Appendix 1: Summary of Results

Post Approval Centers

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

Total 267 100%

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 30 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.H. Anderson, “Clinical evaluation of heart valve substitutes,” J Heart Valve Dis 7:1998:163-6.

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 1980) on reporting mortality and mortality after cardiac valve operations did not exist. At that time, the FDA 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.” 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 one center to another.

Most Common Preoperative Diagnosis

- Aortic Stenosis 65.2%
- Aortic Regurgitation 21.2%
- Mitral Stenosis 10.5%
- Mitral Regurgitation 6.7%
- Mixed Stenosis and Regurgitation 0.9%

Freedom from Complications at 20 Years

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Valve-Related Expirations</th>
<th>Thromboembolism</th>
<th>Thrombosis</th>
<th>Endocarditis/Sepsis</th>
<th>Explant due to SVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 65</td>
<td>96.3 ± 2.3%</td>
<td>91.7 ± 2.7%</td>
<td>93.7 ± 2.4%</td>
<td>96.4 ± 2.0%</td>
<td>96.0 ± 2.3%</td>
</tr>
<tr>
<td>≥ 70</td>
<td>69.0 ± 20.5%</td>
<td>77.1 ± 2.7%</td>
<td>81.5 ± 9.6%</td>
<td>71.7 ± 2.7%</td>
<td>69.0 ± 2.0%</td>
</tr>
</tbody>
</table>

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

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%
- Aortic Regurgitation 21.2%
- Mitral Stenosis 10.5%
- Mitral Regurgitation 6.7%
- Mixed Stenosis and Regurgitation 0.9%

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician. See Appendix 3: Structural Valve Deterioration.

Appendix 4: 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 prostheses 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 9 patients (3.4%).

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 valve operations.

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 (78.0%), alive 38 (1.8%), explanted 46 (17.2%), and 22 lost to follow-up (8.2%).

Results

Valve-Related Survival

There were a total of 48 valve-related expirations in this patient population, 1 valve-related expiration occurred in the operative period and consisted of bleeding.

Appendix 5: References

3. David T, et al. Late Results of Heart Valve Replacement with The Hancock II Bioprosthesis in the latest long-term study uses a similar methodology as that used for the PERIMOUNT bioprosthesis.
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=2), congestive heart failure (n=3), and others (n=6). Actual freedom from valve-related expirations at 20 years was 85.8 ± 2.5%; actuarial freedom from valve-related expirations at 20 years was 67.9 ± 6.6% (Figure 2).

**Freedom from Valve-Related Expiration**

Figure 2

Nineteen additional expirations were due to either unknown causes (n=4) 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 77.2 ± 3.0%, the actuarial freedom from valve-related expiration at 20 years was 55.4 ± 6.4%.

**Thromboembolism/Thrombosis**

Eleven patients (4.1%) experienced an embolus during the operative period; 3 patients required a reoperation. Forty-one late thromboembolic events were reported for a linearized rate of 1.7%/pY. The primary mode of failure was calcification in 35 patients and leaflet tear in one. The mean duration of implantation of prostheses with SV was 17.3 ± 4.0 years.

**Endocarditis/Sepsis**

Nineteen occurrences of endocarditis/sepsis were reported in the postoperative period for a linearized rate of 0.8%/pY. Of these, 4 patients subsequently expired and 2 underwent reoperation. Actual freedom from endocarditis/sepsis at 20 years was 91.7 ± 1.7%; actuarial freedom from endocarditis/sepsis at 20 years was 89.3 ± 2.4% (Figure 5). No occurrence of valve thrombosis was reported in this patient cohort.

**Freedom from Thromboembolism/Thrombosis**

Figure 3

The operative rate of bleeding was 1.9% and included the only valve-related expiration. Ten patients (0.4%/pY) reportedly experienced bleeding in the postoperative period; 1 patient subsequently died. Actual freedom from bleeding at 20 years was 94.0 ± 1.5%; actuarial freedom from bleeding at 20 years was 91.7 ± 2.2% (Figure 4).

**Freedom from Bleeding**

Figure 4

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. Freedom from explant due to SVD are presented according to patient age at implant (Figures 6-9).

**Freedom from Explant Due to Structural Valve Deterioration**

Patients > 60 Years

Figure 6

Patients 61-70 Years

Figure 7

Patients > 70 Years

Figure 8

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.

**NYHA Functional Class**

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### Freedom from Valve-Related Expiration

<table>
<thead>
<tr>
<th>Years Postoperative</th>
<th>Actuarial freedom at 20 years</th>
<th>Actual freedom at 20 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>67.9% ± 6.6%</td>
<td>85.8% ± 2.5%</td>
</tr>
</tbody>
</table>

**Figure 2**

Nineteen additional expirations were due to either unknown causes (n=4) 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. Those deaths were conservatively classed as valve-related; accordingly, the resulting actuarial freedom from valve-related expiration was 77.2 ± 3.0%, the actuarial freedom from valve-related expiration at was 55.4 ± 6.4%.

### Thromboembolism/Trombosis

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 0.8%/ptyr. Of these, 4 patients subsequently expired and 2 underwent reoperation. Actual freedom from endocarditis/sepsis at 20 years was 91.7 ± 1.7%; actuarial freedom from endocarditis/sepsis at 20 years was 89.3 ± 2.4% (Figure 5).

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### Freedom from Thromboembolism/Trombosis

<table>
<thead>
<tr>
<th>Years Postoperative</th>
<th>Actual freedom at 20 years</th>
<th>Actuarial freedom at 20 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>89.3% ± 2.4%</td>
<td>91.7% ± 1.7%</td>
</tr>
</tbody>
</table>

**Figure 3**

**Figure 4**

**Figure 5**

**Figure 6**

**Figure 7**

**Figure 8**

**Figure 9**

**Table 1: Preoperative vs. Last Reported NYHA Functional Class**

<table>
<thead>
<tr>
<th>NYHA Functional Class</th>
<th>Preoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>II</td>
<td>38</td>
<td>17</td>
</tr>
<tr>
<td>III</td>
<td>44</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>81</td>
<td>54</td>
</tr>
</tbody>
</table>

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.
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- **Mean Follow-up:** 9.0 ± 5.5 years
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- **Most Common Preoperative Diagnosis**
  - **Aortic Stenosis:** 65.2%

**Freedom from Complications at 20 Years**

<table>
<thead>
<tr>
<th>Actual</th>
<th>Actuarial</th>
<th>Linearized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valve-Related Expirations</td>
<td>85.8 ± 2.5%</td>
<td>67.0 ± 6.6%</td>
</tr>
<tr>
<td>Thrombomembran&quot;</td>
<td>82.4 ± 2.6%</td>
<td>68.2 ± 6.8%</td>
</tr>
<tr>
<td>Thrombosis</td>
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<td>97.3 ± 2.2%</td>
</tr>
<tr>
<td>Endocarditis/Sepsis</td>
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</tr>
<tr>
<td>Expiated due to SVD</td>
<td>92.6 ± 2.0%</td>
<td>77.1 ± 7.2%</td>
</tr>
<tr>
<td>≥ 65</td>
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When the PERIMOUNT bioprosthesis was first introduced into clinical studies in 1981, the STS Guidelines (first published in 1980) on reporting morbidity and mortality after cardiac valve 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 leaks 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." 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) to exclude or evaluate the possibility of pathology, many centers use the more definitive diagnostic 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.

**References**


3. Edwards Lifesciences devices placed on the European market meeting the essential requirements 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's 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 #B60057 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 class 0). Eighty-three (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, 17%) were the most common preexisting conditions. 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**

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>&lt; 70</th>
<th>70-79</th>
<th>≥ 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (1.5%)</td>
<td>12 (4.5%)</td>
<td>14 (5.7%)</td>
<td></td>
</tr>
</tbody>
</table>

**Appendix 4: Statistical Analysis**

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician. See instructions for use for full prescribing information.

**Results**

**Valve-Related Survival**

There were a total of 48 valve-related expirations in this patient population; 1 valve-related expiration occurred in the operative period and consisted of bleeding. Twenty-eight patients exhibited valve deterioration and 1 due to bleeding. There were 15 other expirations that were considered to be valve-related. Of these, six were reoperations, three were due to paravalvular leak and one each was due to stenosis, regurgitation, and other causes. Of the 48 valve-related expirations, 15 were related to bioprosthetic valve failure, 11 to mechanical valve failure, and 22 were related to non-valve-related causes.

**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 valve operations.

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 (17.3%), and 22 lost to follow-up (8.2%).