Long-Term Outcome of the Carpentier-Edwards Pericardial Valve in the Aortic Position in Japanese Patients

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Background: According to the Japanese Circulation Society guidelines, a bioprosthesis is recommended for aortic valve replacement (AVR) in patients aged ≥65 years who have no risk factors for thromboembolism. There are few data, however, regarding the actual durability of bioprosthetic valves in Japanese patients. The purpose of this study was to assess the long-term durability of Carpentier-Edwards pericardial (CEP) valves in Japanese AVR patients, and to assess the risk factors for reoperation due to structural valve deterioration (SVD).

Methods and Results: From 1986 to 2001, a total of 591 patients underwent AVR with CEP valves in 9 hospitals. Of these, 574 patients (mean age, 71.9±8.5 years) were analyzed in this study. There were 26 in-hospital deaths (4.5%). The 10-year follow-up rate was 82.6% and the median follow-up time was 9.2 years. Freedom from reoperation due to SVD was 99.5%, 96.7%, and 87.5% at 5, 10, and 15 years, respectively. Factors that raised the risk of reoperation due to SVD included younger age at operation and history of prior operation. In patients aged ≥65 years, freedom from reoperation due to SVD was 94.4% at 15 years.

Conclusions: The durability of CEP valves in patients with AVR was excellent, especially in elderly patients. Thus, it seems appropriate to follow the current Japanese Circulation Society recommendations for the use of bioprosthetic valves. (Circ J 2014; 78: 882–889)

Key Words: Aortic valve replacement; Bioprosthesis; Durability; Structural valve deterioration

According to the recent American College of Cardiology (ACC)/American Heart Association (AHA) treatment guidelines for valvular heart disease published in 2006,1 a bioprosthetic valve is recommended for aortic valve replacement (AVR) in patients aged ≥65 years who have no risk factors for thromboembolism. This recommendation is a class IIa recommendation. This is based on the fact that there have been many reports on the excellent durability of tissue valves published over the last 2 decades.2-7 Since these guidelines were published, a significant trend towards bioprosthetic valves has been emerging even in younger patients, not only in Western countries, but also in Japan. In fact, the annual number of tissue AVR implantations has continued to increase since the late 1990s, and exceeded the number of mechanical AVR implantations in 2005 according to the annual report issued by the Japanese Association for Thoracic Surgery.8 This trend continues to gain momentum to the present day.9 Accordingly, in 2012, the Japanese Circulation Society revised their guidelines for surgical and interventional treatment of valvular heart disease.10 Their recommendations concerning the use of bioprosthetic valves in patients undergoing AVR includes all patients aged ≥65 years who have no significant risk factors for thromboembolism. This recommendation is now a class I recommendation, but there have been no studies on the durability of tissue valves in Japanese patients. Certain physicians have raised questions about whether bioprosthetic valves perform equally

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well and last as long in Japanese patients as they do in other patient populations. Thus, we organized a multicenter research group, which we called the CEPIA-J Study Group (Durability Evaluation of Carpentier-Edwards PERIMOUNT Pericardial Valve in Aortic Position in Japanese Patients Study Group). The aims of this study were as follows: (1) to assess the long-term durability of pericardial valves in Japanese patients undergoing AVR; and (2) to identify the factors that influence outcomes, including all-cause death and valve-related adverse events including thromboembolic events, major bleeding, and prosthetic valve endocarditis (PVE), as well as reoperation due to structural valve deterioration (SVD).

Methods

Patients
In Japan, the Carpentier-Edwards PERIMOUNT pericardial (CEP) bioprosthesis (Edwards Lifesciences, Irvine, CA, USA) was approved for clinical use in 1985. All adult patients undergoing AVR using CEP valves in the participating 9 hospitals (Supplementary File 1; Appendix S1) from January 1986 to December 2001 were included in this study. Of note, those who underwent aortic root replacement with composite grafts, concomitant procedures such as coronary artery bypass grafting, mitral or tricuspid valve repair or replacement, and aortic aneurysm repair were also included. A flowchart of the patient selection and follow-up process is shown in Figure 1. At first, 591 patients were identified as eligible for this study. Of these, 574 patients were enrolled as study patients. This cohort represented approximately 11% of all the patients undergoing AVR with CEP valves in all of Japan during the study period.

Patient characteristics and operative data were obtained from medical records at each study facility by independent clinical research coordinators (Supplementary File 1; Appendix S2) according to pre-specified criteria. In addition, all of the patients who survived the surgery underwent follow-up surveys. Late outcome was determined from medical records when available, from written correspondence with patients’ physicians, or direct patient contact via mailed questionnaires or telephone interviews when necessary. Clinical data at the latest follow-up were collected by contacting referring physicians. This study was approved by the Institutional Review Board at all the participating hospitals and the Ethics Committee of the Kyoto University Graduate School and Faculty of Medicine. All patients or their family members gave informed consent.

Definitions of Events
Definitions of SVD, and other valve-related events are based on

![Figure 1. Flow chart of patient selection and follow-up. AVR, aortic valve replacement; CEP, Carpentier-Edwards pericardial valve.](image-url)
were not counted. In-hospital mortality was defined as death occurring within 30 days of surgery or at any time during the index hospitalization.

**Statistical Analysis**

All clinical events were evaluated at the participating hospitals, and then assessed by the independent clinical events evaluation committee (Supplementary File 1: Appendix S3) if necessary. Postoperative overall survival, freedom from valve-related death, valve-related events, and reoperation due to SVD were estimated.
using the Kaplan-Meier method. The association of potential risk factors to survival and events was assessed with log-rank test. All continuous variables are expressed as mean±SD. All P-values are 2-sided and P<0.05 was considered statistically significant. All data analysis was carried out by an academic statistician (S.T.) using SAS version 9.2 (SAS Institute, Cary, NC, USA).

**Results**

Patient baseline characteristics are given in Table 1. The total number of patients was 574, with a mean age of 71.9±8.5 years (range, 21–89 years). A total of 90.8% of patients were aged ≥65 years. Their mean body surface area was 1.50±0.17 m². In terms of preoperative comorbidities, 54.9% had systemic hypertension, 13.4% had dyslipidemia, and 11.2% had diabetes mellitus. Also, 21.2% of patients had atrial fibrillation (AF). Chronic kidney disease (defined as estimated glomerular filtration rate [eGFR] <60ml·min⁻¹·1.73 m⁻², calculated using the Modification of Diet in Renal Disease Formula for Japanese Patients: eGFR [ml·min⁻¹·1.73 m⁻²]=194×serum creatinine⁻¹.098×age⁻⁰.287×0.739 [if female]¹²) was very common and found in 44.9% of patients. Coronary artery disease was also common, identified in 26.9% of patients. Left ventricular ejection fraction (LVEF)<40% was found in only 8.9% of patients. In terms of valve pathology, congenital bicuspid valve disease was identified in 15.0% of patients, whereas 82.8% of patients were found to have tricuspid aortic valve. Rheumatic pathology was rare, found in only 4.3% of patients. Infective endocarditis and previously implanted prosthetic valve dysfunction were also rare, found in only 2.6% and 2.1% of patients, respectively. Aortic valve lesion as the reason for AVR consisted of stenosis in 35.8%, regurgitation in 35.1%, and mixed lesions in 29.2%. With regard to operative variables, size of pericardial valve used is given in Table 2. The most commonly used size was 21 mm, followed by 23 mm, then 19 mm. A few patients (3.7%) had a prior history of open heart surgery, predominantly on aortic valves. Isolated AVR was performed in 57.0% of patients, while combined procedures were performed in 43.0%. Details of combined procedures are given in Table 2. The mean aortic cross-clamp time and cardiopulmonary bypass time were 100±41 min and 139±596 min, respectively.

**Early Outcome**

There were 26 in-hospital deaths (4.5% of the total cohort). Inhospital mortalities in isolated AVR and complex AVR (concomitant with other procedures) were 1.9% and 7.2%, respectively. Also, redo patients had a higher mortality rate compared to that of first-time AVR patients (10% vs. 3.8%). The causes of in-hospital death are listed in Table 3.

**Late Outcome**

The mean follow-up period was 8.2±5.4 years (maximum follow-up, 27 years; median follow-up, 9.2 years). The 10-year follow-up rate was 82.6%. There were 269 late deaths. The causes of late death are given in Table 3. The leading cause of late death was malignant neoplasm, followed by cardiac- and valve-related deaths. In terms of late complications, there were only 8 cases of PVE (1.6%). Thromboembolic events and major bleeding occurred in 7.5% and 9.5% of patients, respectively. The majority of the thromboembolic events were strokes. The most common major bleeding incidents were gastrointestinal bleeding, followed by intracranial bleeding. The number of thromboembolism and major bleeding events according to the
from PVE at 15 years was 97.5%. Preoperative AF was found to be a significant risk factor for thromboembolism on log-rank test (P<0.01). Freedom from reoperation due to SVD, as shown in Figure 4, was 99.3%, 97.4%, and 94.4% at 5, 10, and 15 years, respectively. Younger age at the time of operation was identified as a significant risk factor for reoperation due to SVD (log-rank P<0.01). Also, prior history of aortic valve operation was a significant risk factor for reoperation due to SVD (log-rank P<0.01). Freedom from each event at 5, 10, and 15 years and the 95% confidence intervals are listed in Table S1.

Discussion
This study is, to the best of our knowledge, the largest retrospective study on the long-term outcomes for Japanese patients undergoing AVR with tissue valves. At present, there are 6 types of stented tissue valves currently available in Japan. Among these bioprostheses, the CEP valve is the oldest. In fact, it was approved in 1985 in Japan, and has been widely used ever since. Another unique point of this study is that this cohort represented approximately 11% of all AVR using CEP valves performed in all of Japan during the study period, which should certainly strengthen the clinical significance of this study. The present results are compared to those of other studies in Table 4. Freedom from reoperation due to SVD at 15 years was 87.5% overall, and 94.4% in patients aged ≥65 years in the present study. The durability of pericardial valves was found to be similar to the results reported by other teams in the USA.
Durability of the Pericardial Valve in Japan

There are very few data comparing pericardial valves with porcine valves in terms of durability. Gao et al reported that there were no differences in survival and valve-related complications, including thromboembolism and endocarditis, between the valves, but the 10-year freedom from explant was lower for porcine valves than for pericardial valves.

Perhaps, the most important difference between pericardial valves and porcine valves is their hemodynamic performance. Previous studies have shown that pericardial bioprostheses have better echocardiographic hemodynamics in the aortic position compared to porcine valves, but pericardial valves do not.

As an alternative to pericardial valves, the porcine bioprosthesis is another choice for AVR. The long-term durability of porcine valves has also been reported to be excellent. David et al reported that freedom from reoperation due to SVD at 20 years in patients who had undergone AVR with Hancock II porcine bioprosthetic valves at ages 60–70, and ≥70 were 85.2% and 99.8%, respectively. There are very few data comparing pericardial valves with porcine valves in terms of durability. Gao et al reported that there were no differences in survival and valve-related complications, including thromboembolism and endocarditis, between the valves, but the 10-year freedom from explant was lower for porcine valves than for pericardial valves.

Table 4. Comparisons of Clinical Data

<table>
<thead>
<tr>
<th>First author (Location)</th>
<th>Journal/Year</th>
<th>Freedom from reoperation due to SVD</th>
<th>n</th>
<th>Mean follow-up (years)</th>
<th>Thromboembolism (%/patient-year)</th>
<th>Bleeding (%/patient-year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study (Japan)</td>
<td>Circ J 2014</td>
<td>87.5% at 15 years (mean age, 71.9 years)</td>
<td>574</td>
<td>8.2</td>
<td>0.8</td>
<td>1.1</td>
</tr>
<tr>
<td>McClure (Boston, USA)</td>
<td>Ann Thorac Surg 2010</td>
<td>89.4% at 15 years, age 65–75 years 99.5% at 15 years, age &gt;75 years</td>
<td>1,000</td>
<td>6.0</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Banbury (Cleveland, USA)</td>
<td>Ann Thorac Surg 2001</td>
<td>80% at 15 years, age 50–70 years</td>
<td>267</td>
<td>12</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Poirier (Quebec, Canada)</td>
<td>Ann Thorac Surg 1998</td>
<td>87.9% at 14 years, age 60–69 years 100% at 14 years, age ≥70 years</td>
<td>598</td>
<td>4.8</td>
<td>1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Pellerin (Paris, France)</td>
<td>Ann Thorac Surg 1995</td>
<td>83% at 13 years (mean age, 65 years)</td>
<td>124</td>
<td>7.7</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Aupart (Tours, France)</td>
<td>J Heart Valve Dis 2006</td>
<td>77% at 18 years, age 60–70 years 99% at 18 years, age &gt;70 years</td>
<td>1,133</td>
<td>5.5</td>
<td>0.6</td>
<td>0.3</td>
</tr>
</tbody>
</table>

SVD, structural valve deterioration.

Figure 4. Freedom from reoperation due to structural valve deterioration (SVD) (Left) in all patients and (Right) stratified by age at operation. AVR, aortic valve replacement.

Canada, and France (these studies reported freedom from reoperation due to SVD ranging from 83% to 100% at>10 years postoperatively in patients ≥60 years). Thus, there does not seem to be any difference due to race in terms of the durability of these pericardial valves.
provide any survival advantage over porcine valves in patients aged ≥65 years undergoing AVR.17

Since the first-generation pericardial valve was made available in the early 1970s, various structural refinements and tissue treatments have been applied to prevent wear and calcification of the leaflets that cause SVD. The CEP bioprosthesis is unique in several ways: (1) the 3 leaflets are uniform in thickness and elasticity as a result of computer-aided design; (2) leaflets are mounted inside an Eligiloy® (cobalt-nickel alloy) wire stent for flexibility and distendability; and (3) leaflets are treated with the calcium mitigation agents polysorbate-80 and ethanol (XenoLogiX™) as an advanced anti-calcification treatment.6

Recently, a third-generation anti-calcification treatment, called Thermafix®, was added to the newer model of the CEP, called the CEP-Magna, which has a true supra-annular configuration to achieve better hemodynamics and flow characteristics, especially in small valves.15 Thermafix technology has been shown to yield better prevention of late calcification of the leaflet in vitro. Thus, it is expected to have better long-term durability than CEP valves, although this needs to be verified by further clinical study.

Despite the aforementioned diligent efforts to develop anticalcification technology, SVD is inevitable for all AVR recipients over time. It was obvious that in the present study, as in other studies, many patients may have developed SVD to some extent, but they died from other causes before reoperation became necessary. Thus, most younger patients will probably require reoperation eventually due to SVD at some point. Historically, reoperation has carried a higher risk of perioperative mortality and morbidities including bleeding, myocardial dysfunction, surgical site infection, kidney dysfunction, and cerebrovascular incidents. The contemporary overall risk of reoperation, however, has definitely decreased due to improvements and refinements in surgical techniques and perioperative management. Potter et al reported that the risk of reoperation for AVR is similar to that for primary AVR after excluding patients with PVE, and the data support the extended use of bioprosthetic valves in younger patients.18

With regard to anticoagulation therapy, it is recommended to use warfarin for 3 months after surgery unless contraindicated according to the published treatment guidelines.1 Early anticoagulation is thought to decrease the risk of thromboembolism while the cloth sewing ring is endothelialized. It is a common protocol that warfarin is discontinued after 3 months in patients without risk factors for thromboembolism such as chronic AF in most of the hospitals in this study. The rate of thromboembolism was 0.83%/patient-year in the current study, and this risk increases in patients with chronic AF (log-rank P<0.01). It should be noted that in this study, a significant number of events defined as thromboembolic events may have been misdiagnosed due to a lack of detailed information, which is common in retrospective cohort studies. Conditions that can be mistaken for thromboembolic events include atheromatous plaque of the carotid or vertebral arteries, or other intracranial artery diseases, which are common causes of cerebrovascular events that do not fit the definition of thromboembolism. Although the occurrence of thromboembolic events may have been overestimated, the present findings are similar to those of other studies (Table 4). In contrast, the rate of bleeding was 1.12%/patient-year in the present study, which was slightly higher than in other studies (Table 4). These risks may be balanced by more meticulous control of anticoagulation, but we do not have sufficient data regarding anticoagulation therapy at the time of thromboembolic events or major bleeding events during the follow-up period, making it difficult to discuss this in greater detail.

**Study Limitations**

There were several limitations in this study. First, this was a retrospective, non-randomized study. Also, many of the patients died several years prior to the study, and the events occurred years before the study, making it difficult to obtain accurate information, especially for valve-related events. Likewise, the 10-year follow-up completeness was 82.6%. These factors may have influenced the results significantly.

**Conclusions**

The durability of the CEP bioprosthesis in the aortic position is excellent in the Japanese population, with a very low risk of reoperation due to SVD, particularly in elderly patients aged ≥65 years. Thus, it is appropriate to follow the current indications concerning bioprosthetic valves issued by the Japanese Circulation Society and contained in the ACC/AHA guidelines.

**Acknowledgments**

We are indebted to the participating hospitals, investigators, and clinical research coordinators for their great contributions to data collection. The hospitals, clinical research coordinators and investigators are listed in Appendices S1 and S2. Also, we deeply thank the Independent Clinical Events Evaluation Committee of this study listed in Appendix S3. This work was supported by an educational grant from the Research Institute for Production Development (Kyoto, Japan).

**References**


Durability of the Pericardial Valve in Japan


**Supplementary Files**

**Supplementary File 1**

- **Appendix S1.** Participating hospitals and investigators
- **Appendix S2.** Independent clinical research coordinators
- **Appendix S3.** Independent clinical events evaluation committee

**Table S1.** Freedom from events (%)

Please find supplementary file(s); http://dx.doi.org/10.1253/circj.CJ-13-1068