SURGERY FOR ACQUIRED HEART DISEASE

LONG-TERM RESULTS OF VALVE REPLACEMENT WITH THE ST. JUDE MEDICAL PROSTHESIS

To assess with truly long follow-up the long-term results of valve replacement with the St. Jude Medical prosthesis (St. Jude Medical, Inc., St. Paul, Minn.), we reviewed the case histories of the first 1112 patients undergoing 1244 valve replacements with this valve between June 12, 1978, and June 12, 1987: 690 male (62%) and 422 female patients, mean age 56 years. A total of 773 patients (69%) had the aortic valve replaced, 207 (19%) the mitral valve, and 132 (12%) the aortic and mitral valves. There were 42 hospital deaths (3.8%). Follow-up was 97.5% complete (8988 patient-years). There were 213 late deaths. Ninety-one (43%) were considered valve-related: sudden death, $n = 27$; anticoagulant-related hemorrhage, $n = 22$; thromboembolism, $n = 19$; prosthetic valve endocarditis, $n = 13$; valve thrombosis, $n = 9$; and noninfectious perivalvular leak, $n = 1$. Overall actuarial survival, including hospital mortality, was $68\% \pm 6\%$ (95% confidence limits) 14 years after the operation. Linearized rates of late valve-related events were as follows: thromboembolism, 1.09% per patient-year; anticoagulant-related hemorrhage, 0.94% per patient-year; prosthetic valve endocarditis, 0.32% per patient-year; valve thrombosis, 0.33% per patient-year; and perivalvular leak, 0.19% per patient-year. Actuarial freedom, at 14 years, from thromboembolism was $89\% \pm 3\%$, anticoagulant-related hemorrhage $83\% \pm 8\%$, valve thrombosis $97\% \pm 1\%$, and reoperation $95\% \pm 3\%$. Actuarial freedom from all valve-related deaths and valve-related morbidity and mortality, at 14 years, was $84\% \pm 6\%$ and $61\% \pm 8\%$, respectively. We conclude that, because of its low thrombogenicity, low incidence of valve-related events, and low valve-related mortality, the St. Jude Medical valve is one of the best performing mechanical prosthesis currently available. Nevertheless, the late valve-related complications and deaths illustrate that the quest for a "perfect" prosthesis remains unfulfilled. (J THORAC CARDIOVASC SURG 1995;109:858-70)

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The St. Jude Medical valve prosthesis (St. Jude Medical, Inc., St. Paul, Minn.) was designed¹ to satisfy, as much as possible, the features of an

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"ideal" valve and was first used clinically in October 1977.² Because of its attractive characteristics, the St. Jude Medical prosthesis was introduced into our unit in June 1978 and became the mechanical prosthesis routinely used. By the end of October 1994, 3074 St. Jude Medical valves had been implanted in 2746 patients: 1844 aortic, 574 mitral, and 328 double aortic and mitral replacements. We³ reported our 5½-year experience with the valve in 1985.

Despite the low incidence of valve-related problems reported in early clinical studies,²⁻⁴ the St. Jude Medical valve remains exposed to the usual complications of any mechanical valve substitute.

Table I. Valve pathophysiologic conditions

	Aortic		Mitral	
	No.	%	No.	%
Stenosis	296	32.7	82	24.2
Regurgitation	384	42.5	158	46.6
Combined	221	24.4	98	28.9
Prosthesis replacement	4	0.4	1	0.3
Total valves	905	100	339	100

The purpose of this review was to assess long-term results in the first 1112 patients undergoing 1244 valve replacements between June 1978 and June 1987 and to evaluate, with a long follow-up, the overall valve-related complications and mortality associated with the St. Jude Medical valve.

Patients and methods

Patients. Between June 12, 1978, and June 12, 1987, 1244 St. Jude Medical valves were implanted in 1112 patients. A total of 773 patients (69%) underwent isolated aortic valve replacement (AVR), 207 (19%) isolated mitral valve replacement (MVR), and 132 (12%) double aortic and mitral valve replacement (DVR). The series comprised 690 male (62%) and 422 female patients (38%), with a mean age of 55.9 years (range 9 months to 82 years). Twenty-five patients (2.2%) were 15 years or younger and 146 (13%) were aged 70 years or older. In the AVR group mean age was 57.3 years, and 122 of these patients (15.8%) were older than 70; mean age in the MVR group was 52.9 years, and 15 of them (7.2%) were older than 70; and in the DVR group mean age was 52.5 years, nine (6.8%) being older than 70 years. Male sex predominated in the AVR group (69%) and female sex in the MVR and DVR groups (54% and 53.8%, respectively). Two hundred ten patients (19%) were in atrial fibrillation before the operation. Valve pathophysiologic conditions are shown in Table I. Of the 384 predominant aortic regurgitations, 54 were due to bacterial endocarditis and nine to aortic dissection. Of the 158 predominant mitral regurgitations, 13 were due to bacterial endocarditis. Twelve patients had undergone a previous mitral commissurotomy. Regarding rereplacement, four patients were reoperated on, three for rereplacement of an isolated aortic bioprosthesis after tissue failure and one for rereplacement of both aortic and mitral Edwards-Duromedics bileaflet prostheses (Baxter Healthcare Corp., Edwards Div., Santa Ana, Calif.; Hemex Scientific, Inc., Austin, Tex.) because of an early prosthetic valve endocarditis. Thus four aortic prostheses and one mitral prosthesis were replaced by St. Jude Medical valves. All patients over 30 years of age had preoperative coronary angiography.

Surgical technique. Cardiopulmonary bypass with moderate hypothermia (30° C) was performed with a disposable bubble or membrane oxygenator. Myocardial protection was accomplished by the use of antegrade cold potassium crystalloid cardioplegia with topical cooling. The mean aortic crossclamp time was 52 minutes for AVR, 38 minutes for MVR, and 71 minutes for DVR. The

Table II. Operative characteristics

	No.	%
Aortic size (mm)		
19-21	150	16.5
23-25	441	49
27-29*	264	29
31	50	5.5
Mitral size (mm)		
19-21	1	0.3
23-25	9	2.7
27-29	162	48
31-33	167	49
Additional procedures		
Coronary artery bypass grafting	94	8.5
Tricuspid valve repair	20	1.8
Mitral valve repair	41	3.7
Septal myectomy	45	4
Aortic graft	33	3
Aortic enlargement	9	0.8
Congenital heart disease	5	0.5
Ventricular aneurysmectomy	1	

*Includes 11 patients with a 26 mm aortic valve.

prostheses were anchored to the valve annulus by interrupted figure-of-eight sutures for AVR and by continuous suture for MVR.

Until 1979, the leaflets of the valve prostheses were oriented parallel to the septum in the aortic position and parallel to the native leaflets (anatomic orientation) in the mitral position. However, anatomic considerations and consequent hydrodynamic deductions^{3,5,6} led us to change both these orientations. Prosthetic leaflets are now oriented perpendicular to the septum in the aortic position and perpendicular to the native leaflets (antianatomic orientation) in the mitral position. Of the 905 aortic prostheses, 705 (78%) were size 23 to 29 mm, and 814 (90%) were implanted with the prosthetic leaflets oriented perpendicular to the septum. Of the 339 mitral prostheses, 329 (97%) were size 27 to 33 mm, and 312 (92%) were implanted with prosthetic leaflets in the antianatomic orientation.

Associated surgical procedures were performed in 248 patients (22%): 201 patients (26%) in the AVR group, 31 patients (15%) in the MVR group, and 16 patients (12%) in the DVR group. Only 94 patients (8.5%) had concomitant coronary atherosclerosis requiring coronary artery bypass grafting. Of the nine patients undergoing annular or supravalvular enlargement, six patients underwent an annulus-enlarging procedure to allow implantation of at least a 19 mm prosthesis. Because of good hemodynamic performance of the St. Jude Medical valve in small sizes,⁷ annular enlargement was never performed to implant a larger valve than sized. Other concomitant procedures are listed in Table II.

Anticoagulant therapy. In 1978, a protocol of early anticoagulation involving three steps was initiated⁸. Inter-mittent intravenous injection of heparin (step 1) was started during the sixth postoperative hour and relayed with subcutaneous calcium heparin (step 2) during the twenty-fourth postoperative hour; oral anticoagulation

Table III. Hospital mortality (42/1112 patients = 3.8%) and causes of deaths by valve position

Cause	AVR (n = 773)	MVR (n = 207)	DVR (n = 132)
Surgical			
Bleeding	3	2	2
Tamponade	3		
Aortic dissection	1		
Valve-related			
Prosthetic valve infection	1		
Cardiac			
Myocardial failure	4	4	
Infarction	2	1	1
Complete atrioventricular block	2		
Arrhythmia	3		
Noncardiac			
Septicemia	2	1	
Pulmonary failure	1	2	
Cerebral damage	5	1	
Gastrointestinal bleeding	1		
Total	28 (3.6%)	11 (5.3%)	3 (2.3%)

therapy with warfarin (step 3) was instituted 48 hours after the operation, and subcutaneous infusion of calcium heparin was continued until the target prothrombin time was brought to 1.6 to 1.9 times the control value. In addition, special attention was given to fibrinogen level. This was measured on the fourth postoperative day and then every 2 days, because fibrinogen level only starts to rise at this time, reaching sometimes 6, 10, or 12 gm/L. To counteract this thrombogenic factor, once the fibrinogen level exceeds 5 gm/L (normal fibrinogen level 2 to 4 gm/L) we routinely use nonsteroidal antiinflammatory drugs (NSAIDs), such as diclofenac (50 mg orally per day) or ketoprofen (150 mg orally per day), for a mean duration of 3 to 5 days, except in patients with a history of gastritis or renal insufficiency. NSAID therapy generally is sufficient to lower the fibrinogen level and allow the optimal prothrombin time to be reached faster. Because the prothrombin time is an approximate assessment of the exact level of anticoagulation required for an individual patient, we have used the international normalized ratio (INR) since September 1992. According to the anticoagulation recommendations proposed by Horstkotte and associates^{9, 10} for patients undergoing valve replacement with a St. Jude Medical prosthesis, our current target INRs are 2.4 to 2.6 for patients with AVR; 2.4 to 2.8 for those with MVR in sinus rhythm and with a left atrial size less than 30 mm²; and 2.7 to 3.1 for those with MVR in atrial fibrillation or with a left atrial size larger than 30 mm². In the first year of our experience, 78 patients (AVR, 65; MVR, 10; DVR, 3), all in sinus rhythm, gave informed consent to receive an antiplatelet regimen of aspirin and dipyridamole only. However, because there were four aortic and two mitral thromboses (with two deaths) and seven episodes of transient ischemic attack or

peripheral embolism in this group, all were given anticoagulants secondarily.

Follow-up. Patient follow-up was accomplished by mail and/or telephone contact with the referring cardiologist, the house physician, the patient, or the family. Follow-up data were obtained during a 6-month closing interval (May 1993 until the end of October 1993). Of the 1070 hospital survivors, 27 (2.5%) could not be located and were considered lost to follow-up. Thus follow-up was 97.5% complete (1043 patients, mean age at follow-up 65.5 years). Patient-years of follow-up were 6419 for AVR, 1580 for MVR, and 989 for DVR. Total follow-up was 8988 patient-years, with a mean follow-up of 117 months, for a period ranging from 3 to 181 months (the very first late death occurred in a patient discharged from the hospital 3 months earlier). Hospital and late deaths, as well as valve-related events, were stringently defined according to published Guidelines of The American Association for Thoracic Surgery.¹¹

Statistical methods. Actuarial estimates of survival and event-free curves for the incidence of thromboembolic events, valve thrombosis, anticoagulant-related bleeding, and reoperation, as well as for all valve-related deaths and all valve-related morbidity and mortality, were calculated with the Kaplan-Meier method¹² and reported with 95% confidence limits. Patients were censored, withdrawn from the study, at the time of replacement of the St. Jude Medical valve or at the time of death. Late valve-related events defined as embolism, valve thrombosis, anticoagulant-related bleeding, prosthetic valve endocarditis, paravalvular leak in the absence of infection, and pannus formation were expressed in linearized form (percent per patient-year). Estimates were reported plus or minus the standard error of the estimate. Comparisons of curves were made with the log-rank test.^{13, 14} A Pearson χ^2 test was used to seek differences between groups concerning hospital and late mortality.

Results

Early valve-related events. Early recurrent prosthetic valve endocarditis developed in one patient and was fatal despite reoperation. In five patients (AVR, 2; MVR, 3; 0.4%), minor clinical hemolytic anemia was demonstrated in the early postoperative period and resumed spontaneously. In all five cases, hemolysis was unrelated to paravalvular leak. Apart from these events, no cases of early mechanical failure, valve dysfunction, thromboembolic episodes, or valve thrombosis were observed.

Hospital mortality. Forty-two hospital deaths (3.8%) occurred, of which only one (2.4%) was valve-related. The causes of hospital deaths are analyzed in Table III. Apart from one intraoperative death resulting from posterior aortic root disruption, bleeding of surgical cause and tamponade, despite reoperation, were responsible for low output state leading to multiorgan failure or brain death. Delayed pacing was also responsible for neurologic

Table IV. Linearized rate of late valve-related complications

Complication	Valve position			All positions
	Aortic	Mitral	Double	
Embolism	0.84 (54)	1.77 (28)	1.62 (16)	1.09 (98)
Valve thrombosis	0.25 (16)	0.44 (7)	0.70 (7)	0.33 (30)
Hemorrhage	0.95 (61)	0.89 (14)	1.01 (10)	0.94 (85)
Endocarditis	0.30 (19)	0.44 (7)	0.30 (3)	0.32 (29)
Perivalvular leak	0.18 (12)	0.25 (4)	0.10 (1)	0.19 (17)
Pannus formation	0.03 (2)	0.00 (0)	0.00 (0)	0.02 (2)
All complications	2.55 (164)	3.79 (60)	3.74 (37)	2.90 (261)

Data are shown as percent per patient-year and (in parentheses) as number of events. Patient-years of follow-up were 6419 for AVR, 1580 for MVR, and 989 for DVR (total = 8988 patient-years).

damage. In three patients having AVR, ventricular fibrillation could not be successfully converted to sinus rhythm. Finally, of the five patients who died of primary cerebral damage in the AVR group, three had massive intracranial bleeding on the second postoperative day. These three deaths in patients operated on for infective endocarditis could be attributable to the rupture of a concomitant mycotic intracranial aneurysm. Despite the fact that the hospital mortality seemed higher in the MVR group than in the AVR or DVR group, no significant difference in hospital mortality according to valve location was detected ($p = 0.40$).

Late valve-related events. During the period of follow-up, 236 patients had 261 valve-related events (linearized rate: 2.90% per patient-year). Some patients had more than one complication. Table IV lists the specific valve-related events and linearized rates.

Thromboembolism. Ninety-eight thromboembolic events occurred in 78 patients (1.09% per patient-year): 54 occurred in the AVR group (46 patients, 1.2 episodes per patient), 28 occurred in the mitral group (20 patients, 1.4 episodes per patient), and 16 occurred in the double valve group (12 patients, 1.3 episodes per patient). Thirty-five patients had a permanent neurologic deficit, which was fatal in 19. Of these patients, 27 (77%) were in sinus rhythm and eight (23%) were in atrial fibrillation. Forty-three patients had a transient ischemic attack (39 patients) or peripheral embolism (4 patients). Of these, 32 (74%) were in sinus rhythm and 11 (26%) were in atrial fibrillation. Regarding cardiac rhythm according to valve subgroup, 42 of the 46 patients with AVR and eight of the 12 with DVR were in sinus rhythm, whereas 11 of the 20 patients with MVR were in atrial fibrillation. This means that only 19 patients (24%) were in atrial fibrillation and that, in our series, atrial fibrillation did not appear significantly associated with thromboembolism. This find-

ing is confirmed by our early experience with no anticoagulation in 78 patients, all in sinus rhythm: four embolic episodes were observed in the 65 patients with AVR and three embolic episodes in the 10 with MVR, in addition to valve thrombosis in six others.

These embolic complications occurred at a mean delay of 60 months. Transthoracic and, after 1987, transesophageal echocardiography were performed in most of the 52 patients hospitalized, and a direct relation between valve thrombosis and the embolic event was detected in only nine of them. The only embolic events that could be related to a decrease in prothrombin time were related to valve thrombosis. Most embolic events occurred in patients in whom prothrombin time was within the therapeutic range.

The actuarial freedom from thromboembolic complications is shown in Fig. 1.

Valve thrombosis. Thirty episodes of valve thrombosis (AVR, 18; MVR, 12) occurred in 27 patients (0.33% per patient-year). Six of them (AVR, 4; MVR, 2) occurred in the group of 78 patients, all in sinus rhythm, who were initially not given anticoagulants. All the others occurred in patients who had a history of poor compliance in taking warfarin or, in most cases, who discontinued oral anticoagulation, resulting in a prothrombin time near 1 at the time of valve thrombosis. Five patients died before any treatment; nine patients were reoperated on and two of them died; and 13 patients were treated with fibrinolysis, with two deaths. The actuarial freedom from this event is shown in Fig. 2.

Anticoagulant-related bleeding. Eighty-five patients (0.94% per patient-year) had major anticoagulant-related hemorrhage necessitating hospital admission or blood transfusion or resulting in death. In all patients this complication occurred as a result of accidental excessive anticoagulation, and an elevated prothrombin time was always documented at

Fig. 1. Actuarial freedom from thromboembolism at 14 years (overall and stratified by valve position). CL, Confidence limits.

Fig. 2. Actuarial freedom from valve thrombosis at 14 years (overall and stratified by valve position). CL, Confidence limits.

that time. Twenty-two of these patients died of either gastrointestinal bleeding or intracranial hemorrhage (mainly subdural hematoma).

According to the guidelines, minor bleeding episodes were not taken into account. The actuarial freedom from this complication is shown in Fig. 3.

Prosthetic valve endocarditis. Twenty-nine episodes of prosthetic valve endocarditis occurred in 27 patients (AVR, 17; MVR, 7; DVR, 3): 0.32% per patient-year. According to valve site, the rate was 0.30% per patient-year for AVR and DVR and 0.44% per patient-year for MVR. Thirteen patients

Fig. 3. Actuarial freedom from anticoagulant-related hemorrhage at 14 years (overall and stratified according to valve site). CL, Confidence limits.

had a periprosthetic leakage, which was minor in five. Thus eight patients only, with AVR, underwent nine reoperations in the acute phase of endocarditis for hemodynamic failure, with two deaths. The five others, as well as the 14 patients with septicemia without paravalvular leak or evident clinical or echocardiographic involvement of the valve, were treated medically. Eleven of these 14 patients died, more as a result of septicemia than of heart failure. The causative organism was identified as *Staphylococcus* in many of them, *Enterococcus* in two, *Hemophilus* in one, and *Corynebacterium* in one. Often blood culture failed to identify any causative organism, however, mainly in patients having an isolated septicemic syndrome. The mortality of this complication was consequently high (48%).

Paravalvular leak. Noninfectious periprosthetic leaks developed in 17 patients (0.19% per patient-year). Ten patients had a moderate leak that was treated medically. The remaining seven patients underwent surgical repair without replacement, with one death at reoperation.

Reoperation. Twenty-eight reoperations were performed in 27 patients, with five deaths (18.5%). Indications for reoperation included valve thrombosis in nine patients, prosthetic valve endocarditis in eight patients, and paravalvular leak in seven patients. Two patients in the AVR group were reop-

erated on for subaortic ring because of fibrous pannus formation, and one patient from the DVR group underwent heart transplantation for end-stage left ventricular dysfunction 12 years later. The linearized risk for reoperation was 0.31% per patient-year for all patients, and the actuarial estimate of the percentage free from reoperation is shown in Fig. 4.

Late deaths and patient survival. Two hundred thirteen of 1043 patients (20%) had died by the last date of follow-up, at a linearized rate of 2.4% per patient-year. The causes of late deaths, classified as valve-related and non-valve-related, are shown in Table V. Two of the late valve-related deaths (one sudden death in the AVR group and one mitral thrombosis in the DVR group) occurred in the 78 patients who were initially not given anticoagulants. No significant difference between the different valve locations was detected for valve-related deaths or for total late deaths ($p = 0.69$ and $p = 0.37$, respectively).

The overall actuarial patient survivals including hospital mortality were 73% and 68% at 11 and 14 years, respectively (Fig. 5). Actuarial survival according to valve site among the AVR, MVR, and DVR groups was not significantly different at 11 years (74%, 71%, and 69%, respectively).

The overall actuarial freedom from all valve-related deaths was 89% at 11 years and 84% at 14

Fig. 4. Actuarial freedom from reoperation at 14 years (overall and stratified according to valve site). CL, Confidence limits.

Table V. Late mortality (213/1043 patients = 20%) and causes of deaths by valve position

Cause of death	Aortic (n = 729)		Mitral (n = 190)		Double (n = 124)	
	No.	%	No.	%	No.	%
Valve-related: 91 (43%)	60	8.2	19	10	12	9.7
Sudden death	18	2.5	7	3.7	2	1.6
Thromboembolism (cerebral)	14	1.9	2	1.05	3	2.4
Anticoagulant-related bleeding	15	2	4	2.1	3	2.4
Prosthetic valve endocarditis	8	1.1	4	2.1	1	0.9
Valve thrombosis	4	0.6	2	1.05	3	2.4
Noninfectious perivalvular leak	1	0.1				
Non-valve-related: 122 (57%)	93	12.7	13	6.8	16	12.9
Cardiac	29	4	8	4.2	6	4.8
Noncardiac	55	7.5	4	2.1	9	7.3
Unknown	9	1.2	1	0.5	1	0.8
Total late deaths	153	20.9	32	16.8	28	22.6

years (Fig. 6), and the overall freedom from all valve-related morbidity and mortality was 70% at 12 years and 61% at 14 years (Fig. 7).

At 14 years in DVR recipients there was a slight trend toward lower freedom from all valve-related morbidity and mortality, as well as lower survival; however, even though differences did not reach statistical significance ($p = 0.3$), statistical power of this analysis is low because the number of MVR and DVR recipients is relatively small, especially at 13 and 14 years.

Comparison of New York Heart Association functional class before operation and by the last

date of follow-up in the 830 long-term survivors showed that whereas 54% of these patients were in class III or IV before the operation, at follow-up (minimum 6 years, maximum 15 years), 95% of these survivors were in functional class I or II.

Discussion

For more than 16 years the St. Jude Medical valve has been routinely used in our unit when a mechanical prosthesis was needed for valve replacement. In the choice of valve substitutes, mechanical versus tissue, two parameters are generally considered a contraindication for mechanical valve insertion: pre-

Fig. 5. Actuarial patient survival at 14 years including hospital mortality (overall and stratified according to valve position). Numbers below figure indicate AVR, MVR, and DVR patients at risk during follow-up. CL, Confidence limits.

existing or comorbid conditions and advanced age, both predisposing to bleeding when anticoagulants are used. All patients were screened before the operation to rule out those having any disease likely to be responsible for anticoagulant-related bleeding. With regard to age, the current increasing life expectancy of patients operated on before 75 years of age, the poorer durability of bioprostheses, and the surgical risk of reoperations in octogenarians should be considered, as well as the absence of statistically significant differences in the incidence of major anticoagulant-related bleeding in our series between patients older than 70 years (11 episodes in 132 patients, 8.3%) and those younger than 70 years (74 episodes in 911 patients, 8.1%) ($p = 0.93$). Thus it appears that “advanced” age did not result in a higher rate of bleeding complications. We therefore considered that the classic “advanced” age had to be extended to 75 years. This policy is supported by Kratz and associates,¹⁵ who emphasize that there was, in their series, “a trend toward operating on older patients as well as expanded indications for the use of the St. Jude prosthesis in that age group.” Moreover, when referring to the other St. Jude Medical valve replacement series,¹⁵⁻¹⁹ it appears that age range was similar and mean age was slightly higher than in our series: 44 of the 1200 patients

(3.7%) in the series reported by Fernandez and associates¹⁸ were octogenarians. This means that many centers also extended the frontier of “advanced” age, contraindicating mechanical valve insertion beyond 70 years.

One wonders about the true importance of a specific orientation of prosthetic leaflets in the aortic and mitral positions. Chaux and Blanche,²⁰ and Laub and coworkers²¹ outlined that the clinical performance of the St. Jude Medical valve is excellent in either orientation and that the prosthesis can be oriented in any direction if no subvalvular tissue or foreign material is present that would interfere with leaflet motion. However, several factors should be taken into consideration to determine how the valve should be placed, according to individual patient circumstances. Embolic events and valve thrombosis, in our series, occurred in either orientation, as well as in the aortic or mitral position. However, at the very beginning of our experience,³ intraoperative anatomic considerations in two aortic thrombosed valves showed that, in case of excessive bulging of a hypertrophied septum, as confirmed by Chaux and Blanche, anterior flow could be disturbed when prosthetic leaflets were oriented parallel to the septum, which could be an additional thrombogenic factor. In the mitral position, our

Fig. 6. Long-term actuarial freedom from all valve-related deaths (overall and stratified by valve position). Numbers below figure indicate AVR, MVR, and DVR patients at risk during follow-up. CL, Confidence limits.

suggestion of antianatomic orientation was also founded on intraoperative considerations,³ because it appears that with the anatomic orientation the posterior leaflet in the open position is close to the left ventricular wall. Thus the posterior area of the prosthesis is less likely to allow as free flow as the anterior area. These theoretic considerations have been supported by many authors: Asynchronous leaflet closure was found echocardiographically to be reduced in valves implanted in the antianatomic orientation.^{22, 23} Duncan and colleagues²⁴ found that the theoretic advantages of this proposed orientation appeared sound and adopted its use. More recently, Laub and colleagues²¹ confirmed experimentally that "on average the clearance was 59.2% larger with the valve oriented antianatomically" and concluded that "there is evidence to support that this [anatomic orientation] is not the ideal orientation." Thus, in our opinion, the main advantage of these proposed orientations consists in optimizing the hydrodynamic performance of the valve more than avoiding leaflet impingement, because the St. Jude Medical valve is really the bileaflet prosthesis exhibiting the lowest profile. Potential impingement risk is low and, whatever the valve size, was never observed.

The rate of concomitant aorta-coronary bypass grafting (8.5%) was lower than in the other reported series^{15-18, 24} (16% to 48%). Because all our patients older than 30 years of age underwent coronary angiography, this finding could be due to the fact that our patient population is almost exclusively referred from the southwestern part of France, in which epidemiologic studies suggest that the population is less likely to have early atheromatous coronary artery disease. Most of our patients with coronary disease are older than 70 years of age.

Our operative mortality of 3.8% did not differ from that in our previous report and compares favorably with that reported for the St. Jude Medical valve¹⁵⁻¹⁹ and other mechanical prostheses.²⁵⁻²⁸

Regarding the rate of late deaths, late mortality, since our previous report, increased from 6.3% at 5½ years to 20% at 14 years, with an incidence of valve-related deaths increasing from 34% to 43%. However, the linearized incidence of late deaths (2.4% per patient-year) with a mean follow-up of 9.75 years is almost identical to that reported by Ibrahim and coworkers¹⁹ but appears to be lower than that reported in other series (4.53% to 6.6% per patient-year).¹⁵⁻¹⁸ Because the strongest risk factor for late death is the presence and extent of

Fig. 7. Long-term actuarial freedom from all valve-related morbidity and mortality (overall and stratified by valve position). Numbers below figure indicate AVR, MVR, and DVR patients at risk during follow-up. CL, Confidence limits.

associated coronary atherosclerosis, the low incidence of concomitant coronary disease in our patients could explain this difference. This study revealed that the most frequent late valve-related events were thromboembolism (1.09% per patient-year) and hemorrhagic complications related to anticoagulants (0.94% per patient-year). These events represented 38% and 33% of late events, respectively, and were responsible for 9% and 10% of late valve-related deaths, respectively. In fact, incidence of thromboembolism compares with other series of St. Jude Medical valves^{15-19, 24} (0.8% to 3.5% per patient-year), but appears lower than that reported for other mechanical and/or porcine prostheses by Orszulak,²⁵ Daenen,²⁸ and their associates (2.5% to 4.6% per patient-year). Most instances of major anticoagulant-related bleeding occurred many months or years after the operation in patients in whom comorbid conditions developed, such as duodenal or gastric ulcer or gastrointestinal carcinoma nonexistent at preoperative screening. In addition, bleeding was always favored by an elevation of prothrombin time far above the therapeutic range. When these bleeding complications are evaluated in elderly patients, it appears that there was no difference in the incidence of anticoagulant-related late

deaths in the three groups: AVR 2%, MVR 2.1%, and DVR 2.4%, despite the fact that 15.8% of patients in the AVR group were older than 70 years (versus 7.2% in the MVR and 6.8% in the DVR group). Moreover, the linearized rate of hemorrhage was similar in the three groups (0.95%, 0.89%, and 1.01% per patient-year, respectively). Finally, as mentioned previously, there was no statistically significant difference in the number of major bleeding episodes in patients older or younger than 70 years of age. Comparison of the overall incidence of anticoagulant-related bleeding in our series (0.94% per patient-year) was similar to that reported by Fernandez and associates¹⁸ (0.95% per patient-year), higher than that reported by Arom and colleagues¹⁷ (0.56% per patient-year), and lower than that reported by Duncan,²⁴ Czer,¹⁶ Kratz,¹⁵ and their colleagues (1.13% to 2.89% per patient-year).

When valve thrombosis occurred, a decreased prothrombin time, near 1, was always documented. This serious complication carried a mortality of 33% in our series. To manage this complication, we rapidly used fibrinolytic treatment with streptokinase and/or urokinase in 13 patients. The treatment was successful in 11 patients, whereas two of the nine patients who underwent reoperation died.

From our experience with fibrinolytic treatment,²⁹⁻³² our current opinion is that the prostheses most likely to be treated by fibrinolysis are those in the aortic position. Usually only one leaflet is blocked, so that there is sufficient residual flow to allow a sufficient amount of fibrinolytic agent to reach the thrombosed valves. To the contrary, in mitral thrombosis, both leaflets are generally completely blocked, resulting in a low output state with shock. Thus fibrinolysis is systematically and routinely used as the only treatment of thrombosed aortic mechanical valves, but surgical intervention should be proposed in thrombosed mitral prostheses.

Incidence of prosthetic valve endocarditis in our series (0.32% per patient-year) also compares with that of others^{15, 16, 18, 24} (0.16% to 1.13% per patient-year) and carries a similar high mortality, despite antibiotic treatment and surgical intervention.

Late clinical hemolysis did not occur in our practice. However, five patients were concerned in the early postoperative period by an association of slight jaundice and anemic syndrome unrelated to paravalvular leak. It was an uncommon complication that could be due, as emphasized by Arom and colleagues,¹⁷ either to previous unapparent or hidden hemolytic disease or, more probably, to "spontaneous hemolysis of lethal or sublethal red blood cell damage caused by extracorporeal circulation." As far as biologic hemolysis is concerned, 94 patients operated on starting in June 1978, and without clinical evidence of hemolysis were systematically submitted 5 to 19 months after operation to blood testing so that the risk of hemolysis could be assessed. Our results reported in 1981³³ showed that reticulocyte count, platelet count, hemoglobin level, and bilirubin level were unchanged from preoperative values, but haptoglobin level was below normal and total and fractionated lactic dehydrogenase levels were slightly elevated (250 IU/L), suggesting subclinical hemolysis despite intact function of the St. Jude Medical prosthesis. In addition, red cell filterability was also found to be impaired (filtration time increase).

Over a 16-year experience, no early or late structural dysfunction of the valves was observed. The long-term durability of the St. Jude Medical valve, emphasized by many authors, is best illustrated by absence of any measurable wear for any part of the critical pivot area or device deterioration in two St. Jude Medical prostheses (aortic, size 26 mm, and

mitral, size 31 mm) explanted from a patient undergoing heart transplantation 12 years after DVR.

The only critical remaining problem is the prevalence of systemic embolism and anticoagulant-related hemorrhage. These complications could be reduced according to the concept of risk-adjusted intensity of oral anticoagulation developed by Butchart and coworkers³⁴ to reach an effective degree of anticoagulation in the individual patient and a lower risk of bleeding complications. Since September 1992, our experience with lowering the intensity of anticoagulation with target INRs ranging from 2.4 to 3.1 indicated that revision of anticoagulation management proposed by Horstkotte did not increase the risk of thromboembolism and valve thrombosis but did reduce bleeding complications.

The results of our long-term experience with the St. Jude Medical valve have been corroborated by many authors: this valve is one of the best performing mechanical prosthesis currently available and thus can be considered as an advance in cardiac valve replacement. Nevertheless, even though the St. Jude Medical valve satisfied most of the features of an excellent mechanical valve substitute, the late valve-related complications and deaths illustrate that our quest for a "perfect" prosthesis remains unfulfilled.

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REFERENCES

1. Kalke BR, Lillehei CW, Kaster RL. Evaluation of a double-leaflet prosthetic heart valve of new design for clinical use. In: Brewer LA, ed. Prosthetic heart valves. Springfield, Ill.: Charles C Thomas, 1969:285-302.
2. Nicoloff DM, Emery RW, Arom KV, et al. Clinical and hemodynamic results with the St. Jude Medical cardiac valve prosthesis. *J THORAC CARDIOVASC SURG* 1981;82:674-83.
3. Baudet EM, Oca CC, Roques XF, et al. A 5½-year experience with the St. Jude Medical cardiac valve prosthesis. *J THORAC CARDIOVASC SURG* 1985;90:137-44.
4. Chaux A, Gray RJ, Matloff JM, Feldman H, Sustaita H. An appreciation of the new St. Jude valvular

- prosthesis. *J THORAC CARDIOVASC SURG* 1981;81:202-11.
5. Baudet EM. Cardiac valve replacement with the St. Jude Medical prosthesis. Proceedings of the First European Symposium on the St. Jude valve, Paris, France, June 1980. St. Paul: St. Jude Medical, Inc., 1980:1-10.
6. Baudet EM. Our experience concerning orientation of the St. Jude Medical prosthesis: a suggestion for a specific orientation in aortic and mitral position. Proceedings of the Second International Symposium on the St. Jude valve, San Diego, March 1981. St. Paul: St. Jude Medical, Inc., 1981:9-10.
7. Wortham DC, Tri TB, Bowen TE. Hemodynamic evaluation of the St. Jude Medical valve prosthesis in the small aortic anulus. *J THORAC CARDIOVASC SURG* 1981;81:615-20.
8. Baudet EM. Anticoagulation and prosthetic heart valves. In: Horstkotte D, Loogen F, eds. Update in heart valve replacement. Proceedings of the Second European Symposium on the St. Jude Medical heart valve, Düsseldorf, Germany, February 1984. New York: Springer-Verlag, 1986:109-15.
9. Horstkotte D, Bergemann R, Althaus U, et al. German experience with low intensity anticoagulation (GELIA): protocol of a multi-center randomized, prospective study with the St. Jude Medical valve. *J Heart Valve Dis* 1993;2:411-9.
10. Horstkotte D, Schulte H, Bircks W, Strauer B. Unexpected findings concerning thromboembolic complications and anticoagulation after complete 10 year follow-up of patients with St. Jude Medical prostheses. *J Heart Valve Dis* 1993;2:291-301.
11. Edmunds LH Jr, Clark EC, Cohn LH, Miller DC, Weisel RD. Guidelines for reporting morbidity and mortality after cardiac valvular operations. *J THORAC CARDIOVASC SURG* 1988;96:351-3.
12. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
13. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966;50:163-70.
14. Cox DR. Regression models and life-tables (with discussion). *J R Stat Assoc (B)* 1972;34:187-220.
15. Kratz JM, Crawford FA Jr, Sade RM, Crumbley AJ, Stroud MR. St. Jude prosthesis for aortic and mitral valve replacement: a ten-year experience. *Ann Thorac Surg* 1993;56:462-8.
16. Czer LSC, Chaux A, Matloff JM, et al. Ten-year experience with the St. Jude Medical valve for primary valve replacement. *J THORAC CARDIOVASC SURG* 1990;100:44-55.
17. Arom KV, Nicoloff DM, Kersten TE, Northrup WF, Lindsay WG, Emery RW. Ten years' experience with the St. Jude Medical valve prosthesis. *Ann Thorac Surg* 1989;47:831-7.
18. Fernandez J, Laub GW, Adkins MS, et al. Early and late-phase events after valve replacement with the St. Jude Medical prosthesis in 1200 patients. *J THORAC CARDIOVASC SURG* 1994;107:394-407.
19. Ibrahim M, O'Kane H, Cleland J, Gladstone D, Sarsam M, Patterson C. The St. Jude Medical prosthesis: a thirteen-year experience. *J THORAC CARDIOVASC SURG* 1994;108:221-30.
20. Chaux A, Blanche C. Technical aspects of valvular replacement with the St. Jude prosthesis. *J Cardiovascular Surg* 1987;28:363-8.
21. Laub GW, Muralidharan S, Pollock SB, Adkins MS, McGrath LB. The experimental relationship between leaflet clearance and orientation of the St. Jude Medical valve in the mitral position. *J THORAC CARDIOVASC SURG* 1992;103:638-41.
22. Duveau D, Michaud JL, Despins P, et al. Mitral valve replacement with the St. Jude Medical prosthesis: 242 cases, with clinical results and an evaluation of prosthesis positioning. In: DeBakey ME, ed. Advances in cardiac valves, clinical perspectives. Proceedings of the Third International Symposium on the St. Jude valve, Scottsdale, Ariz., November 1982. New York: Yorke Medical Books, 1983:183-90.
23. Feldman HJ, Gray RJ, Chaux A. Non invasive in vitro and in vivo study of the St. Jude mitral valve prosthesis. *Am J Cardiol* 1982;49:1101-9.
24. Duncan JM, Cooley DA, Reul GJ, et al. Durability and low thrombogenicity of the St. Jude Medical valve at 5-year follow-up. *Ann Thorac Surg* 1986;42:500-5.
25. Orszulak TA, Schaff HV, DeSmet JM, Danielson GK, Pluth JR, Puga FJ. Late results of valve replacement with the Björk-Shiley valve (1973 to 1982). *J THORAC CARDIOVASC SURG* 1993;105:302-12.
26. Vallejo JL, Gonzalez-Santos JM, Albertos J, et al. Eight years' experience with the Medtronic-Hall valve prosthesis. *Ann Thorac Surg* 1990;50:429-36.
27. de Luca L, Vitale N, Giannolo B, Cafarella G, Piazza L, Cotrufo M. Mid-term follow-up after heart valve replacement with Carbomedics bileaflet prostheses. *J THORAC CARDIOVASC SURG* 1993;106:1158-65.
28. Daenen W, Nevelsteen A, van Cauwelaert P, de Maesschalk E, Willems J, Stalpaert G. Nine years' experience with the Björk-Shiley prosthetic valve: early and late results of 932 valve replacements. *Ann Thorac Surg* 1983;35:651-63.
29. Ledain L, Lorient-Roudaut MF, Gateau P, et al. Fibrinolytic treatment of prosthetic heart valves. *Eur Heart J* 1982;3:371-81.
30. Ledain L, Gateau P, Colle JP, Baudet E, Page A, Besse P. Fibrinolytic treatment of prosthetic valve thrombosis [Abstract]. *Am J Cardiol* 1982;49:938.
31. Ledain LD, Ohayon JP, Colle JP, Lorient-Roudaut FM, Roudaut RP, Besse PM. Acute thrombotic obstruction with disc prostheses: diagnostic consider-

- ations and fibrinolytic treatment. *J Am Coll Cardiol* 1986;7:743-51.
32. Roudaut R, Labbe T, Lorient-Roudaut MF, et al. Mechanical cardiac valve thrombosis. Is fibrinolysis justified? *Circulation* 1992;86(Suppl):II8-15.
 33. Baudet E, Fel G, Roudaut R, Gibson D, Roques X, Garbe JF. Cardiac valve replacement with the St. Jude Medical prosthesis: clinical, echocardiographic, and biological results. In: Bircks W, Ostermeyer J, Schulte HD, eds. *Cardiovascular surgery* 1980. Berlin: Springer Verlag, 1981.
 34. Butchart EG, Lewis PA, Bethel JA, Breckenridge IM. Adjusting anticoagulation to prosthesis thrombogenicity and patient risk factors. *Circulation* 1991; 84(Suppl):III61-9.

Discussion

Dr. Kit V. Arom (*Minneapolis, Minn.*). This study has again confirmed that the patients who received St. Jude Medical prostheses are doing well after 10 years but thromboembolism and anticoagulant-related hemorrhage are still the main concerns.

I have a couple of questions, Dr. Baudet: You did not mention the method of follow-up of these patients. As you know, complications related to these particular valves are dependent on the anticoagulation level; however, the INR is the better method to describe the mean anticoagulation level, not PTR or prothrombin time ratio. Which method did you use? If you used the PTR, have you converted the PTR to INR? If you did, what is the recommended INR for the St. Jude Medical prosthesis, both in the mitral and in the aortic position?

My second question has to do with stroke risk factors. Many of the emboli may not arise from the prosthesis itself, and stroke risk factors may play a significant role in this complication. Have you analyzed the embolic rate according to the stroke risk factors, for example, in the presence of atrial fibrillation and enlarged left atrium? If you did, have you seen more stroke or embolism in this particular subset than you reported?

Dr. Baudet. Thank you, Dr. Arom, for your kind comments. To answer your first question concerning our anticoagulation management, since 1978 we have used an early anticoagulation protocol involving three steps: intermittent intravenous heparin injection is used from the sixth postoperative hour, relayed by subcutaneous calcium heparin at the twenty-fourth hour. Oral anticoagulation is instituted 48 hours after the operation, and subcutaneous calcium heparin is maintained until the target prothrombin time is 1.5 of the control value. In addition, if the fibrinogen level increases, which we consider to be a thrombogenic factor, we would use an NSAID for 3 to 5 days to normalize fibrinogen level. As far as long-term anticoagulation is concerned, we now follow Horstkotte's rules using the INR, with target INRs of 2.4 to 2.6 for patients with aortic prostheses, 2.4 to 2.8 for those with mitral prostheses who are in sinus rhythm and have a left atrial diameter smaller than 26 mm/m², and 2.7 to 3.1 for patients with mitral prostheses who are in atrial fibrillation with a left atrial diameter larger than 30 mm/m².

In response to your second question regarding the stroke risk factors, preoperatively 19% of patients were in atrial fibrillation. Among the 78 patients who had postoperative thromboembolic complications, mainly neurologic deficits, only 19 also had atrial fibrillation.