Comparison of Carpentier-Edwards pericardial and supraannular bioprostheses in aortic valve replacement


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Abstract

Objective: This study aimed at calculating and comparing the long-term outcomes of patients after aortic valve replacement with the Carpentier-Edwards bovine pericardial and porcine supraannular bioprostheses using microsimulation.

Methods: We conducted a meta-analysis of eight studies on the Carpentier-Edwards pericardial valves (2685 patients, 12,250 patient-years) and five studies on the supraannular valves (3796 patients, 20,127 patient-years) to estimate the occurrence rates of valve-related events. Eighteen-year follow-up data sets were used to construct age-dependent Weibull curves that described their structural valvular deterioration. The estimates were entered into a microsimulation model, which was used to calculate the outcomes of patients after aortic valve replacement.

Results: The annual hazard rates for thromboembolism after aortic valve replacement were 1.35% and 1.76% for the pericardial and supraannular valves, respectively. For a 65-year-old male, median time to structural valvular deterioration was 20.1 and 22.2 years while the lifetime risk of reoperation due to structural valvular deterioration was 18.3% and 14.0%, respectively. The life expectancy of the patient was 10.8 and 10.9 years and event-free life expectancy 9.0 and 8.8 years, respectively.

Conclusions: The microsimulation methodology provides insight into the prognosis of a patient after aortic valve replacement with any given valve type. Both the Carpentier-Edwards pericardial and supraannular valve types perform satisfactorily, especially in elderly patients, and show no appreciable difference in long-term outcomes when implanted in the aortic position.

Keywords: Aortic valve replacement; Bioprostheses; Prognostic modeling

1. Introduction

Bovine pericardial and porcine bioprostheses have been used for aortic valve replacement (AVR) since the early 1970s when their first-generation prostheses became commercially available. The second-generation of these valves were introduced in the early 1980s with the aim of reducing structural valvular deterioration (SVD) and improving hemodynamic performance. The Carpentier-Edwards (Perimount) pericardial (Edwards Lifesciences LLC, Irvine, CA, USA) and the Carpentier-Edwards supraannular (Baxter Healthcare Corp, Irvine, CA, USA) bioprostheses were the initial second-generation valves introduced in their respective categories, and are widely implanted at present [1,2].

Compared with its predecessor, the first-generation Ionescu-Shiley valve (Shiley, Inc., Irvine, CA, USA), the Carpentier-Edwards pericardial valve incorporates significant design modifications including improved tissue fixation and a sophisticated method of leaflet mounting [3]. This permits more symmetrical opening of the valve resulting in better hemodynamics [4]. In contrast to the first-generation porcine valves, the Carpentier-Edwards supraannular valve has its tissue fixed at 2 mmHg and has a supraannular configuration to maximize the effective orifice of the prosthesis [1]. Although these technological innovations have resulted in improved hemodynamics and greater durability, knowledge on important end points and long-term outcome of patients is still incomplete. Such information would be useful in complementing the available data, comparing the two valve types and in the optimal choice of a valve for a given patient.

We used meta-analysis and multi-center data on SVD to feed a microsimulation model, which was then used to
provide insight into the age-related life expectancy and lifetime risks of valve-related events for patients after AVR and thereby compare the second-generation Carpentier-Edwards pericardial and porcine valves, respectively.

2. Methods

2.1. Systematic literature review and meta-analysis

We conducted a Medline search using the PubMed search interface in order to identify reports that examined the outcomes of patients who received the Carpentier-Edwards pericardial and supraannular valves for AVR. The search was limited to the English language and to the publication period 1 January 1995 through 31 December 2002. The text word ‘Carpentier-Edwards’ and the terms ‘bioprosthesis’ and ‘tissue heart valve’ in combination with ‘bovine’, ‘pericardial’ and with ‘porcine’, ‘supraannular’, respectively, were used for the search. Abstracts of reports obtained from the search were examined for those that contained information on valve-related events, their sequelae and long-term survival of patients after AVR. This resulted in 30 published reports on the Carpentier-Edwards pericardial valve and 18 reports on the Carpentier-Edwards supraannular valve.

We then applied several criteria to these selected reports with a view to obtain a similar group of studies for each valve type. These criteria were (1) valve sizes 19–31 mm, not focusing on a particular size or range; (2) patients >15 years of age, not focusing on a particular age group; (3) predominately first time AVR; (4) AVR with or without coronary artery bypass grafting (CABG), excluding other valve replacements; and (5) predominately patients who did not require long-term anti-coagulation. Valve-related events in these reports were defined according to the guidelines of Edmunds and colleagues [5,6]. Reports that contained overlapping patient populations were excluded. This resulted in a selection of eight reports on the pericardial valves and five on the supraannular valves (see Appendix A), the contents of which were then reviewed in detail to obtain data required for calculation of the occurrence rates of valve-related events.

Assuming constant hazards over time, weighted mean estimates of linearized annual occurrence rates were computed for the valve-related events other than SVD. The combined mortality and reoperation rates due to the valve-related events were also calculated.

2.2. Analysis of primary data to determine hazards of SVD

The risk of SVD in a bioprosthesis increases with the time elapsed since implantation and decreases with implantation age of the patient. The Weibull distribution has been shown to be efficient in summarizing SVD in bioprostheses [7] and hence an age-dependent Weibull model was used for this purpose. The Weibull model was constructed on Egret windows version 2.0.1 (Cytel Software Corporation, Cambridge, MA, USA).

We used primary data on 267 patients, implanted with Carpentier-Edwards pericardial valve between 1981 and 1984, to directly calculate the parameters of the Weibull model for the pericardial valves. These patients formed part of the original four-center pre-marketing clinical investigation conducted for the US Food and Drug Administration [4]. The mean age of the patients at implantation was 65 ± 12 years, 64% were men and the follow-up extended to 18 years. For the Carpentier-Edwards supraannular valve, we used primary data on 1847 operations that were conducted between 1981 and 1999 at the University of British Columbia, Vancouver, Canada [8]. The mean age of the population was 68.9 ± 10.9 years and follow-up extended up to 20 years.

2.3. The microsimulation model

The microsimulation model is a computer application designed to simulate the remaining lifetime of a patient after AVR with a given valve type, taking into account the risk of experiencing valve-related events and mortality. The mortality of a patient after AVR is composed of the mortality of the general population (background mortality), mortality due to valve-related events and an ‘additional’ mortality component. The latter may be associated with underlying valve pathology, left ventricular function and the valve replacement procedure, respectively [9]. This ‘additional mortality’ component has not been quantified in the literature as yet and hence, was incorporated into the model by way of hazard ratios. The mortality due to valve-related events and the ‘additional mortality’ constitute the excess mortality experienced by patients after AVR.

Repeated simulations by the model of a particular patient result in a ‘virtual’ patient population, consisting of patients with identical characteristics and all possible outcomes that may occur after AVR. From this large simulated data set of identical patients (for example, 10,000), the model calculates the average outcome for that particular individual. In principle, the model can be applied for any valve type and for patients of either sex and any given age. In this analysis, the model was used to calculate outcomes of male patients who received the Carpentier-Edwards pericardial and supraannular valves for AVR at different implantation ages. Real-life estimates of the occurrence of valve-related events after AVR, obtained from the meta-analysis and from Weibull analysis of individual patient data for SVD, were used as input for the model. A detailed account of the microsimulation methodology has been published previously [10,11].

2.4. Validation

In order to verify the validity of its calculations, we compared the age- and sex-specific survival calculations of the microsimulation model for the Carpentier-Edwards pericardial valve with the corresponding Portland experience with the same valve. The latter did not constitute part of the model input. The Portland pericardial data, from the Providence Health System, Portland, OR, USA, contain 1021 patients who received the prosthesis between 1991 and 2002. The mean age of the patients was 74.3 years. We also compared the age- and sex-specific model estimates of survival for the porcine valve with the Portland 25-year follow-up survival data on patients who underwent AVR with the Carpentier-Edwards ‘standard’ bioprosthesis [12].
2.5. Sensitivity analysis

How precise are the model predictions? A one-way sensitivity analysis was performed to investigate the effect of uncertainty in the parameter estimates. In one-way sensitivity analysis, a single parameter is varied while the others are kept constant. Since variation of the estimates of valve-related events by their 95% confidence intervals yielded negligible changes in the long-term outcomes, we increased and decreased the baseline values by 25% for this analysis. The hazard ratios representing the ‘additional’ mortality were also systematically varied.

3. Results

3.1. Meta-analysis

The eight reports selected for meta-analysis of the Carpentier-Edwards pericardial valve comprised 2685 patients and a total follow-up of 12,250 patient-years. The five reports on the Carpentier-Edwards supraannular valve included 3796 valve recipients and 20,127 patient-years of follow-up. The mean ages of the two cumulative populations were 66.9 and 69.8 years. Approximately 62% of patients in both groups were males. The pooled incidence of valve-related events and their outcomes for both the pericardial and the supraannular group are given in Table 1. Thromboembolism was the most frequent event to occur in both valve types, with hazard rates of 1.35% and 1.76% per 100 patient years, respectively.

3.2. Analysis of primary data

The parameters of the Weibull model for reoperation due to SVD of pericardial valves were: $\sigma = e^{2.31 + 0.0124 \text{age}}$ and $\beta = 3.76$; for reoperation due to SVD of supraannular valves: $\sigma = e^{2.20 + 0.0156 \text{age}}$ and $\beta = 3.35$. According to the Weibull model, the median time to reoperation due to SVD in the pericardial valves were 17.1 (95% CI: 15.7—18.7), 19.9 (95% CI: 18.0—21.9), and 23.0 (95% CI: 20.5—25.9) years for 55-, 65-, and 75-year male patients, respectively. The estimates for the supraannular valves were 19.0 (95% CI: 17.9—20.1), 22.0 (95% CI: 20.3—23.8), and 25.5 (95% CI: 22.9—28.4), respectively.

3.3. Microsimulation model calculations

The microsimulation model calculates total life expectancy (LE), event-free life expectancy (EFLE), and reoperation-free life expectancy (RFLE) after AVR for male and female patients of a given age. We give the results for male patients in this analysis. For a 65-year-old male patient, for example, LE was 10.8 and 10.9 years; RFLE was 9.9 and 10.1 years, and the EFLE 9.0 and 8.8 years, respectively, after implantation with the Carpentier-Edwards pericardial and supraannular valves. The LE, RFLE, and EFLE after AVR at different ages of valve implantation, for both valves, are given in Fig. 1.

The microsimulation model also calculates the cumulative incidence or lifetime risk of valve-related events and reoperation after valve implantation (‘actual’ analysis). The lifetime risk of a reoperation due to SVD was 18.3% and 14.0% for a 65-year-old male and 5.4% and 3.8% for a 75-year-old male, respectively, after AVR with pericardial and supraannular valves (Fig. 2).

We further compared the LE of patients who received the two types of prostheses with that of age-matched males of the general American population. As the LE was similar between the two valve types, we depict this comparison using only the supraannular valve (Fig. 3). It is seen that relative LE increased with advancing age of implantation, from about 60% at 50 years to nearly 100% for a 75-year patient. The relative LEs of hypothetical patients who were

### Table 1

<table>
<thead>
<tr>
<th>Valve-related events</th>
<th>Events (number)</th>
<th>Hazard rate (per 100 patient-years)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CEP</td>
<td>CESA</td>
<td>CEP</td>
</tr>
<tr>
<td>Valve thrombosis</td>
<td>2</td>
<td>1</td>
<td>0.03</td>
</tr>
<tr>
<td>Thrombo-embolism</td>
<td>166</td>
<td>355</td>
<td>1.35</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>53</td>
<td>92</td>
<td>0.43</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>70</td>
<td>79</td>
<td>0.62</td>
</tr>
<tr>
<td>Non-structural dysfunction</td>
<td>4</td>
<td>46</td>
<td>0.13</td>
</tr>
<tr>
<td>Structural valvular deterioration</td>
<td>55</td>
<td>173</td>
<td>—</td>
</tr>
</tbody>
</table>


* Weibull models incorporating age dependency were constructed from primary data sets.
immune from valve-related events and operative mortality were also analyzed. These showed similar trends of increase with advancing age of implantation and was >100% that of a person in the general population at 75 years. The difference between the LE curve and the other two hypothetical curves represents the mortality associated with valve-related events and the operative procedure. The difference between curve for the hypothetical patient immune from valve-related events and operative mortality and the general population standard (i.e. 100%) represents the ‘additional mortality’ component.

### 3.4. Validation

For 55-, 65-, and 75-year-old male patients, for example, the 10-year survival estimates were 64.1% and 63.7%, 51.2% and 48.9%, and 33.1% and 32.3%, respectively. Further, the survival outputs of the microsimulation model for patients of different ages receiving the Carpentier-Edwards supraannular valve compared favorably with the corresponding curves of the Carpentier-Edwards ‘standard’ Portland experience, through 25 years post-implantation (Fig. 4).

### 3.5. Sensitivity analysis

The effect on LE and EFLE of a 65-year-old male on individually increasing and decreasing the baseline valve-related event estimates is given in Table 2. The most prominent effect on LE and EFLE was achieved by variation in events and the operative procedure. The difference between curve for the hypothetical patient immune from valve-related events and operative mortality and the general population standard (i.e. 100%) represents the ‘additional mortality’ component.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Plausible range for hazard rates (per 100 patient-years)</th>
<th>EFLE in years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valve thrombosis</td>
<td>0.02 Favorable, 0.04 Unfavorable</td>
<td>9.0 Favorable, 9.0 Unfavorable</td>
</tr>
<tr>
<td>Thrombo-embolism</td>
<td>1.01 Favorable, 1.69 Unfavorable</td>
<td>9.2 Favorable, 8.8 Unfavorable</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>0.32 Favorable, 0.54 Unfavorable</td>
<td>9.1 Favorable, 8.9 Unfavorable</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0.47 Favorable, 0.78 Unfavorable</td>
<td>9.1 Favorable, 8.9 Unfavorable</td>
</tr>
<tr>
<td>NSD</td>
<td>0.10 Favorable, 0.16 Unfavorable</td>
<td>9.0 Favorable, 9.0 Unfavorable</td>
</tr>
</tbody>
</table>

The EFLE for a 65-year-old male patient after AVR with CEP and CESA was 9.0 and 8.8 years, respectively, with baseline hazard rates. The plausible range was estimated by increasing and decreasing the baseline values by 25%. The 95% confidence interval was also used for SVD. Probable values were selected for the hazard ratio that represents ‘additional mortality’. CEP: Carpentier-Edwards pericardial bioprosthesis, CESA: Carpentier-Edwards supraannular bioprosthesis, NSD: non-structural dysfunction, SVD: structural valvular deterioration.

*Baseline values of the valve-related events are given in Table 1. The baseline median time to SVD was 20.1 and 22.2 years for CEP and CESA, respectively. The hazard ratio was 1.2 for a 65-year-old male patient.

b Median time to SVD.
4. Discussion

The second-generation pericardial and porcine valves were developed in the early 1980s to improve durability and enhance hemodynamic function. Although previous studies have described and compared the outcomes after implantation with both valves [13], knowledge on long-term patient prognosis is still incomplete. We combined a systematic literature review, meta-analysis and separate data on SVD with microsimulation to calculate life expectancy and lifetime risk of reoperation for patients receiving these two valve types. This information would be useful for supporting prosthetic valve choice and in the management of individual patients after AVR.

4.1. Risk of SVD

The risk of SVD after valve replacement is not constant but depends on the age of implantation and the time elapsed since the operation. Kaplan—Meier curves are usually used to describe this changing risk [14]. Grunkemeier and colleagues [7] demonstrated that the Weibull curve was efficient in summarizing SVD in biological valves. However, they suggested that at least 12 years of follow-up were needed to produce reliable estimates. We used primary data on the Carpentier-Edwards pericardial and supraannular valves, with over 18 years of follow-up, to calculate the respective Weibull parameters. Although the estimates of median time to reoperation calculated from the fitted Weibull distributions favor the supraannular valves, they were implanted on average in older patients (69.8 years vs 66.9 years). As there is a tendency for enhanced durability in older patients [7], these results do not permit us to conclude on the superior durability of either valve type. Jamieson and colleagues who compared their experience in Vancouver on the Carpentier-Edwards pericardial and supraannular valves found no significant difference in the actuarial freedom from SVD between the two groups. While the overall actual freedom from SVD favored the pericardial valves (93.5 ± 1.5 vs 89 ± 1.0), there was negligible difference between the 61–70 and >70 years age groups [13].

4.2. Actuarial versus actual analysis

The Kaplan—Meier (actuarial) analysis was originally designed to describe the freedom from death. As previously indicated, this method has been extended to summarize complications such as SVD, which are not necessarily fatal. In the latter instance, it describes the risk of SVD for the patient based on the assumption of immortality. However, in reality, death occurring before implanted valve failure acts as a competing risk, resulting in an over-estimation of the actual risk of SVD. This error is magnified with advancing age of implantation and serves to underestimate the benefits of biological valve replacement. Conversely, cumulative incidence or ‘actual’ analysis considers the competing risk of death and calculates the percentage of patients who will experience an event before they die. It provides a better estimate of the durability of a bioprosthesis, especially in the elderly [14–17]. The microsimulation model calculates the lifetime risk of SVD and of other valve-related events. For a 65-year-old male for example, the lifetime risk of reoperation due to SVD is 18.3% and 14% after AVR with the Carpentier-Edwards pericardial and supraannular valves (Fig. 2). The risk is further reduced for a 75-year-old male, estimated at 5.4% and 3.8%, respectively. This information is useful in deciding on an age cut-off point for the choice of a mechanical valve or bioprosthesis.

4.3. Life expectancies of patients

The LE, RFLE, and EFLE for males of different ages as estimated by the microsimulation model, is depicted in Fig. 1. The point estimates for LE and EFLE for both valve types, at various ages of implantation do not show appreciable difference. Kvidal and colleagues [18], who investigated the excess mortality after heart valve replacement, described an increasing excess hazard during follow-up and a decreasing excess hazard with advancing age of implantation. This supports a ‘multiplicative’ excess mortality, which was a structural assumption in our model. The alternative assumption of an ‘additive’ excess mortality may increase LE estimates, especially in patients under 70 [19,20]. RFLE is shown to be higher in the supraannular valves, which is explained by the higher median time to SVD of these valves.

4.4. Hemodynamics of valve prostheses

The improvement of hemodynamics after AVR is related to normalization of left ventricular mass and function [21]. This in turn may reduce ‘additional’ mortality of a patient [9]. We have not yet addressed the possibility that ‘additional mortality’ may vary with different valve types and valve sizes, necessitating the use of different hazard ratios. In this context, the Carpentier-Edwards pericardial valve has been shown to be less obstructive in the aortic position than the Carpentier-Edwards supraannular valve [22]. This could translate to greater and more rapid regression of left ventricular hypertrophy after AVR with a pericardial valve conferring a higher survival benefit than presently calculated by the microsimulation model. We have used sensitivity analysis to underscore the importance of the ‘additional mortality’ factor on the outcomes of patients after AVR (Table 2).

4.5. Limitations of this methodology

These included certain structural assumptions in the microsimulation model and the uncertainty associated with the input parameters. For example, a constant hazard was assumed for valve-related events other than SVD. However, these hazards may vary with increasing age and age at implantation. Although we previously assumed endocarditis to take two phases of risk, comparisons of different calendar periods of implantation have shown a significant decline in early prosthetic endocarditis in recent years [23]. The
model’s user-friendly input interface permits addition and change of data when required. Many other patient- and surgery-related factors have been shown to influence overall survival after AVR [24,25]. However, at present, the model calculates outcome for an average risk profile only. The change of data when required. Many other patient- and surgery-related factors have been shown to influence overall survival after AVR [24,25]. However, at present, the model calculates outcome for an average risk profile only. The references