analysis (HR 2.5, CL 1.1-5.4, $p = 0.0232$) was predictive of thromboembolism. The apparent differences (see Appendix II), did not reach statistical significance (as in Appendix I).

Table IV: Valve-related reoperation: Overall and by age category after aortic valve replacement (AVR) or mitral valve replacement (MVR).

Complication	Total	Age category (years)		
		≤ 60	61-70	>70
After AVR				
PVE	3	1	0	2
SVD	1	1	0	0
Thrombosis	2	0	2	0
After MVR				
NSD	3 (1)	1	1 (1)	1
SVD	1	0	1	0
Thrombosis	1	0	0	1

Values in parentheses are mortalities. Abbreviations as Table III.

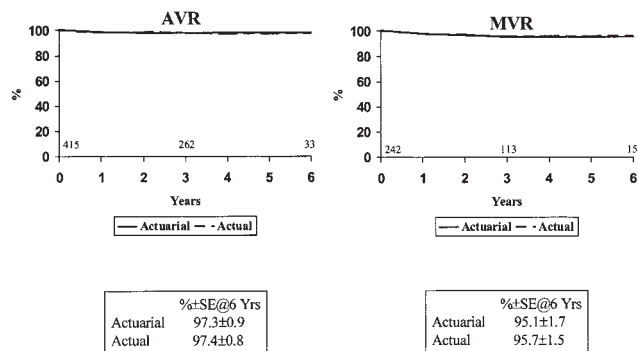


Figure 5: Freedom from valve-related mortality after aortic valve replacement (AVR) or mitral valve replacement (MVR).

Among seven patients there was a total of eight hemorrhagic events, contributed to by anticoagulant/antiplatelet therapy. There were two fatalities, and one patient had residual morbidity. There were no early events, the late (overall) rate of hemorrhage being 1.1% per pt-yr (n = 8).

There were two cases of SVD. After MVR, the rate of valve-related mortality was 1.3% per pt-yr (11 events).

The number of valve-related mortality events after MVR, both overall and by age category (inclusive of early mortality) is summarized in Table III by valve-related complications. The number of valve-related reoperations, both overall and by age category, inclusive of mortality after MVR by valve-related complications, is detailed in Table IV.

At the last follow up, the distribution of NYHA classification among MVR patients was 53.7% in class I, 19.4% in class II, 7.0% in class III, and 2.1% in class IV. The NYHA class was unavailable for 17.8% of the patients.

Structural valve deterioration

There were four cases of SVD (two AVR and two MVR). Two cases of SVD (one AVR, one MVR) under-

went successful reoperation (Table IV). The aortic prosthesis patient was in the ≤60-year age group, and the mitral prosthesis patient was in the 61- to 70-year age group. Mortality occurred in one AVR patient in the ≤60-year age group, and in one MVR patient in the >70-year age group (Table III). The aortic reoperation was performed in a male patient at eight years post-implantation, and all three leaflets had moderate calcification and tears; the patient was in the regulatory study cohort and reoperation was performed in the year 2003. The mitral reoperation was performed in a female patient at 19 months after implantation; this woman was identified as having severe regurgitation on echocardiography and minimal calcification of two leaflets and tear at reoperation. The patient was in the regulatory study cohort, and the reoperation was performed in the year 2001.

The AVR fatality (a male patient) had chronic renal failure for which he was receiving hemodialysis, and also had insulin-dependent diabetes mellitus. The valve failure was diagnosed 10 months after implantation, when echocardiography revealed severe stenosis (mean gradient 82 mmHg, peak gradient 139 mmHg, effective orifice area 0.53 cm², and effective orifice area index 0.25 cm²/m²) and trivial regurgitation. The MVR fatality (also a male patient) was implanted three years previously and died in early 2003. Echocardiography revealed severe regurgitation, moderate stenosis with restricted leaflets, pulmonary hypertension and ventricular dysfunction with an ejection fraction of 25%, a mean diastolic gradient of 20 mmHg, and an effective orifice area of 0.8 cm².

The two successfully reoperated patients were in the regulatory cohort, whereas those patients who died without reoperation were not. Autopsy was not performed in the non-operative cases.

Prosthesis thrombosis

Three patients (two AVR, one MVR) underwent reoperation for prosthesis thrombosis. The first reoper-

Table V: Summary of thromboembolism (TE) after aortic valve replacement (AVR) or mitral valve replacement (MVR): Late events (% per patient-year).

Complication	International*		Canadian* centers		Vancouver* (Canadian)		Vancouver (Total experience)	
	AVR	MVR	AVR	MVR	AVR	MVR	AVR	MVR
Late TE	1.3	1.4	1.8	1.7	1.9	2.5	2.1	2.6
Major TE	0.6	0.4	0.8	0.5	0.4	0.8	0.6	0.7
Minor TE**	0.7	0.9	1.1	1.2	1.5	1.6	1.4	1.7
Thrombosis	0.1	0.1	0.1	0.2	0.2	0.0	0.1	0.3

*Data from the Medtronic-Longitudinal Study.

** Includes Minor + RIND.

ation was performed in a non-compliant patient with a history of substance abuse at 10 months after implantation. The reoperative surgery was carried out at a remote center, with hyperplasia of the aortotomy site, thrombosed prosthesis and thrombosed coronary bypass grafts. The second patient had re-replacement of an aortic prosthesis at three months for organized thrombus which restricted the movement of one leaflet. The third patient had re-replacement of a mitral prosthesis at 15 months for stenosis due to prosthesis and atrial thrombus, with one leaflet restricted due to pannus formation. A fourth patient was found on echocardiography at nine months to have a small mobile mass on the mitral prosthesis. This was confirmed by transesophageal echocardiography six weeks later to be a prosthesis thrombus; the patient was started on anticoagulation, and this was followed after two days by major thromboembolism with residual morbidity. The two AVR and the two MVR thrombosis cases were males, and only the first aortic reoperative case was in the regulatory cohort.

Discussion

Thomson et al. (3), when reporting on nine Canadian centers, and Fradet et al. (1), when reporting on the 17 worldwide centers, did not identify - at the four-year interval - any cases of SVD with the Mosaic bioprosthesis. Eichinger et al. (5) reported on the experience of five European centers in 2002, identified one case of structural failure of an aortic prosthesis, and found the four-year freedom from SVD after AVR to be 98.9%. The case of structural failure resulted in a fatal reoperation. There had been no cases of structural failure of the mitral prosthesis.

Among the present study cases of structural valve failure, only two patients had reoperations while the other two (non-study) patients died without reoperation with echocardiographic evidence of severe calcification causing critical stenosis. One patient had

chronic renal failure requiring hemodialysis, in addition to insulin-dependent diabetes mellitus. The reoperated patients were in the regulatory and longitudinal cohort, though one was diagnosed definitively beyond the closing period of the evaluations produced by Fradet et al (4), and Thomson et al (10). One reoperation, which was performed in 2001, was not included in Medtronic's data because of the timing of the longitudinal consenting process.

The cases of thrombosis of two aortic and two mitral prostheses were managed with reoperation in three patients, while the fourth patient was managed conservatively, resulting in major thromboembolism with residual morbidity. Only one of the four cases was in the regulatory cohort, and was documented at reoperation in 1995. Eichinger et al. (5) reported four cases of thrombosis of aortic prostheses from a European study. The four cases of valve thrombosis came to reoperation with one fatality. However, the authors did not provide any details on these cases of thrombosis.

There have been reports of SVD of both porcine and pericardial bioprosthesis types commencing between seven and 10 years post-implantation (11-16). In order to evaluate the magnitude of the problem, it would be necessary to conduct a controlled study of case-matched patients, or to perform a randomized trial. However, the latter approach would project the answer on the effectiveness of calcium-mitigation therapies too far into the future.

Currently, few published data exist of any significant issue relating to thromboses and major thromboembolism with second-generation bioprostheses, namely the Hancock II and Carpentier-Edwards SAV porcine and Carpentier-Edwards PERIMOUNT pericardial bioprostheses (11-18).

The present authors have reported periodically on the performance of the Carpentier-Edwards SAV bioprosthesis (11-13). In 1988, with the five-year performance report, the rate of thromboembolism was 2.4% per pt-yr with a major rate of 1.3% per pt-yr, as well as

Table VI: Summary of thromboembolism (TE) after aortic valve replacement (AVR) or mitral valve replacement (MVR): Early events (%).

Complication	Canadian* centers		Vancouver (Total experience)	
	AVR	MVR	AVR	MVR
Early TE	2.3	4.3	2.9	2.5
Major TE	0.9	1.8	1.5	1.2
Minor TE**	1.5	2.5	1.4	1.2
Thrombosis	0.0	0.0	0.0	0.0

*Data from the Medtronic-Longitudinal Study.

** Includes Minor + RIND.

two reoperations for thrombotic complications (11). A further report identified the thromboembolic rate at 2.6% per pt-yr, with the major rate at 1.3% per pt-yr (12). The thrombotic reoperation rate was 0.1% per pt-yr. Fradet (4), Thomson (10) and colleagues have studied the status of the Medtronic Mosaic bioprosthesis in the longitudinal regulatory trial. For aortic prostheses, Thomson et al. (10) have identified the late thromboembolism rate as being 1.8% per pt-yr and the major rate as 0.8% per pt-yr, whilst for mitral prostheses these rates were 1.7% per pt-yr and 0.5% per pt-yr, respectively (Table V). In the Canadian cohort, the thrombosis rate was 0.1% per pt-yr for aortic prostheses and 0.2% per pt-yr for mitral prostheses (Table V). Fradet and co-investigators (4) reported from the total international cohort, and found the aortic late thromboembolic rate to be 1.3% per pt-yr and the mitral late thromboembolic rate to be 1.4% per pt-yr (Table V). The major rate was 0.6% per pt-yr for aortic prostheses, and 0.4% per pt-yr for mitral prostheses in this international cohort (Table V). The early thromboembolic event rates were not reported in the total international documentation (4).

Although multiple factors contribute to thromboembolism, other studies on the Medtronic Mosaic porcine bioprosthesis have not evaluated the risk factors. It is known that the mean age of both the international and Canadian (10) cohorts of the regulatory longitudinal studies and the present study all contained patients with a mean age of approximately 70 years. In the present study, almost 60% of the patients were aged over 70 years for both AVR and MVR, and so have inherent risk of thromboembolic events, even without valve replacement. Age was a predictor of thromboembolism for AVR only by univariate analysis, and not by multivariate analysis. A prior cerebrovascular incident was the only independent predictor of thromboembolism for MVR. The effect of the relatively low patient numbers may have influenced the determination of independent predictors of thromboembolism.

There were clear differences in the rates of thromboembolism among the six longitudinal study centers, with late Canadian rates marginally above the international rates (10). The Canadian experience is included in the total international experience. The late event rates and thrombosis rates were probably not differentiated in the International and Canadian studies and the present single-center Vancouver study. The early thromboembolic events were not incorporated with the late rates in the report on the total international experience (4). The early event rates in the present study were 2.9% for AVR and 2.5% for MVR, while rates for the Canadian cohort of the international trial were 2.3% and 4.3%, respectively (10) (Table VI).

The late rates of thromboembolism in the Vancouver

component of the regulatory longitudinal study were 1.9% per pt-yr for AVR and 2.5% per pt-yr for MVR (Table V). Thomson (10) provided the late thromboembolism rates for the Canadian cohort as 1.8% per pt-yr for AVR and 1.7% per pt-yr for MVR (Table V). This was comparable to the late rates of the present study (exclusive of thrombosis) of 2.1% per pt-yr for AVR and 2.6% per pt-yr for MVR. The intensity of follow up of the Vancouver patients seemed to uncover minor thromboembolic events, as was apparent from publications produced by this institution (11-13). The present study differentiated minor transient events (reversible within 24 h) and RIND (fully reversible at >24 h but less than three weeks). Anticoagulation in the Vancouver experience was not routine during the postoperative weeks, and was only administered at the discretion of the cardiac surgeon and the cardiologist, depending on the risk factors of specific patients. This policy - which is currently under evaluation - might have contributed to the thromboembolism rate in the Vancouver experience, but was not different from the international regulatory trial or the Canadian component of the trial (10). The use of anticoagulation during the postoperative period may have contributed to reductions in both early and late thromboembolic and thrombotic events.

In conclusion, the Medtronic Mosaic porcine bioprosthesis was seen to be safe and effective during the first six years postoperatively. The rate of SVD at six years was low, and was zero in the aortic position in patients aged over 60 years. It was also zero in the mitral position in patients aged less than 60 years. The incidence of early and late thromboembolism is contributed to by the advanced age of the patient population. Continuing follow up is warranted in order to assess the long-term performance of this bioprosthesis.

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Appendix I: Descriptive variables of thromboembolism for aortic valve replacement.

Variable	Thromboembolism (% and events)		p-value
Age continuous	No - 376 (70.4 ± 11.0 yr)	Yes - 39 (71.1 ± 7.9 yr)	NS
Age (≤65 vs. >65 yr)	≤65 yr - 4.0% (4/100)	>65 yr - 11.1% (35/315)	0.0540
CAB - Prior	No - 8.8% (35/396)	Yes - 21.1% (4/19)	NS
CAB - Concomitant	No - 9.9% (20/203)	Yes - 9.0% (19/212)	NS
Rhythm - Preoperative	NSR 9.5% (37/388)	AF/PM - 7.4% (2/27)	NS
Rhythm - Follow up	NSR 8.8% (32/365)	AF/PM - 14.0% (7/50)	NS
CVD	No - 9.7% (35/361)	Yes - 7.4% (4/54)	NS
Ejection fraction (%)	>50 - 9.8% (32/327)	35-50 - 9.0% (6/67)	NS
	<35 - 4.8% (1/21)		
Diabetes mellitus	No - 8.9% (32/359)	Yes - 12.5% (7/56)	NS
COPD	No - 9.7% (38/390)	Yes - 4.0% (1/25)	NS
Anticoagulation (discharge)	No - 8.7% (32/368)	Yes - 14.9% (7/147)	NS

AF: Atrial fibrillation; CAB: Coronary artery bypass; COPD: Chronic obstructive pulmonary disease; CVD: Cerebrovascular disease; NS@ Not significant; NSR: Normal sinus rhythm; PM: Pacemaker.

Appendix II: Descriptive variables of thromboembolism for mitral valve replacement.

Variable	Thromboembolism (% and events)		p-value
Age continuous	No - 218 (70.4 ± 9.8 yr)	Yes - 24 (71.1 ± 6.7 yr)	NS
Age (≤65 vs. >65 yr)	≤65 yr - 6.0% (3/50)	>65 yr - 10.9% (21/192)	NS
CAB - Prior	No - 10.5% (24/229)	Yes - 0.0% (0/13)	NS
CAB - Concomitant	No - 8.5% (11/129)	Yes - 11.5% (13/113)	NS
Rhythm - Preoperative	NSR 10.0% (18/180)	AF/PM - 9.7% (6/62)	NS
Rhythm - Follow up	NSR 11.0% (20/182)	AF/PM - 6.7% (4/60)	NS
CVD	No - 8.5% (18/212)	Yes - 20.0% (6/30)	NS
Ejection fraction (%)	>50 - 9.3% (11/118)	35-50 - 13.9% (10/72)	NS
	<35 - 5.8% (3/52)		
Diabetes mellitus	No - 10.4% (21/202)	Yes - 7.5% (3/40)	NS
COPD	No - 10.2% (22/215)	Yes - 7.4% (2/27)	NS
Anticoagulation (discharge)	No - 8.7% (10/115)	Yes - 11.0% (14/127)	NS

Abbreviations as Appendix I.