Prospective randomized comparison of CarboMedics and St Jude Medical bileaflet mechanical heart valve prostheses: An interim report

Kelvin H. H. Lim, MSc, FRCSEd^a

Massimo Caputo, MD, MCh^a

Raimondo Ascione, MD^a

Jan Wild^a

Robert West, MA, PhD, FSS^b

Gianni D. Angelini, MD, MCh, FRCS^a

Alan J. Bryan, MD, FRCS^a

Sponsor: Antonio Maria Calafiore, MD

Objective: This is a midterm report of a study comparing the clinical performance of CarboMedics and St Jude Medical heart valve prostheses through a projected 10-year period.

Methods: Between 1992 and 1996, a total of 485 patients undergoing mechanical valve replacement were prospectively randomly assigned to receive either CarboMedics (n = 234) or St Jude Medical (n = 251) prostheses for aortic (n = 288), mitral (n = 160), or double (n = 37) valve replacements and were followed up annually.

Results: Baseline and operative characteristics were similar between the two groups with respect to major demographic characteristics, preoperative clinical status, and operative data. Mean follow-up was 50 ± 22 months for the CarboMedics group (97% complete) and 47 ± 20 months for the St Jude Medical group (96% complete), yielding a total of 1959 patient-years. The 30-day mortality, and 5-year actuarial survival, and linearized survival were 6.0%, $82.4\% \pm 2.6\%$, and 4.3% per patient-year in the CarboMedics group and 4.4%, $79.9\% \pm 2.8\%$, and 4.7% per patient-year in the St Jude Medical group (log-rank $P = .7$). Freedom at 5 years from valve-related mortality, major thromboembolism, hemorrhage, and other nonstructural valve dysfunction was, respectively, $96.7\% \pm 1.4\%$ (0.7% per patient-year), $90.9\% \pm 2.1\%$ (2.2% per patient-year), $87.3\% \pm 2.5\%$ (3.6% per patient-year), and $96.1\% \pm 1.4\%$ (0.7% per patient-year) in the CarboMedics group and $95.9\% \pm 1.5\%$ (1.0% per patient-year), $92.5\% \pm 1.8\%$ (2.0% per patient-year), $82.6\% \pm 2.8\%$ (4.3% per patient-year), and $96.0\% \pm 1.3\%$ (0.6% per patient-year) in the St Jude Medical group, with no overall intergroup differences. No statistically significant intergroup differences in international normalized ratio values were detected during the study period.

Conclusions: This study shows no significant differences in the early and midterm clinical outcomes between patients who received CarboMedics valve prostheses and those who received St Jude Medical mechanical prostheses. Choices with respect to valve type can be based on considerations other than patient outcome.

From the Bristol Heart Institute,^a University of Bristol, Bristol, United Kingdom, and Welsh Heart Research Institute,^b University of Wales College of Medicine, Cardiff, United Kingdom.

St Jude Medical and Sulzer-CarboMedics provided financial support for a clerical assistant for the duration of this study.

Read at the Eighty-first Annual Meeting of The American Association for Thoracic Surgery, San Diego, Calif, May 6-9, 2001.

Received for publication June 14, 2001; accepted for publication July 16, 2001.

Address for reprints: Alan J. Bryan, MD, FRCS, Bristol Heart Institute, Bristol Royal Infirmary, Bristol BS2 8HW, United Kingdom (E-mail: alan.bryan@ubht.swest.nhs.uk).

J Thorac Cardiovasc Surg 2002;123:21-32

Copyright © 2002 by The American Association for Thoracic Surgery.

0022-5223/2002 \$35.00 + 0 12/6/119703

doi:10.1067/mtc.2002.119703

Since their introduction, the standard CarboMedics (CM; CarboMedics, Inc, Austin, Tex) and the standard St Jude Medical (SJM; St Jude Medical Inc, Minneapolis, Minn) bileaflet valve prostheses have become two of the most widely used mechanical heart valve replacements. They both offer good hemodynamic function and excellent durability, and the clinical performance of these two bileaflet mechan-

ical valves has been extensively reported in observational studies.¹⁻⁵ In a collective review, Akins⁶ concluded that rates for valve-related complications were essentially highly comparable between CM and SJM valves, although the data for the CM valve from a smaller study population^{7,8} did show a slightly higher rate of thromboembolic complications in the mitral position, despite adequate anticoagulation. This finding has been supported by others.⁹⁻¹¹ In contrast, Jamieson and colleagues^{12,13} found no significant differences in thromboembolic tendency between the CM and SJM prostheses in isolated mitral valve replacement (MVR) or double valve replacement (DVR). Long-term randomized prospective studies to evaluate the experience with these prostheses have been lacking to date.

Although there is general agreement that randomized prospective trials are not essential in the evaluation of prostheses, the conflicting and occasionally worrisome outcomes reported in other observational studies do make randomized prospective studies in a particular patient population, with the prevailing level of anticoagulation, an important contribution to the assessment of the clinical performance of particular valve prostheses. This report describes the midterm results of a prospective randomized study comparing the clinical outcomes of patients who received either CM or SJM mechanical heart valves implanted at a single institution.

Methods

Patient Recruitment

From July 1992 to June 1996, patients who were scheduled to undergo mechanical heart valve replacement surgery under the care of five consultant surgeons at Bristol Heart Institute were recruited by individual consent into the study protocol, which was reviewed by the local hospital ethical committee. Exclusion criteria included receipt of other valve prostheses, surgery to the ascending aorta, inability to obtain informed consent, and known difficulty in follow-up. Any active history of bleeding diathesis, blood dyscrasia, neurologic seizures, or long-term hemodialysis also precluded entry into the study. Random assignment was by selection of unmarked envelopes, each of which contained a card indicating either the CM or SJM prosthesis, at the time of surgery.

Surgery

All operations were performed through a median sternotomy with cardiopulmonary bypass and mild systemic hypothermia (28°C–32°C). Myocardial protection consisted of intermittent antegrade cold (6°C) St Thomas crystalloid or blood cardioplegia. The prostheses used in both the CM and SJM groups were of the standard design. Interrupted or continuous suturing technique was used at the discretion of the operating surgeon. All patients received post-operative subcutaneous heparin until the international normalized ratio (INR) was above 2 with warfarin administration. On discharge, anticoagulation was managed in the community by general medical practitioners and at anticoagulation clinics at local hospitals according to the British Society for Haematology guidelines,¹⁴

as published in the British National Formulary, which essentially recommend a target INR range of 3 to 4.5.

Follow-up

Annual follow-up was performed primarily by patient questionnaire on the anniversary of the operation and by direct contact as necessary for the clarification of details. The family practitioners or hospital cardiologists were contacted, and the hospital health records were used as appropriate. The death registry of the General Register Office for UK National Statistics was used to provide details of deaths that were otherwise unobtainable. When adverse events were reported, these were categorized by an independent clinician in association with the study coordinator (J.W.), both of whom were blinded to the type of valve implanted. Anticoagulation data, drug dosages, and INR values were obtained through an anticoagulation history booklet, which is carried by the patient and filled in by the responsible physician during each monitoring episode. For the purpose of this interim report, data are presented for follow-up until the end of September 1999.

Statistical Analysis and Data Reporting

The "Guidelines for Reporting Morbidity and Mortality After Cardiac Valvular Operations" were strictly followed for definitions of valve-related complications, analysis, and presentation of data and results.¹⁵ The gathered information was recorded onto a standard form and stored in a computerized database (Microsoft Access for Windows; Microsoft Corporation, Redmond, Wash). Subsequent data analysis was performed in consultation with a qualified statistician. Continuous data are represented as mean $\pm$ SD. Intergroup comparisons were performed with the unpaired *t* test or nonparametric Mann-Whitney test as appropriate. Categorical data were analyzed by cross-tabulation with the χ^2 test or the Fisher exact test. The actuarial method was used to estimate event-free survival with 95% confidence limits, and Mantel-Haenszel log-rank test was used to compare event-free survival. Early deaths within 30 days were included in reported 5-year survivals. Calculated linearized rates (percentage per patient-year) during the entire follow-up period include early and late events. Statistical analyses were performed with the aid of StatView version 5 for Windows (SAS Institute, Inc, Cary, NC).

Results

Patient characteristics

During the recruitment period a total of 590 patients underwent mechanical prosthetic valve replacement at our institution. In this subgroup 495 (84%) patients were initially randomly assigned to a prosthesis group, but 10 of these patients were subsequently excluded from the study because of unavailability of the randomized prosthesis (*n* = 2), need for aortic surgery (*n* = 6), and early emigration making follow-up impossible (*n* = 2). The final 485 patients included in this study thus comprised 234 patients receiving CM and 251 patients receiving SJM prosthetic valves as AVR (*n* = 288), MVR (*n* = 160), or DVR (*n* = 37, Figure 1). The mean ages were 60 years (range 12–85 years) in the CM

Figure 1. Flow chart represents random assignment of patients in this study. There were no differences between CM and SJM groups in number of valves allocated in overall and in subgroup analyses.

TABLE 1. Baseline patient characteristics

Variables	All		AVR		MVR		DVR	
	CM	SJM	CM	SJM	CM	SJM	CM	SJM
Patients (No.)	234	251	139	149	75	85	20	17
Age (y, mean $\pm$ SD)	60 $\pm$ 13	61 $\pm$ 11	60 $\pm$ 12	61 $\pm$ 12	60 $\pm$ 13	62 $\pm$ 10	62 $\pm$ 12	60 $\pm$ 9
Male (No.)	128 (55%)	138 (55%)	90 (65%)	100 (67%)	31 (41%)	30 (35%)	7 (35%)	8 (47%)
Previous myocardial infarction (No.)	28	25	14	16	13	8	1	1
Previous heart surgery (No.)	47	60	17	20	22	34	8	6
Valve-related complication (No.)	40	55	10	17	22	32	8	6
Atrial fibrillation (No.)	71	79	10	14	49	55	12	10
History of thromboembolism (No.)	25	36	8	16	14	19	3	1
Anticoagulation (No.)	65	71	12	8	39	54	14	9
NYHA functional class								
I	10	13	7	10	3	2	0	1
II	87	104	61	71	19	30	7	3
III	78	88	41	44	32	36	5	8
IV	59	46	30	24	21	17	8	5
Coronary artery disease	67	67	41	41	24	23	2	3

group and 61 years (range 10-82 years) in the SJM group, with 45% female patients in either group. Subanalysis according to position of valve replacement did not reveal any significant differences between CM and SJM groups with respect to age and sex (Table 1). Most patients were admitted on an elective basis, with 85 (18%) listed for urgent valve replacement and 18 (4%) for emergency valve replacement. Most patients were in New York Heart Association (NYHA) functional class II (39%) or III (34%), with no difference observed in overall NYHA class distribution between the CM and SJM groups ($P = .3$).

Proportionately more patients were in NYHA class III or IV among those who underwent MVR (66%) and DVR (70%) than among those who underwent isolated AVR (48%, $P < .001$).

Preoperative atrial fibrillation and anticoagulation therapy were more prevalent among patients who underwent MVR or DVR (>60%) than among those who underwent AVR (7%). There was a higher incidence of preoperative thromboembolism among those undergoing MVR (18%) than among those undergoing AVR (8%). Cross-table analysis revealed no difference between the CM and SJM groups

TABLE 2. Perioperative characteristics

Variables	All		AVR		MVR		DVR	
	CM	SJM	CM	SJM	CM	SJM	CM	SJM
Patients (No.)	234	251	139	149	75	85	20	17
Operation status (No.)								
Elective	178	206	104	125	57	69	17	12
Urgent	47	36	27	18	17	14	3	4
Emergency	9	9	8	6	1	2	0	1
Cardiopulmonary bypass time (min, mean $\pm$ SD)	123 $\pm$ 51	125 $\pm$ 65	117 $\pm$ 45	121 $\pm$ 70	120 $\pm$ 45	122 $\pm$ 54	177 $\pm$ 76	174 $\pm$ 53
Aortic crossclamp time (min, mean $\pm$ SD)	81 $\pm$ 33	79 $\pm$ 28	77 $\pm$ 28	77 $\pm$ 20	76 $\pm$ 31	75 $\pm$ 34	125 $\pm$ 41	120 $\pm$ 20
Valve size (mm, mean $\pm$ SD)								
Aortic			22.8 $\pm$ 2.6	22.7 $\pm$ 2.1			21.7 $\pm$ 2.4	21.8 $\pm$ 2.0
Mitral					29.7 $\pm$ 2.2	30.0 $\pm$ 1.8	29.0 $\pm$ 2.1	30.0 $\pm$ 1.7
Tricuspid								31*
Suture technique (No.)								
Interrupted	155	164	91	108	37	37	27	19
Continuous	23	32	2	3	16	28	5	1
Pledgeted	76	72	46	38	22	20	8	14
Associated CABG (No.)	53	56	30	36	21	19	2	1
Tricuspid valve repair (No.)	2	10†	0	0	2	7	0	3
Inotropic support >24 h (No.)	44	49	20	20	17	24	7	5
IABP used (No.)	11	12	6	5	4	7	1	0
Myocardial infarction (No.)	3	4	1	2	2	2	0	0
Tracheostomy (No.)	6	4	0	1	2	3	4	0
Dialysis for renal failure (No.)	8	6	7	2	0	3	1	1
Reopen chest (No.)								
For any indication	13	9	7	4	3	3	4	2
For bleeding	12	9	7	4	2	3	3	2
Intensive care stay (d, mean $\pm$ SD)	2.1 $\pm$ 3.3	2.5 $\pm$ 5.8	1.7 $\pm$ 1.8	1.9 $\pm$ 2.3	2.1 $\pm$ 2.7	3.5 $\pm$ 9.4	5.5 $\pm$ 8.0	2.7 $\pm$ 1.9
Hospital stay (d, mean $\pm$ SD)	11 $\pm$ 8	11 $\pm$ 9	9 $\pm$ 7	10 $\pm$ 6	12 $\pm$ 8	13 $\pm$ 13	17 $\pm$ 12†	10 $\pm$ 6

CABG, Coronary artery bypass grafting; IABP, intra-aortic balloon pump.

*Only one value.

† $P < .05$.

in the distributions of these variables or in perioperative characteristics of cardiopulmonary bypass and ischemic times, implanted valve sizes, suture techniques used, and the frequency of concomitant coronary artery bypass grafts (Table 2).

The main cause of native valve dysfunction among patients undergoing AVR was calcific stenosis, with a rheumatic origin most common among those undergoing MVR and DVR (Table 3). Subanalysis showed more patients in the CM group than in the SJM group who had active endocarditis of the aortic valve. There were 44 (9.1%) patients undergoing reoperation to replace dysfunctional previously implanted prosthetic valves (CM 18, 7.7%, SJM 26, 10.4%, $P = .3$).

Mortality

The early (30-day) mortality was 5.1% ($n = 25$, CM $n = 14$, SJM $n = 11$, $P = .5$, Table 4). There were no valve-related

early deaths in this series, whereas non–valve-related cardiac causes accounted for 88% ($n = 22$, CM $n = 14$, SJM $n = 8$, $P = .19$) and 12% ($n = 3$) were due to noncardiac causes. Heart failure, alone ($n = 12$) or as part of multiorgan failure syndrome ($n = 5$), accounted for 68% of all early deaths. Other causes included fatal arrhythmias ($n = 2$), acute myocardial infarction ($n = 1$), mediastinitis ($n = 1$), hemopericardium ($n = 1$), perioperative stroke ($n = 1$), bronchopneumonia ($n = 1$), and peritonitis ($n = 1$). There were 89 deaths overall (CM $n = 42$, SJM $n = 47$) during the follow-up period of 1959 patient-years (CM 968 patient-years, SJM 991 patient-years). Postmortem diagnoses were available in 54% of cases (CM 60%, SJM 49%). In other cases the cause of death was determined by clinical diagnosis. During late follow-up (>30 days after the operation) there were 64 deaths (CM $n = 28$, SJM $n = 36$, $P = .5$), of which 17 (CM $n = 7$, SJM $n = 10$) were classified as valve related, 24 (CM $n = 11$, SJM $n = 13$) were cardiac but not valve related, and 23 (CM $n = 10$, SJM $n = 13$)

TABLE 3. Valve dysfunction and origin

Variables	AII		AVR		MVR		DVR	
	CM	SJM	CM	SJM	CM	SJM	CM	SJM
Patients (No.)	234	251	139	149	75	85	20	17
Valves replaced (No.)	254	268	139	149	75	85	40	34
Dysfunction (No. of valves)								
Aortic regurgitation	44	43	36	37			8	6
Aortic stenosis	85	92	78	88			7	4
Mixed aortic valve dysfunction	30	30	25	24			5	6
Mitral regurgitation	54	53			47	48	7	5
Mitral stenosis	21	21			11	16	10	5
Mixed mitral valve dysfunction	20	29			17	21	3	8
Cause (No. of valves)								
Congenital	14*	4	10	4	2	0	2	0
Calcific	95	115	88	108	6	5	1	2
Degenerative	34	34	11	9	21	25	2	0
Rheumatic	65	70	8	10	30	36	27	24
Endocarditis (all)	26	18	18*	7	6	5	2	6
Endocarditis (acute)	20	16	15*	5	3	5	2	6
Ischemic	2	1	0	0	2	1	0	0
Redo valve replacement	18	26	4	11	8	13	6	2

* $P < .05$.**TABLE 4. Follow-up and mortality**

Variables	AII		AVR		MVR		DVR	
	CM	SJM	CM	SJM	CM	SJM	CM	SJM
Patients (No.)	234	251	139	149	75	85	20	17
Follow-up (mo)								
Mean $\pm$ SD	50 $\pm$ 22	47 $\pm$ 20	51 $\pm$ 22	49 $\pm$ 19	48 $\pm$ 23	45 $\pm$ 20	48 $\pm$ 20	44 $\pm$ 25
Maximum	85	85	85	85	84	79	72	74
Patient-year	968	991	587	608	300	321	81	62
Completion of follow-up (%)	97	96	97	96	99	96	95	100
Early mortality (<30 d, No.)	14	11	10	4	3	4	1	3
Overall mortality (No.)	42 (4.3%)	47 (4.7%)	22 (3.7%)	20 (3.3%)	17 (5.7%)	23 (7.2%)	3 (3.7%)	4 (6.5%)
Cardiac deaths (No.)								
Overall	32 (3.3%)	31 (3.1%)	17 (2.9%)	13 (2.1%)	12 (4.0%)	14 (4.4%)	3 (3.7%)	4 (6.5%)
Valve-related	7 (0.7%)	10 (1.0%)	2 (0.3%)	4 (0.7%)	5 (1.7%)	5 (1.6%)	0	1 (1.6%)
Sudden unexplained	2 (0.2)	3 (0.3%)	0	0	2 (0.7%)	3 (0.9%)	0	0
Thromboembolism	2 (0.2%)	3 (0.3%)	0	1 (0.2%)	2 (0.7%)	1 (0.3%)	0	1 (1.6%)
Hemorrhage	1 (0.1%)	3 (0.3%)	0	3 (0.5%)	1 (0.3%)	0	0	0
Prosthetic valve infection	1 (0.1%)	1 (0.1%)	1 (0.2%)	0	0	1 (0.3%)	0	0
Nonstructural dysfunction	0	0	0	0	0	0	0	0
Structural valve deterioration	0	0	0	0	0	0	0	0
Reoperation	1 (0.1%)*	0	1 (0.2%)*	0	0	0	0	0
Cardiac nonvalve causes	25 (2.6%)	21 (2.1%)	15 (2.6%)	9 (1.5%)	7 (2.3%)	9 (2.8%)	3 (3.7%)	3 (4.8%)
Other causes	10 (1.0%)	16 (1.6%)	5 (0.9%)	7 (1.2%)	5 (1.7%)	9 (2.8%)	0	0

Percentages are per patient-year.

*Reoperation for paraprosthetic leak.

were due to other noncardiac causes, such as malignancies. Late valve-related deaths were due to complications of stroke (n = CM 2, SJM n = 3), prosthetic valve infections (CM n =

1, SJM n = 1), reoperation for paraprosthetic leak (CM n = 1), hemorrhage (CM n = 1, SJM n = 3), and sudden unexplained death (CM n = 2, SJM n = 3).

Figure 2. Kaplan-Meier survival plots showing no differences between CM and SJM groups in overall survival (A), freedom from valve-related death (B), and survivals in isolated AVR (C) and MVR (D).

The actuarial survival for the whole study group at 5 years was $81.1\% \pm 1.9\%$ (4.5% per patient-year), and the survivals were $82.4\% \pm 2.6\%$ (4.3% per patient-year) and $79.9\% \pm 2.8\%$ (4.7% per patient-year) in the CM and SJM groups, respectively (log-rank $P = .7$). Subanalysis according to position of valve replacement showed no significant differences in survival between the CM and SJM groups (Figure 2).

Valve-Related Events

Thromboembolic events. There were 40 thromboembolic events overall (CM $n = 21$, SJM $n = 19$) during the entire study period, of which 3 events (CM $n = 2$, SJM $n = 1$) occurred early, within 30 days after the operation (Table 5). Most of these were among patients with single thromboembolic episodes, but 5 patients who had MVR (CM $n = 3$, SJM $n = 2$) had two episodes each during follow-up. Five patients (CM $n = 2$, SJM $n = 3$) died of cerebrovascular

accident presumed to be related to thromboembolism during the late follow-up period. The remaining thromboembolic events were not fatal; 34 were classed as neurologic events and 1 was a peripheral embolism. Nonfatal neurologic events were considered transient ischemic attacks for 23 events (CM $n = 13$, SJM $n = 10$), reversible ischemic neurologic deficit for 1 (CM $n = 1$), and strokes for the remaining 10 (CM $n = 5$, SJM $n = 5$). Most thromboembolic events were among patients who had undergone MVR, with 20 such events (CM $n = 10$, SJM $n = 10$) registered (3.2% per patient-year). This compares with 17 events (CM $n = 9$, SJM $n = 8$) in the AVR group (1.4% per patient-year) and 3 events (CM $n = 2$, SJM $n = 1$) in the DVR group (2.1% per patient-year). There were no cases of prosthetic valve thrombosis detected in the study population during this period.

The 5-year thromboembolic event-free rates were $90.9\% \pm 2.1\%$ (2.17% per patient-year) and $92.5\% \pm 1.8\%$ (1.92%

TABLE 5. Valve-related complications (overall, including fatal events)

Variables	AII		AVR		MVR		DVR	
	CM	SJM	CM	SJM	CM	SJM	CM	SJM
Patients (No.)	234	251	139	149	75	85	20	17
Patient-y	968	991	587	608	300	321	81	62
Thromboembolism (No.)								
All	21 (2.2%)	19 (2.0%)	9 (1.5%)	8 (1.3%)	10 (3.3%)	10 (3.1%)	2 (2.5%)	1 (1.6%)
Peripheral	0	2	0	0	0	1	0	0
Neurologic event	21 (2.2%)	18 (1.8%)	9 (1.5%)	8 (1.3%)	10 (3.3%)	9 (2.8%)	2 (2.5%)	1 (1.6%)
Fatal	2	3	0	1	2	1	0	1
Stroke	5	5	2	2	3	3	0	0
Reversible >24 h	1	0	0	0	1	0	0	0
Transient ischemic attack (<24 h)	13	10	7	5	4	5	2	0
Hemorrhage (No.)	35 (3.6%)	43 (4.3%)	19 (3.2%)	25 (4.1%)	11 (3.7%)	13 (4.0%)	5 (6.2%)	5 (8.1%)
Prosthetic valve infection (No.)	1 (0.1%)	4 (0.4%)	1 (0.2%)	1 (0.2%)	0	1 (0.3%)	0	2 (3.2%)
Nonstructural dysfunction (No.)								
All	7 (0.7%)	6 (0.6%)	3 (0.5%)	5 (0.8%)	3 (1.0%)	1 (0.3%)	1 (1.2%)	0
Paraprosthetic leak	7 (0.7%)	5 (0.5%)	3 (0.5%)	4 (0.7%)	3 (1.0%)	1 (0.3%)	1 (1.2%)	0
Fistula*	0	1 (0.1)	0	1 (0.2)	0	0	0	0
Structural valve deterioration (No.)	0	0	0	0	0	0	0	0
Redo valve (No.)	3 (0.3%)	4 (0.4%)	2 (0.3%)	3 (0.5%)	1 (0.3%)	0	0	1 (1.6%)
Paraprosthetic leak	2	1	1	1	1	0	0	0
Prosthetic valve infection	1	3	1	2	0	0	0	1
Fistula* closure (No.)	0	1	0	1	0	0	0	0

Percentages are per patient-year.

*Aorta–right ventricular fistula.

per patient-year) for the CM and SJM groups, respectively (log-rank $P = .7$). After stratification by valve position there was no difference between the CM and SJM groups (Figure 3), but it was observed that the 5-year event-free rates were better for AVR than MVR, at $94.1\% \pm 1.6\%$ and $87.6\% \pm 2.7\%$, respectively (log-rank $P = .007$).

The heart rhythm was atrial fibrillation in 38% of thromboembolic events (CM $n = 8$, SJM $n = 9$); the remainder occurred in sinus rhythm. This compares with 27% of patients overall during last follow-up with atrial fibrillation. All patients were receiving warfarin during thromboembolic episodes, and of these 2 patients in the CM group were also receiving an antiplatelet drug. In 30 of the 40 thromboembolic episodes the INR was measured acutely. Among these the INR value was at least 3 in 60% and less than 2 in 6%, with no statistical difference detected between CM and SJM groups.

Bleeding events. A total of 35 bleeding events were reported for the CM group during the study period, compared with 43 such events in the SJM group. Bleeding-associated deaths occurred in 3 patients from the SJM group and 1 from the CM group. The 5-year event-free rates for bleeding were $87.3\% \pm 2.5\%$ (3.6% per patient-year) and $82.6\% \pm 2.8\%$ (4.3% per patient-year) for the CM and SJM groups, respectively (log-rank $P = .25$, Figure 4).

After stratification by position of valve replacement, there were no detectable differences between the CM and SJM groups or between AVR and MVR (Figure 4 and Table 5). The DVR group had a higher rate of hemorrhagic events, although not statistically significantly different, with a 5-year event-free rate of $68.6\% \pm 10.4\%$ (CM $76.7\% \pm 13.3\%$, SJM $60.6\% \pm 15.7\%$, log-rank $P = .58$) compared with $86.9\% \pm 2.2\%$ for AVR (CM $89.4\% \pm 2.9\%$, SJM $84.6\% \pm 3.3\%$, log-rank $P = .24$) and compared with $84.1\% \pm 3.4\%$ for MVR (CM $85.4\% \pm 4.7\%$, SJM $83.1\% \pm 4.9\%$, log-rank $P = .84$).

Patients received anticoagulation with an INR between 3 and 4.5 in 49% of total hemorrhagic events. The INR value was greater than 4.5 in 30% of cases and less than 3 in 5%. There was no difference in anticoagulation pattern during hemorrhagic events either according to valve position or between CM and SJM groups. All patients received warfarin during follow-up, and 6.2% of patients (CM $n = 2$, SJM $n = 2$) were also receiving antiplatelet therapy during hemorrhagic events. This compares with 7.7% patients overall who were receiving both therapies (Figure 5).

Prosthetic valve endocarditis. There were 5 confirmed cases of prosthetic valve endocarditis (CM $n = 1$, SJM $n = 4$), 2 of which occurred after AVR (CM $n = 1$, SJM $n = 1$), 1 of which occurred after MVR (SJM $n = 1$), and 2 of which

Figure 3. Kaplan-Meier plots showing freedom from thromboembolism for overall study population (A), by position of valve replacement (B), in AVR (C), and in MVR (D). No difference in rates was observed between CM and SJM groups. B, Isolated AVR group had a significantly higher thromboembolic event-free rate than did MVR group (log-rank $P = .007$).

occurred after DVR (SJM $n = 2$). In treatment, reoperation was necessary for 3 patients (CM AVR $n = 1$, SJM AVR $n = 1$, and SJM DVR $n = 1$). Two patients died, one from the SJM MVR group and the other from the CM AVR group. The linearized rates are indicated in Table 5.

Nonstructural dysfunction and other valve-related complications. Echocardiographic evidence of paraprothetic leak was recorded in 12 patients (CM $n = 7$, SJM $n = 5$, $P = .57$), with no significant difference observed after stratification according to valve position or operating surgeon. In 3 cases (CM $n = 2$, SJM $n = 1$), reoperation was indicated. One patient of the SJM group had an aorta-right ventricular fistula develop during AVR, and this had to be repaired in a second operation. There were no cases of structural valve deterioration detected in this series during

this follow-up period. The 5 year event-free rates for non-structural valve dysfunction were $96.1\% \pm 1.4\%$ (0.7% per patient-year) and $96.0\% \pm 1.3\%$ (0.6% per patient-year) for the CM and SJM groups, respectively (log-rank $P = .57$).

NYHA Functional Class

Symptomatic improvement after valve replacement can be expressed by the changes observed in NYHA class during follow-up throughout the 5 years, as shown in Figure 6 and Table 6. Cross-table analyses did not show any significant differences between the CM and SJM groups at any time during follow-up. The proportion of patients in functional classes III and IV decreased from 56% before the operation to 11% 1 year afterward ($P < .001$), but this had increased to 19% by year 3 (year 1 vs year 3, $P < .001$). Thereafter from

Figure 4. Kaplan-Meier plots showing freedom from hemorrhagic events for overall study population (A), by position of valve replacement (B), in AVR (C), and in MVR (D). No difference in rates was observed between CM and SJM groups. Despite trend shown in part B, smaller group of DVR patients did not achieve statistical difference from isolated valve replacement groups.

year 3 to year 5 there was no significant change in the proportion of patients in NYHA functional classes III and IV.

Discussion

It is generally accepted that the clinical performance of a valve prosthesis depends not only on its intrinsic physical design characteristics or implantation technique but also on its interaction with anticoagulation control and patient characteristics.⁶ Many studies have investigated the standard-design CM and SJM bileaflet mechanical prosthetic valves independently and have shown them to perform well, with excellent durability and acceptable rates of valve-related complications. Recent comparative nonrandomized studies have shown no significant real differences between the prostheses described.^{12,13} However, some have reported that the CM valve performed less well than the SJM prosthesis, specifically in relation to thrombosis and embolism in mitral implantations.^{9,10} It was recognized, however, that

it might be difficult to draw firm conclusions from comparisons made in uncontrolled nonrandomized studies. To our knowledge this is the first report of a randomized study to compare the clinical outcome with the use of the CM and SJM standard design bileaflet valve prostheses.

In this study the simple random assignment method used achieved an excellent degree of uniformity in the distribution of major preoperative and perioperative variables. However, it does have limitations. There was a baseline imbalance, with more patients in the CM group with infective endocarditis and congenital valve pathologic conditions (Table 3). In the SJM group overall (all valve positions), more patients underwent associated tricuspid valve repair. In hindsight, we agree that although perfectly balanced randomization is difficult to achieve in reality, such baseline imbalances could have been avoided through the use of a more sophisticated method of randomization that included strategic stratification, block randomization, or minimization.^{16,17}

Figure 5. Box-whisker plot represents INR data during follow-up. There was no difference in mean values of INR between CM and SJM groups in all categories of valve replacement positions according to unpaired *t* test.

Figure 6. NYHA functional class recorded during annual follow-up through 5 years represented as percentage proportion of overall number of patients (see Table 6 for data).

TABLE 6. NYHA functional class: Baseline and annual follow-up to 5 years

	Preoperative		Year 1		Year 2		Year 3		Year 4		Year 5	
	CM	SJM	CM	SJM	CM	SJM	CM	SJM	CM	SJM	CM	SJM
Patients (No.)	234	251	210	225	205	221	198	210	154	182	112	103
NYHA functional class (No.)												
I	10 (4%)	13 (5%)	120 (57%)	116 (52%)	114 (56%)	102 (46%)	95 (48%)	76 (36%)	73 (47%)	73 (40%)	47 (42%)	45 (44%)
II	87 (37%)	104 (41%)	68 (32%)	82 (36%)	65 (32%)	84 (38%)	71 (36%)	85 (40%)	63 (41%)	67 (37%)	45 (40%)	30 (29%)
III	78 (33%)	88 (35%)	18 (9%)	17 (8%)	19 (9%)	23 (10%)	20 (10%)	36 (17%)	11 (7%)	26 (14%)	16 (14%)	16 (16%)
IV	59 (25%)	46 (18%)	4 (2%)	10 (4%)	7 (3%)	12 (5%)	12 (6%)	13 (6%)	7 (5%)	16 (9%)	4 (4%)	12 (12%)

Percentages refer to the CM and SJM groups.

In addressing the issue of variation in reported rates of complications, this study recorded data according to the definitions agreed on in the internationally published guidelines. All event rates quoted include early (<30 days) postoperative complications, with operation designated as time zero. The actual rates of valve-related events in this study were comparable in most respects with those reported by other centers.

With respect to isolated AVR, the linearized rates (percentage per patient-year) of thromboembolism in our series at midterm were 1.5% for the CM valve and 1.3% for the SJM valve, with published ranges of 0.9% to 1.9%^{6,18} for the CM valve and 0.6% to 2.4%^{19,20} for the SJM. For bleeding events in the AVR group, our rates were 3.2% for CM and 4.1% for SJM, with other reported rates ranging from 0.7% to 2.3%^{6,18} for CM and 0.1% to 3.5%^{21,22} for SJM. Similarly, our rate for thromboembolism among patients who underwent MVR was 3.2% per patient-year (CM 3.3%, SJM 3.1%), comparable with other reports, which

have ranged from 0.4% to 5.0%.^{6,12} The incidence of hemorrhagic events in our MVR group was 3.9% per patient-year (CM 3.7%, SJM 4.0%); previous reports have ranged from 1.5% to 6.4%.^{6,12}

It is generally believed that thromboembolic and hemorrhagic events are the same entity at opposite ends of the spectrum in which anticoagulation control is a major determinant of outcome. Anticoagulation management is usually community based in the United Kingdom, and most follow the British National Formulary (BNF) published guidelines as recommended by the British Society for Haematology. The British National Formulary specifies a general target INR range of 3 to 4.5 for mechanical heart valve prostheses, which may be higher than necessary and may predispose these patients toward more bleeding events, at least according to some reports.^{23,24} Despite a higher target, the actual recorded mean INR during follow-up was 3.0, as shown in Figure 5. Of the group who bled, however, 30% had an INR

in excess of 4.5 during the acute event, as compared with 5% overall during follow-up (673 of 13,612 readings) in the study population.

Despite the lack of major differences in bleeding or thromboembolic indices between CM and SJM valves and the fact that no mitral valve thrombosis was detected up to the time of this report, we recognize the need to apply some caution in interpretation of such data and to remember the interim nature of this report. With further follow-up across the projected 10-year period, and as the patient-years accumulate, the levels of power and statistical confidence will increase to provide a more accurate comparison between the two valve types,²⁵ particularly for such uncommon outcome events as valve thrombosis. Thus the total number of 197 prosthetic mitral valves implanted in this study (n = 160 MVR and n = 37 DVR), with the associated levels of linearized hazard rates and the presented duration of follow-up, may not yet provide statistical confidence with a high enough level of power to exclude with certainty any differences in thrombogenicity, or other measured end points, that might be found to exist over the long term between CM and SJM MVRs.

In summary, this randomized study showed no major differences in clinical outcomes between patients who received standard CarboMedics and St Jude Medical bileaflet mechanical valve prosthesis after 5 years' follow-up. Choices with respect to these two valves can therefore be based on other considerations.

We thank St Jude Medical and Sulzer-CarboMedics for providing financial support for a clerical assistant for the duration of this study. None of the authors received any financial benefit from St Jude or Sulzer-CarboMedics Inc. We also wish to thank Mr J.D. Wisheart, Mr J.P. Dhasmana, and Mr J. Hutter for their expertise in implanting the valves, our cardiologist colleagues in the Southwest of England for the care of these patients, and Ms Louise Kingham for her assistance with statistical analysis.

References

- Zellner JL, Kratz JM, Crumbley AJ, Stroud MR, Bradley SM, Sade RM, et al. Long-term experience with the St. Jude Medical valve prosthesis. *Ann Thorac Surg*. 1999;68:1210-8.
- Baudet EM, Puel V, McBride JT, Grimaud JP, Roques F, Clerc F, et al. Long-term results of valve replacement with the St. Jude Medical prosthesis. *J Thorac Cardiovasc Surg*. 1995;109:858-70.
- Craver J. CarboMedics Prosthetic Heart Valve. *Eur J Cardiothorac Surg*. 1999;15 Suppl 1:S3-11.
- Copeland JG. The CarboMedics prosthetic heart valve: a second generation bileaflet prosthesis. *Semin Thorac Cardiovasc Surg*. 1996;8:237-41.
- Stahlberg K, Mattila I, Heikkilä L, Sipponen J, Verkka K, Mattila S. St. Jude versus CarboMedics: follow-up after prosthetic valve replacement. *J Cardiovasc Surg (Torino)*. 1997;38:577-80.
- Akins CW. Results with mechanical cardiac valvular prostheses. *Ann Thorac Surg*. 1995;60:1836-44.
- Copeland JG. An international experience with the CarboMedics prosthetic heart valve. *J Heart Valve Dis*. 1995;4:56-62.
- Burnett C. The clinical report. *CarboMedics*. 1995;7:1-8.
- Chaudhuri N, Hickey MS, Spyt TJ. An unexplained cluster of thrombosed bileaflet mechanical heart valve prostheses. *Ann Thorac Surg*. 1999;67:1542-3.
- Rosengart TK, O'Hara M, Lang SJ, Ko W, Altorki N, Krieger KH et al. Outcome analysis of 245 CarboMedics and St. Jude valves implanted at the same institution. *Ann Thorac Surg*. 1998;66:1684-91.
- Wang SS, Chu SH, Tsai CH, Lin FY. Clinical use of CarboMedics and St. Jude Medical valves. *Artif Organs*. 1996;20:1299-303.
- Jamieson WR, Miyagishima RT, Grunkemeier GL, Germann E, Henderson C, Fradet GJ, et al. Bileaflet mechanical prostheses performance in mitral position. *Eur J Cardiothorac Surg*. 1999;15:786-94.
- Jamieson WR, Munro AI, Miyagishima RT, Grunkemeier GL, Burr LH, Lichtenstein SV, et al. Multiple mechanical valve replacement surgery comparison of St. Jude Medical and CarboMedics prostheses. *Eur J Cardiothorac Surg*. 1998;13:151-9.
- British Society for Haematology. British Committee for Standards in Haematology. Haemostasis and Thrombosis Task Force. Guidelines on oral anticoagulation: second edition. *J Clin Pathol*. 1990;43:177-83.
- Edmunds LH, Clark RE, Cohn LH, Grunkemeier GL, Miller DC, Weisel RD. Guidelines for reporting morbidity and mortality after cardiac valvular operations. Ad Hoc Liaison Committee for Standardizing Definitions of Prosthetic Heart Valve Morbidity of The American Association for Thoracic Surgery and The Society of Thoracic Surgeons. *J Thorac Cardiovasc Surg*. 1996;112:708-11.
- Treasure T, MacRae KD. Minimisation: the platinum standard for trials? Randomisation doesn't guarantee similarity of groups; minimisation does. *BMJ*. 1998;317:362-3.
- Altman DG, Bland JM. How to randomise. *BMJ*. 1999;319:703-4.
- Fiane AE, Geiran OR, Svennevig JL. Up to eight years' follow-up of 997 patients receiving the CarboMedics prosthetic heart valve. *Ann Thorac Surg*. 1998;66:443-8.
- Smith JA, Westlake GW, Mullerworth MH, Skillington PD, Tatoulis J. Excellent long-term results of cardiac valve replacement with the St Jude Medical valve prosthesis. *Circulation*. 1993;88(5 Pt 2):II49-54.
- 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.
- Nakano K, Koyanagi H, Hashimoto A, Kitamura M, Endo M, Nagashima M, et al. Twelve years' experience with the St. Jude Medical valve prosthesis. *Ann Thorac Surg*. 1994;57:697-702.
- Kratz JM, Crawford FA, 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.
- Saour JN, Sieck JO, Mamo LA, Gallus AS. Trial of different intensities of anticoagulation in patients with prosthetic heart valves. *N Engl J Med*. 1990;322:428-32.
- Stein PD, Alpert JS, Dalen JE, Horstkotte D, Turpie AG. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. *Chest*. 1998;114(5 Suppl):602S-10S.
- Grunkemeier GL, Johnson DM, Naftel DC. Sample size requirements for evaluating heart valves with constant risk events. *J Heart Valve Dis*. 1994;3:53-8.

Discussion

Dr Cary W. Akins (Boston, Mass). I commend the authors for performing a prospective randomized comparison of St Jude and CarboMedics bileaflet prostheses. In this interim report of the 5-year data, Lim and coworkers found no statistically significant difference in the clinical performance of the two valves. The principal question that we must ask is whether this finding is expected or even predictable; that is, are the results not so much a function of the apparent equality of the prostheses but rather a function of the study design?

Prospective randomized trials are the criterion standard for allowing one to seek answers to clinical questions univariably, in this case the clinical performance of two mechanical valves. However, prospective randomized trials are only of value if they

contain sufficient statistical power; that is enough patients and long enough follow-up. In this planned 10-year trial there are only 234 total CM recipients and 251 SJM recipients. Will these numbers yield sufficient statistical power? Let's begin with the mitral valves.

In my 1995 review of the literature on mechanical valves, the composite thromboembolism and bleeding rates for mitral valves were 4.16% for SJM valves and 4.99% for CM valves. A simple power calculation performed with just these numbers documents that to distinguish a significant difference between the two mitral valves would require more than 10,000 patient-years of follow-up in each group; that is, 1000 patients in each group followed up for 10 years without deaths or, if one accounts for mortality, 1400 patients in each group. Even according to the more disparate clinical results from Rosengart's 1998 smaller comparative study of the two valves, one would require a complete 10-year follow-up of 700 patients in each group, not just 75 CM valves and 85 SJM valves in the mitral position. Predictable comparison of the results between aortic SJM and CM valves, which have more similar composite thromboembolism and bleeding rates, would require more aortic valve replacements than are performed in the entire United Kingdom in any decade. Unfortunately, I am left to conclude that the results of the study are predictable merely by the virtue of the study design.

Several other features of the study warrant comment. Mean patient age was 60 years, and the 5-year actuarial survival of 81.1% did not differ significantly between the two groups. However, the predicted survival for the general population of the same age at 5 years is 92.1%. Thus patients receiving either of these state-of-the-art bileaflet prostheses had a mortality rate at 5 years that was almost 2.5 times that for the general population.

In addition, although the INR for these patients was quite high, at 3 to 4.5, linearized thromboembolic rates were 3.1% for SJM MVR patients and 3.3% for CM MVR patients. When combined with the linearized bleeding rates of 4% for SJM and 3.7% for CM, the composite thromboembolism bleeding rates for both valves are 7% per patient-year.

In addition to discussing the statistical power of the study, I would like to ask Mr Bryan to comment on the somewhat disappointing mortality and morbidity rates in this study with these two state-of-the-art prostheses.

Finally, AVR recipients differ from MVR recipients, so why include DVR patients in the trial? When a late complication occurs in a patient who has undergone DVR, to which prosthesis do you assign the blame?

Mr Bryan. I thank Dr Akins for his comments and also for some of the literature that he has provided through the years with respect to the evaluation of the mechanical heart valve prosthesis, which we have used as a standard reference in the conduct of this study.

With respect to the power of the study, the original statistical advice was based on a projected total population of 500 patients followed up for 10 years, with a projection of more than 2000 patient-years of follow-up. It was anticipated that with respect to composite end points, such as overall event-free survival at 10 years, a clinically meaningful difference between these two valves could be demonstrated with a high level of confidence. I do agree with Dr Akins that in studies like this there are difficulties in demonstrating statistically significant differences with respect to end points that occur infrequently, but that was not the original stated aim of this study. I think that a more realistic end point is event-free survival at 10 years.

Second, Dr Akins raised a question with regard to the mortality. I am not sure whether he is referring to the early mortality or the late valve-related mortality. With respect to the early mortality, I think that the institutional mortality, considering the significant proportion of patients undergoing reoperative surgery and the proportion of patients undergoing associated coronary bypass, certainly conforms to the time-related mortalities produced by both the Society of Thoracic Surgeons and the UK cardiac surgical register, and indeed all of the mortalities, which were not different between surgeons, were better than predicted when adjusted for standard Parsonnet.

With respect to the late mortality after mechanical prosthetic valve replacement, I think we all must acknowledge that mechanical valve replacement is not necessarily today viewed as the criterion standard. We, like everybody else, prefer to repair mitral valves rather than replace them.

There is no doubt that if you follow up patients prospectively every year laboriously in detail, you will collect a much higher rate of complications than if you send these same patients a letter at 5 or 10 years. That was drawn to my attention by Dr Akins' own review in 1996 in the *Annals of Thoracic Surgery*. I suggest that here we have at least a partial reflection of that kind of finding.

Dr Verdi J. DiSesa (Chicago, Ill). Your data inevitably led you to the conclusion that there was no difference in patient outcome with either valve and that the choice between them should therefore be based on other considerations. Can you enlighten us as to what some of those considerations might be?

Mr Bryan. They might relate to individual surgeon preference; for example, they might relate to differences in implantation techniques that surgeons might perceive. When we are all talking in the coffee room after operations, we may express certain preferences when we are implanting prosthetic valves. These preferences may not necessarily, unfortunately, be scientifically based. But I suggest that with mechanical bileaflet prostheses we can be secure in the knowledge that, at least as far as our interim data are concerned, whichever of these two prostheses we choose, there does not seem to be any actual difference in clinical outcome.