CLINICAL COMMUNIQUÉ 20 YEAR RESULTS

Carpentier-Edwards PERIMOUNT Aortic Pericardial Bioprosthesis

The Carpentier-Edwards PERIMOUNT aortic pericardial bioprosthesis was introduced into clinical use in 1981 and approved for US commercial distribution on September 26, 1991. The data represented below are a summary of the 20-year clinical experience of four of the FDA primary centers (Appendix 1). These four centers were involved in post-approval studies which were conducted in accordance with the post-approval protocol submitted in PMA #P860057 for the PERIMOUNT bioprosthesis.

Materials and Methods

Patients

A total of 267 patients received isolated aortic valve replacement with a PERIMOUNT bioprosthesis between September 1981 and December 1983. Mean age at implant was 65 ± 12 years (range 21 to 86 years, Figure 1). Of these, 64% were men. Preoperatively, 45 (17%) of the patients were in New York Heart Association (NYHA) functional class IV, 115 (43%) in class III, 93 (35%) in class II and 10 (4%) in class I (4 were not classified). Eight (3%) had a previous aortic valve replacement. Coronary artery disease (n=133, 50%), congestive heart failure (n=58, 22%), and previous myocardial infarction (n=45, 18%) were the most common preexisting conditions. The most frequent indication for valve replacement was pure aortic stenosis in 174 patients (65%), pure aortic regurgitation in 46 (17%) and mixed stenosis and regurgitation in 39 (15%).

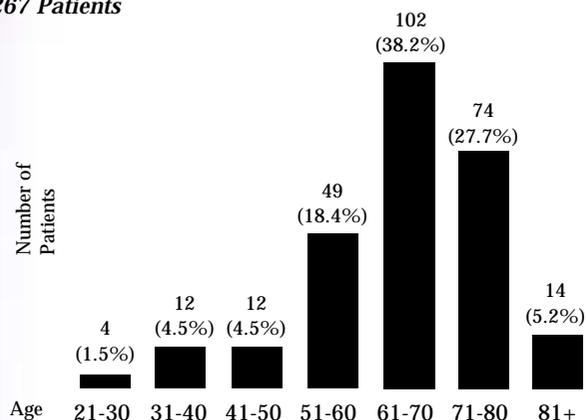## Age Distribution at Implant

267 Patients

Figure 1

Surgical Technique

Aortic valve replacement was performed using standard techniques. Concomitant procedures, performed in 123 patients, included coronary artery bypass grafting (CABG) in 108, and ascending aortic grafting in 7. The size of the prosthesis implanted was 19 mm in 34 patients (13%), 21 mm in 83 patients (31%), 23 mm in 85 patients (32%), 25 mm in 48 patients (18%), 27 mm in 12 patients (4.5%), and 29 mm in 5 patients (1.9%).

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]

A total of 2,407 patient years of data were available for analysis (2,386 late patient years). Mean follow-up was 9.0 ± 5.5 years, with a maximum of 20.3 years. Patient status as of the last follow-up interval included 189 expired (70.8%), 10 alive (3.8%), 46 explanted (17.2%), and 22 lost to follow-up (8.2%).

Results

Valve-Related Survival

There were a total of 48 valve-related deaths in this patient population; 1 valve-related expiration occurred in the operative period and consisted of bleeding. Twenty-eight postoperative valve-related deaths (1.2%/ptyr) included 5 due to thromboembolism, 4 due to endocarditis/sepsis, 3 due to structural valve deterioration and 1 due to bleeding. There were 15 other deaths that were considered to be valve-related because of

lack of information or because the expiration was classified as valve-related by the investigator. These included cardiac arrest (n=2), disseminated intravascular coagulopathy (n=1), congestive heart failure (n=3), and others (n=9). Actuarial freedom from valve-related death was $67.9 \pm 6.6\%$ at 20 years; actual freedom from valve-related death was $85.8 \pm 2.5\%$ (Figure 2).

Freedom from Valve Related Death

N= 267 237 229 215 209 198 184 168 157 139 118 101 78 64 56 43 32 26 19 7 3

- Actual freedom at 20 years is 85.8%
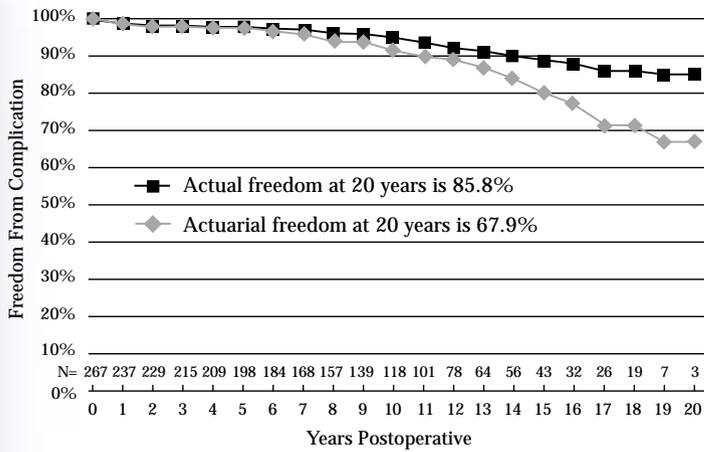- Actuarial freedom at 20 years is 67.9%

Figure 2

Nineteen additional deaths were due to either unknown causes (n=14) or sudden death (n=5) and might have been valve related; however, all 5 of the sudden deaths and 9 of the unknown causes had a history of coronary artery disease or congestive heart failure. These deaths were conservatively classified as valve related; accordingly, the resulting actuarial freedom from valve-related expiration was $55.4 \pm 6.4\%$ at 20 years. The actual freedom from valve-related death in this instance was $77.2 \pm 3.0\%$

Thromboembolism/Thrombosis

Eleven patients (4.1%) experienced emboli during the operative period; 3 patients required a reoperation. Forty-one late thromboembolic events were reported for a linearized rate of 1.7%/ptyr and 5 patients subsequently died from this complication. Actuarial freedom from thromboembolism was $68.2 \pm 6.8\%$ at 20 years (Figure 3). No occurrence of valve thrombosis was reported in this patient cohort.

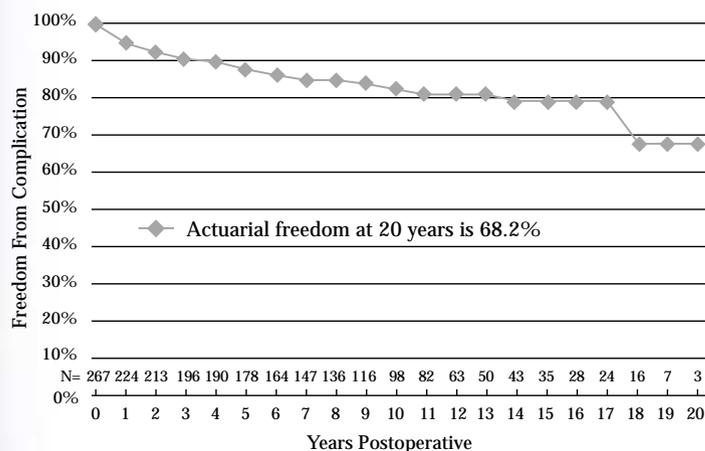**Actuarial Freedom from Thromboembolism**

- Actuarial freedom at 20 years is 68.2%

N= 267 224 213 196 190 178 164 147 136 116 98 82 63 50 43 35 28 24 16 7 3

Figure 3

Bleeding

The operative rate of bleeding was 1.9% and included the only operative valve-related death. Ten patients (0.4%/ptyr) reportedly experienced bleeding in the postoperative period; 1 patient subsequently died. Actuarial freedom from bleeding was $91.7 \pm 2.2\%$ at 20 years (Figure 4).
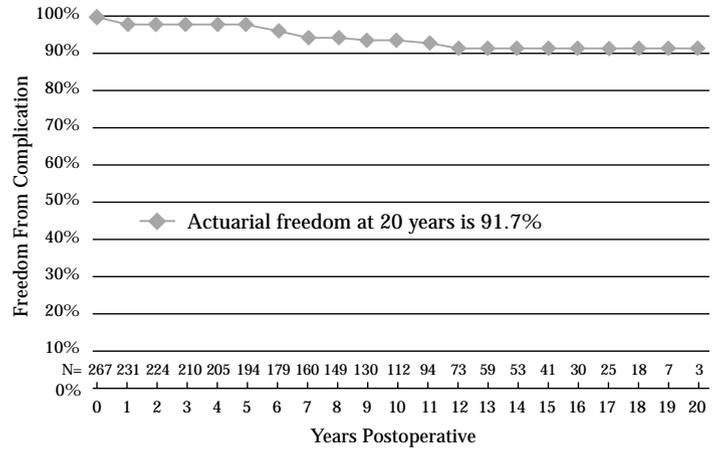
Actuarial Freedom from Bleeding

- Actuarial freedom at 20 years is 91.7%

N= 267 231 224 210 205 194 179 160 149 130 112 94 73 59 53 41 30 25 18 7 3

Figure 4

Endocarditis/Sepsis

Nineteen occurrences of endocarditis/sepsis were reported in the postoperative period for a linearized rate of 0.8%/ptyr. Of these, 4 patients subsequently died and 2 underwent reoperation. Actuarial freedom from endocarditis at 20 years was $89.3 \pm 2.4\%$ (Figure 5).
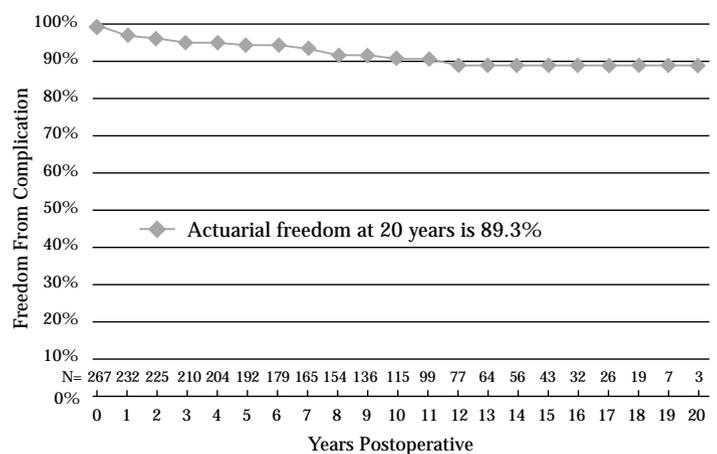
Actuarial Freedom from Endocarditis/Sepsis

- Actuarial freedom at 20 years is 89.3%

N= 267 232 225 210 204 192 179 165 154 136 115 99 77 64 56 43 32 26 19 7 3

Figure 5

Structural Valve Deterioration (SVD)

Explant due to structural valve deterioration (SVD) was required in 36 patients. The primary mode of failure was calcification in 35 patients and leaflet tear in one. The mean duration of implantation of prostheses with SVD was 17.3 ± 4.0 years.

Evaluating the effect of age on tissue valve performance has been discussed frequently in the literature. It is important to evaluate the PERIMOUNT bioprosthesis by patient age at implant to accurately assess its excellent long-term clinical performance. Actuarial and actual freedoms from explant due to SVD are presented according to patient age at implant (Figures 6-9).

Actuarial and Actual Freedom from Explant Due to Structural Valve Deterioration
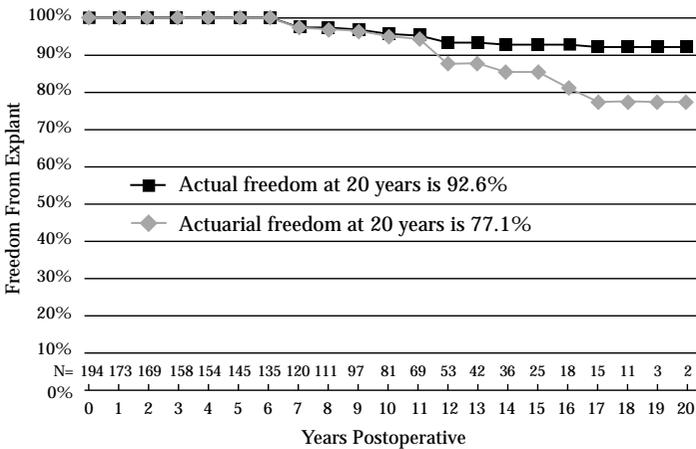
Patients ≥ 60 Years

Actual freedom at 20 years is 92.6%
Actuarial freedom at 20 years is 77.1%

Figure 6

Actuarial and Actual Freedom from Explant Due to Structural Valve Deterioration

Patients ≥ 65 Years

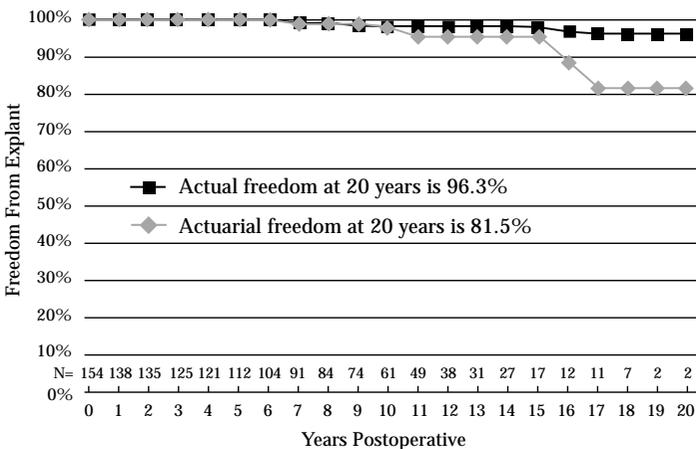Actual freedom at 20 years is 96.3%
Actuarial freedom at 20 years is 81.5%

Figure 7

Actuarial and Actual Freedom from Explant Due to Structural Valve Deterioration

Patients 61-70 Years

Actual freedom at 20 years is 90.5%
Actuarial Freedom at 20 years is 77.9%
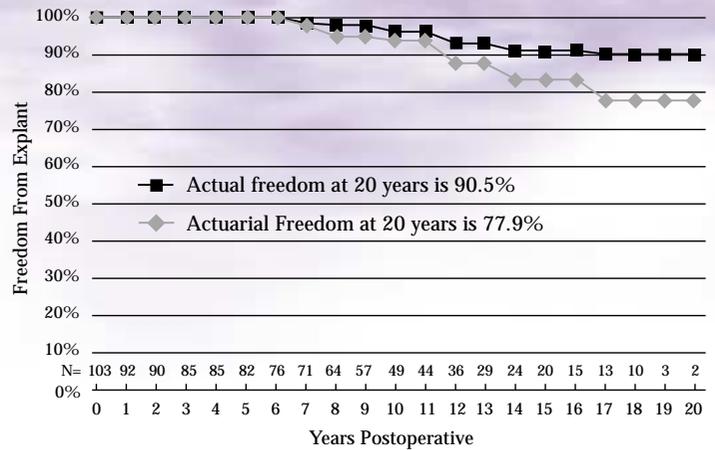
Figure 8

Actuarial and Actual Freedom from Explant Due to Structural Valve Deterioration

Patients > 70 Years

Actual freedom at 18 years is 96.0%
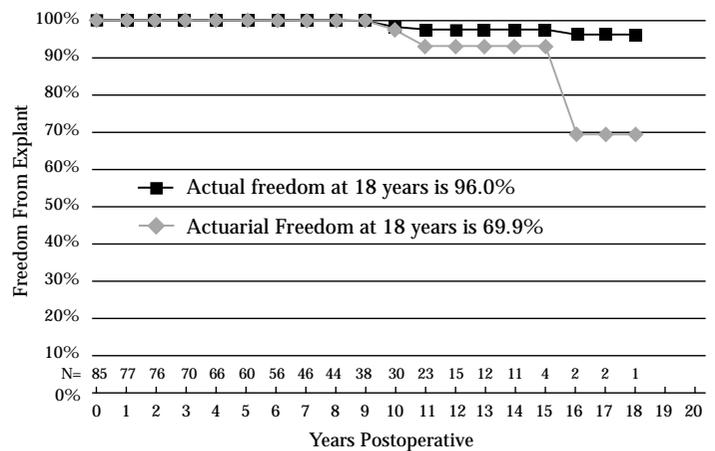Actuarial Freedom at 18 years is 69.9%

Figure 9

NYHA Functional Class

As of the latest follow-up evaluation, 199 patients (82.6%) were reported in functional class I or II (Table 1). The majority of patients showed functional improvement in NYHA classification from the preoperative score.

	Postoperative					
Preoperative	I	II	III	IV	Unknown*	Total
I	6	4	0	0	0	10
II	38	34	12	3	6	93
III	49	35	16	4	11	115
IV	13	17	5	1	9	45
Unknown*	2	1	1	0	0	4
Total	108	91	34	8	26	267

*Lost to follow-up or unavailable at time of follow-up

Table 1: Preoperative vs. Last Reported NYHA

Appendix 1: Summary of Results

Post Approval Centers

	Patients	Percent
Clinic 1: Delos M. Cosgrove, M.D The Cleveland Clinic Foundation	99	37.1%
Clinic 4: Robert W.M. Frater, M.D. Montefiore Medical Center	48	18.0%
Clinic 5: Robert W.M. Frater, M.D. Albert Einstein College of Medicine	47	17.6%
Clinic 10: U. Scott Page, M.D. Good Samaritan Hospital	73	27.3%
Total	*267*	*100%*

Summary of Clinical Data

Number of Patients	267
Implant Time Frame	9/24/81 - 12/28/83
Mean Age	64.9 years
Distribution	171 male (64%) 96 female (36%)
Mean Follow-up	9.0 ± 5.5 years
Total Patient Years	2,407

Most Common Preoperative Diagnosis
- Aortic Stenosis — 65.2%

Freedom from Complications at 20 Years

	Actuarial	Actual	Linearized (%/ptyr)
Thromboembolism	68.2 ± 6.8%	82.3 ± 2.6%	1.7
Endocarditis/Sepsis	89.3 ± 2.4%	91.7 ± 1.7%	0.8
Bleeding	91.7 ± 2.2%	94.0 ± 1.5%	0.4
Valve-Related Expirations	67.9 ± 6.6%	85.8 ± 2.5%	1.2
Explant due to SVD			
>= 60	77.1 ± 7.2%	92.6 ± 2.0%	n.r.*
>= 65	81.5 ± 9.6%	96.3 ± 1.6%	
> 70	69.9 ± 20.5%	96.0 ± 2.3%	

* Not relevant. SVD does not occur as a constant hazard function; consequently, linearized rates are not meaningful.

References
1 Edmunds H, et al. Guidelines for Reporting Morbidity and Mortality After Cardiac Valvular Operations. J Thorac Cardiovasc Surg 1996; 112:708-11.
2 David T, et al. Late Results of Heart Valve Replacement with The Hancock II Bioprosthesis. J Thorac and Cardiovasc Surg. 2001; 121:268-78.

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 risks analysis 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." For example, the reported "Freedom from Structural Valve Deterioration" for the Medtronic Hancock II Bioprosthesis in the latest long-term study uses a similar methodology as that used for the PERIMOUNT bioprosthesis.[2]

Edwards Lifesciences