CLINICAL COMMUNIQUÉ
16 YEAR RESULTS

Carpentier-Edwards PERIMOUNT Mitral Pericardial Bioprosthesis, Model 6900

Introduction

The Carpentier-Edwards PERIMOUNT Mitral Pericardial Valve, Model 6900, was introduced into clinical use in 1984, approved for U.S. commercial distribution in 2000 and bears the CE mark for countries in the European Union. The data represented below is a summary of the clinical experience of seven centers in Europe and Canada.

Materials and Methods

A total of 435 patients were implanted between January 1984 and December 1989. The majority, 333 (77%) patients underwent isolated mitral valve replacement (MVR), and 102 (23%) underwent double (mitral and aortic PERIMOUNT) valve replacement (DVR). The mean age at implant was 60.7 ± 11.6 years and ranged from 8 to 82 years (Figure 1). There were 179 (41%) males and 256 (59%) females.

Age Distribution at Implant

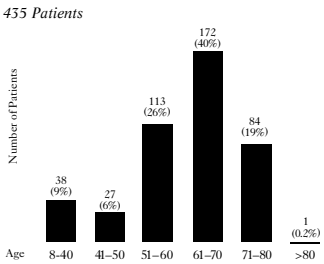

Figure 1

The most common etiology was rheumatic heart disease (54%) followed by degenerative heart disease (22%). The indications for mitral valve replacement were regurgitation (44%), stenosis (26%), mixed disease (21%) (regurgitation and stenosis), and previous prosthetic valve dysfunction (8%) (Figure 2).

Diagnosis	*Number*	*Percent*
Regurgitation	193	44%
Stenosis	112	26%
Mixed Disease	93	21%
Previous Prosthetic Valve Deterioration	36	8%
Prophylactic Replacement	1	0.2%
Total	*435*	*100%*

Figure 2

Of the 435 patients, there were 270 pre-existing conditions. Coronary artery disease, including previous myocardial infarction, was the most common pre-existing condition; 111 patients (41%) had coronary artery disease. Thirty-three patients (12%) presented with pulmonary hypertension and twenty-four percent of the patient population had undergone prior mitral valve replacement or repair. Sixteen patients (6%) presented with a history of congestive heart failure (Figure 3).

Surgical Treatment

Of the 435 patients, 123 patients underwent 132 concomitant procedures. Coronary artery bypass grafting was the most frequently performed concomitant procedure (Figure 3).

Concomitant Procedure	*Number*	*Percent*
Coronary Artery Bypass Graft	64	48%
Tricuspid Valve/Annulus Repair	46	35%
Pacemaker Insertion	6	5%
Aortic Valve/Annulus Repair	4	3%
Aneurysm Repair	3	2%
Other	9	7%
Total	*132*	*100%*

Figure 3

Edwards
LIFESCIENCES

The prosthetic valve size distribution is shown in Figure 4. Sizes 27mm and 29mm were most frequently utilized.

Valve Size Distribution (N=435)

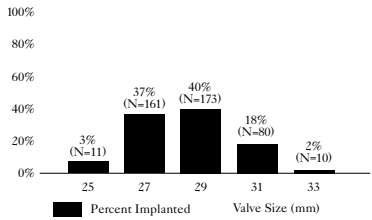

Figure 4

Follow-Up

Patient status in this cohort was assessed annually during office or hospital visits, or by means of detailed questionnaires completed over the telephone or by mail. All valve related complications were identified according to the STS guidelines for reporting morbidity and mortality after cardiac valvular operations.[1]

At current follow-up, 104 (24%) patients were alive, 240 (55%) patients had died, 78 (18%) were explanted, and 13 (3%) were lost to follow-up. Total patient follow-up was 3,684 patient-years with a mean follow-up of 8.5 ± 4.8 years and the maximum follow-up of 17.2 years. Follow-up was 97% complete.

Summary of Clinical Data

Number of Patients	435
Implant Time Frame	Jan 1984-Dec 1989
Mean Age	60.7 years
Distribution	41% male 59% female
Mean Follow-up	8.5 years
Maximum Follow-up	17.2 years
Total Follow-up	3,684 patient years
Most Common Etiology • Rheumatic Heart Disease	54%
Most Common Preoperative Diagnosis • Regurgitation	44%

Figure 5

Antithromboembolic Therapy

Preoperatively, 49% of patients were in atrial fibrillation and 45% were in normal sinus rhythm. Antithromboembolic therapy is reported for the 104 patients alive at last follow-up in Figure 6. Two patients were on two different therapies. Thirty-seven (36%) patients were either on aspirin or were not on any form of antithromboembolic therapy. Of the patients on anticoagulant therapy, 63% had rhythm disturbances.

Postoperative Antithromboembolic Therapy

AC Therapy	*Number*	*Percent*
None	13	12%
Aspirin/Anti-Platelet	24	23%
Coumarine derivatives (Warfarin/Sintrom/Marcoumar)	67	63%
Other	2	2%
Total Therapies	*106*	*100%*

Figure 6

Results

New York Heart Association (NYHA) Functional Class

Functional improvement of all implant patients has been documented by a marked decrease in New York Heart Association (NYHA) classification. Preoperatively, 340 (78%) patients of the entire cohort (N=435) were in either Class III or IV; 82 (19%) patients were in Class II and 11 (3%) were in Class I; the NYHA class was unknown for 2 (0.5%) patients. The last NYHA assessment was performed at a mean implant time frame of 12.9 ± 1.9 years (range 9.1 – 17.2 years). Preoperative NYHA classification compared to the classification at last follow-up is presented (Figure 7).

Comparison of NYHA Functional Class: Preoperative and Last Follow-up

	Postoperative				*Death &*				
Preoperative	*I*	*II*	*III*	*IV*	*Explant*	*Expired*	*Explant*	*Lost*	*Missing*	*Total*
I	0	2	0	0	3	6	0	0	0	11
II	14	8	1	0	22	34	0	3	0	82
III	29	19	8	0	37	127	1	7	1	229
IV	11	10	0	1	14	71	1	3	0	111
Not Available	0	0	0	0	0	2	0	0	0	2
Total	*54*	*39*	*9*	*1*	*76*	*240*	*2*	*13*	*1*	*435*

Figure 7

Valve-Related Survival

There were a total of 26 deaths classified as valve-related in this patient population. Sixty-four additional deaths were conservatively classified as valve-related although the valve relatedness was reported as "unknown" by the investigator. One valve-related expiration occurred in the operative period was due to a thromboembolism. The postoperative deaths included: thirty-two due to cardiac failure, ten due to thromboembolism, three due to hemorrhagic anticoagulation complication, three due to endocarditis, and three due to structural valve dysfunction. Thirty-six deaths were due to either unknown causes (n=17) or sudden death (n=19); these are conservatively classified as valve related. There were two other deaths that were considered to be valve-related because of lack of information to the contrary.

Freedom From Valve-Related Expirations, Including Unknown

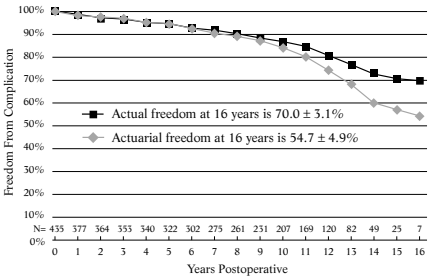

Figure 8

Freedom From Valve-Related Expirations, Excluding Unknown

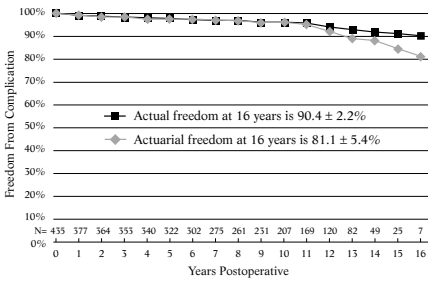

Figure 9

Freedom From Major Thromboembolism

Freedom from major thromboembolism (defined as neurological deficit that did not resolve within 3 weeks of onset) is presented below. There were a total of 37 late events, resulting in a linearized rate of 1.0% per patient-year.

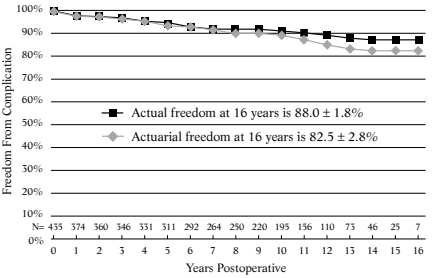

Figure 10

Freedom From Major Anticoagulant-Related Hemorrhage

Freedom from major anticoagulant-related hemorrhage (defined as those requiring hospitalization or transfusion) is presented below. There were a total of 40 late events, resulting in a linearized rate of 1.1% per patient-year.

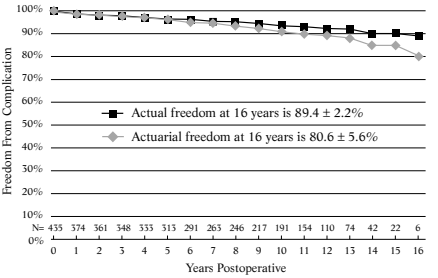

Figure 11

Explants

A total of 80 valves were explanted during the postoperative period. Seventy-eight explants were valve related. Sixty-five explants were due to valve dysfunction, nine due to non-structural deterioration, four due to endocarditis.

Freedom From Explant

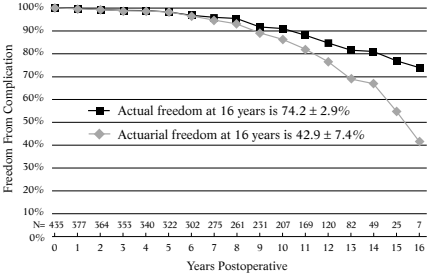

Figure 12

Structural Valve Deterioration

Structural valve deterioration is defined as any change in valve function resulting from an intrinsic abnormality causing stenosis or regurgitation. It excludes infected or thrombosed valves as determined upon explant and includes changes intrinsic to the valve such as wear, calcification, leaflet tear and stent creep. There were a total of 65 patients who experienced explant due to structural valve dysfunction, 66% due to calcification, 19% due to leaflet tear and 15% due to a combination of both.

The effect of age on tissue valve performance has been discussed in the literature. Therefore, analyses by overall ages (Figure 13) and by age segment (Figures 14-15) are presented.

Freedom From Explant Due to Structural Valve Deterioration Overall Ages

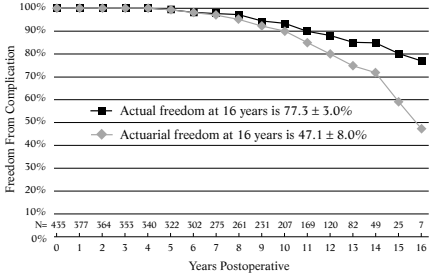

Figure 13

Actual Freedom from Explant Due to Structural Valve Deterioration - Cumulative Age Groups

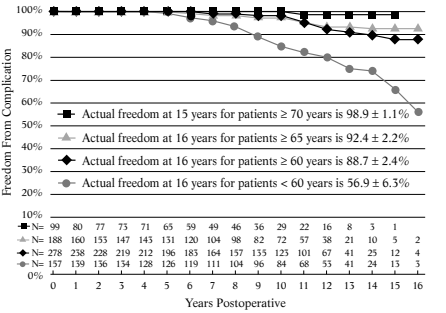

Figure 14

Actuarial Freedom from Explant due to Structural Valve Deterioration - Cumulative Age Groups

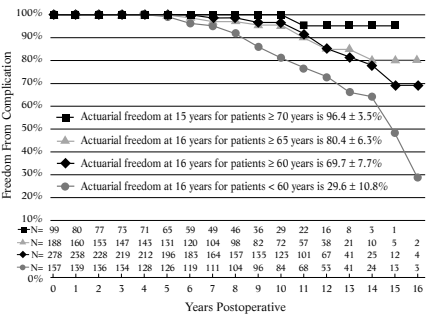

Figure 15

Summary of Actual Freedom from Explant Due to Structural Valve Deterioration - Cumulative Age Groups

Patient Age	*At 5 Years*	*At 10 Years*	*At 15*-16† Years*
< 60	99.3%	85.6%	56.9%†
≥ 60	100%	97.8%	88.7%†
≥ 65	100%	97.3%	92.4%†
≥ 70	100%	100%	98.9%*

Figure 16

APPENDIX 1: Clinical Centers

	Patients	*Percent*
M. Marchand Trousseau University Hospital, Tours, France	139	32%
R. Norton Walsgrave Hospital, Coventry, U.K.	90	21%
M. Pellerin Montreal Heart Institute, Montreal, Canada	76	17%
T. Dubiel University Hospital, Uppsala, Sweden	46	11%
W. Daenen University Hospital, Gasthuisberg, Leuven, Belgium	36	8%
M. Holden Freeman Hospital, Newcastle-Upon Tyne, U.K.	30	7%
T. E. David Toronto General Hospital, Toronto, Canada	18	4%
Total	*435*	*100%*

APPENDIX 2: Statistical Methods

Descriptive statistics were summarized as the mean and standard deviation for continuous variables, with confidence limits computed using the t-statistic, and as frequencies and percentages for categorical variables, with exact confidence limits.

Parametric analysis of adverse events was performed using a constant hazard model, considering only events occurring 31 days or later after implant; confidence limits were computed using Cox's approximate chi-square statistic, as discussed in the paper of G.L. Grunkemeier and W.N. Anderson, "Clinical evaluation and analysis of heart valve substitutes", J Heart Valve Dis 7;1998:163-9.

Nonparametric estimates of adverse events were obtained by the method of Kaplan and Meier, with standard errors computed using Greenwood's algorithm and groups compared using the log-rank test. Competing risk analyses of adverse events (i.e. actual freedom from SVD) used the matrix form of the Kaplan-Meier and Greenwood algorithms, as presented in Andersen et al., Statistical Models based on Counting Processes, Springer-Verlag 1993.

APPENDIX 3: Structural Valve Deterioration

When the PERIMOUNT bioprosthesis was first introduced into clinical studies in 1981, the STS Guidelines (first published in 1988) on reporting morbidity and mortality after cardiac valvular operations did not exist.

At that time, the FDA's guideline was to report bioprosthetic valve performance in terms of "valve dysfunction" defined as "either an explant of a study valve due to regurgitation or stenosis; or a murmur associated with the study valve which had clinical consequences for the patient."

These were the guidelines originally used to define valve dysfunction for the Edwards long-term clinical cohort. Furthermore, the FDA guidelines did not differentiate between murmurs due to abnormalities extrinsic to the valve, including paravalvular leak or pannus overgrowth. Thus, over-reporting of valve dysfunction could have occurred using the definition originally used by Edwards for the PERIMOUNT bioprosthesis.

According to the 1996 STS Guidelines, Structural Valve Deterioration (SVD) is defined as "any change in function (a decrease of one NYHA functional class or more) of an operated valve resulting from an intrinsic abnormality of the valve that causes stenosis or regurgitation."[1] All patients in Edwards' long-term cohort have been evaluated for valve dysfunction/SVD according to the original criteria defined in 1981 and the most recent STS criteria.

Because of the relative subjectivity in the assessment of SVD using only clinical evaluation (echocardiography, auscultation of murmurs, evaluation of NYHA class), rates vary widely from center to center. Thus, many centers use the more definitive diagnosis of SVD upon explant of the valve, which removes any subjective evaluation of valve failure.

In fact, a review of the literature shows that most published papers that report on bioprosthetic clinical durability do use the more definitive, less subjective definition of "freedom from explant due to SVD." Many published papers report SVD using the "Freedom from Explant" definition but refer to it as "Freedom from Primary Tissue Failure" or "Freedom from Structural Valve Deterioration."

REFERENCES
1. Edmunds H, et al. Guidelines for Reporting Morbidity and Mortality After Cardiac Valvular Operations. J Thorac Cardiovasc Surg 1996; 112:708-11.

Edwards Lifesciences

Edwards Lifesciences LLC · One Edwards Way · Irvine, CA 92614 USA · 949.250.2500 · 800.424.3278 · www.edwards.com
Edwards Lifesciences (Canada) Inc. · 1290 Central Pkwy West, Suite 300 · Mississauga, Ontario · Canada L5C 4R3 · Phone 905.566.4220 · 800.268.3993
Edwards Lifesciences S.A. · Ch. du Glapin 6 · 1162 Saint-Prex · Switzerland · Phone 41.21.823.4300
Edwards Lifesciences Japan · 2-8 Rokubancho · Chiyoda-ku, Tokyo 102-0085 · Japan · Phone 81.3.5213.5700