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Aortic valve replacement with the Cardioprotese Premium bovine pericardium bioprosthesis: four-year clinical results

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Abstract

OBJECTIVES: This study reports the initial clinical and echocardiographic results of the Premium bioprosthetic aortic valve up to 4 years of follow-up.

METHODS: Between October 2007 and July 2011, 121 consecutive patients were submitted for aortic valve replacement with the Premium bioprosthetic valve. The mean age was 68 ± 9 years and 64 patients were males. The patients were periodically evaluated by clinical and echocardiographic examinations. The mean follow-up was 21 months (min = 2, max = 48), yielding 217 patients/year for the analysis.

RESULTS: The hospital mortality was 8%. Late survival at 3 years was 89% (95% CI: 81.9–93.3%), and 80% of the patients were in NYHA functional class I/II. The rates of valve-related complications were low, with a linearized incidence of 0.9%/100 patients/year for thromboembolic complications, 0% for haemorrhagic events and 0.9%/100 patients/year of bacterial endocarditis. There was no case of primary structural valve dysfunction. The mean effective orifice area was 1.61 ± 0.45 cm^2; mean gradient 13 ± 5 mmHg and peak gradient 22 ± 9 mmHg. Significant patient–prosthesis mismatch was found in only 11% of the cases.

CONCLUSIONS: The Premium bioprosthetic aortic valve demonstrated very satisfactory clinical and echocardiographic results up to 4 years, similar to other commercially available, third-generation bioprosthetic valves.

Keywords: Aortic valve • Aortic valve replacement • Bioprosthesis • Heart valves

INTRODUCTION

Although results of randomized studies have suggested some advantages with the use of mechanical valves for aortic valve replacement (AVR), recent data have shown a significant increase in the use of bioprosthetic valves worldwide [1, 2].

This trend can be partially explained by the better long-term results obtained with the last generation of biological valves, with a low incidence of reoperations due to primary structural valve dysfunction in the first 20 years of follow-up, particularly in older patients [3, 4].

The Cardioprotese Premium valve is a new bovine pericardium valve, which has been developed to meet these standards. The *in vitro* hydrodynamic evaluation has demonstrated low gradients and large effective orifice areas (EOA), with small regurgitant volumes. When subjected to accelerated fatigue testing, their durability exceed 1 billion cycles [5]. In addition, preclinical studies have demonstrated the efficacy of glutamic acid in an anticalcification method [6].

The valve has been approved for clinical use in Brazil since 2007 and it is intended to get future CE mark approval. The purpose of this study is to demonstrate the short- and medium-term clinical and echocardiographic results of the first 121 implants of the Premium valve for AVR, with a follow-up extending up to 4 years.

METHODS

Patients

Between October 2007 and July 2011, 121 patients were consecutively submitted for AVR with the Premium valve in two institutions, Santa Casa de Curitiba and the Instituto de Neurologia e Cardiologia de Curitiba, Brazil.

The mean age was 68 ± 9 years (42–89), 74 (61%) were males and the most frequent aetiology was senile calcific valve degeneration in 66 (54%) patients. The patients having concomitant mitral valve replacement were excluded from the study. Patient characteristics are shown in Table 1.

All patients signed their informed consent and the study was approved by the University Ethical Committee (number 0002285/08).

Table 1: Patient characteristics

Number	121
Age (mean ± SD)	68 ± 9
Sex	
Male	74 (61%)
Female	47 (38%)
Electrocardiogram	
Sinus	108 (88%)
Atrial fibrillation	13 (10%)
NYHA functional class	
Class I	13 (10%)
Class II	44 (36%)
Class III	52 (42%)
Class IV	12 (9%)
Aortic valve lesion	
Stenosis	81 (66%)
Insufficiency	20 (16%)
Mixed	20 (16%)
Aetiology	
Degenerative	66 (54%)
Myxomatous degeneration	1 (0.8%)
Prosthetic valve dysfunction	6 (5%)
Chronic aortic dissection	1 (0.8%)
Congenital aortic stenosis	1 (0.8%)
Prosthetic valve endocarditis	1 (0.8%)
Native valve endocarditis	1 (0.8%)
Rheumatic valve disease	9 (7%)
Bicuspid aortic valve	30 (24%)
Others	5 (4%)
Non-cardiac comorbidities	
Dyslipidaemia	44 (36%)
Diabetes mellitus	22 (18%)
Systemic hypertension	104 (85%)
Smoking	11 (7%)
Chronic obstructive pulmonary disease	23 (19%)
Renal failure	6 (5%)
Obesity	23 (19%)

Premium valve

The Premium valve is a glutaraldeheyde-fixed pericardium valve that is mounted inside a flexible Delrin® stent (Fig. 1). The valve has some design characteristics that are important for favourable haemodynamic performance and durability. The Delrin stent has a low profile and is completely covered with a thin pericardium sheet, thus avoiding any direct contact of the valvular cusps with the supporting stent or external Dacron tissue during the opening and closing mechanism of the valve (Fig. 2). The valve cusps are completely inside the stent, which eliminates the greatest point of mechanical stress encountered in some first- and second-generation pericardium valves. Furthermore, pericardium post-treatment with glutamic acid has been demonstrated to be very resistant to calcification in preclinical studies [6].

Operations

The operations were performed through a median sternotomy ($n = 112$) and more recently, in some selected cases, with minimally invasive incisions in the second or third intercostal space ($n = 9$). Extracorporeal circulation was done with hypothermia at 32°C, and myocardial protection was accomplished with intermittent cold blood cardioplegia.

Figure 1: Macroscopic view of the Premium bovine pericardium bioprosthetic valve.

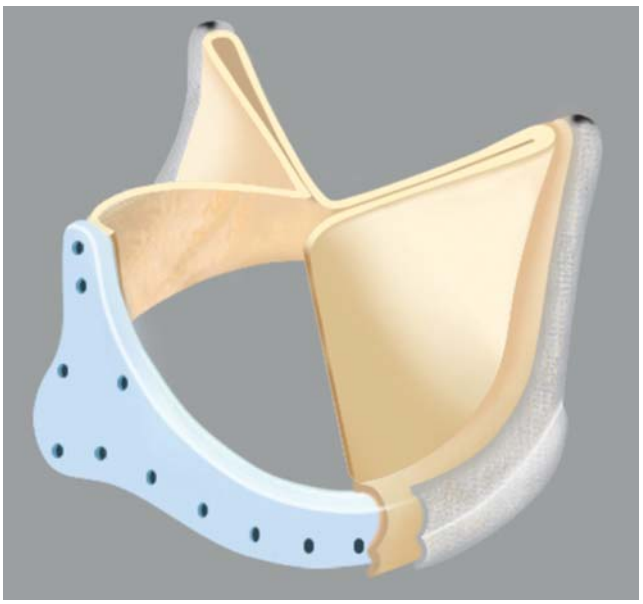

Figure 2: Schematic drawing of the Premium bovine pericardium valve. The pericardium is mounted inside a low profile flexible Delrin stent, which is covered with another thin sheet of pericardium. The external aspect of the valve as well as the sewing ring is made out of Dacron tissue.

The aorta was opened with a transverse incision, the native valve was resected and the annular calcium extensively debrided. After measuring the aortic annulus, the appropriate prosthesis that best fitted the aortic root was chosen. No efforts were made to oversize the bioprosthesis. The valves were implanted using pledgeted 2-0 non-everting sutures, placing it in a supra-annular position. Annular enlargement techniques were not employed in this series and concomitant procedures were performed according to the conventional techniques. The operative data are shown in Table 2.

Table 2: Operative data

Patients	121
Valve size (mm)	
19-mm	8 (6%)
21-mm	29 (23%)
23-mm	39 (32%)
25-mm	28 (23%)
27-mm	10 (8%)
29-mm	1 (0.8%)
Concomitant procedures	
Myocardial revascularization	28 (23%)
Septal myomectomy	1 (0.8%)
Ascending aortoplasty	3 (2%)
Mitral valve repair	3 (2%)
Tricuspid valve repair	2 (1%)
Ascending aorta replacement	5 (4%)
Cross-clamp (min, mean ± SD)	66 ± 19
Extracorporeal circulation (min, mean ± SD)	83 ± 32

Clinical evaluation and follow-up

Until mid-2010, patients were routinely anticoagulated with warfarin for the first 3 months. Thereafter, this protocol was modified and patients received 100 mg/day of aspirin with anticoagulation prescribed only in the presence of specific indications.

All patients were clinically evaluated and submitted to haematological and echocardiographic examinations before their hospital discharge, and oriented to return at 3, 6 and 12 months, and yearly thereafter.

A single physician performed the outpatient follow-up. Clinical evaluation and the occurrence of late postoperative events were performed according to well-established guidelines [7]. The haematological evaluation included values for globular volume and haemoglobin besides lactic desidrogenase, haptoglobin and reticulocyte count.

Echocardiographic analysis was performed by a single examiner utilizing a Philips Envisor US 22. Bioprosthetic performance was determined with the mean and maximum instantaneous gradients across the valve, as well as by the degree of eventual valve regurgitation. We also calculated EOA and related them to the labelled valve size.

Clinical follow-up was possible in 101 patients (87%). The mean follow-up was 21 months (2–48), which corresponded to 217 patients/year for evaluation.

Statistical analysis

Results were expressed as mean and standard deviations for continuous variables and as percentages for categorical variables. Late postoperative events were expressed as percentages and linearized incidences were also calculated. Survival as well as complication event-free curves were calculated with the Kaplan–Meier method.

For the comparison between valve sizes and quantitative variables (EOA, EOAI, ΔP_{mean} and ΔP_{max}), we utilized the non-parametric Kruskal–Wallis test. The statistical analyses were performed using the program Statistica v 8.0.

Table 3: Complications and mortality

	n (%)
Complications	
Reoperation for bleeding	8 (6)
Low output syndrome	18 (14)
Atrial fibrillation	34 (28)
Intra-aortic balloon pump	3 (2)
Respiratory insufficiency	14 (11)
Renal failure	11 (9)
Dialysis	4 (3)
Gastrointestinal bleeding	3 (2)
Myocardial infarction	2 (1)
Early mortality	10 (8)
Respiratory insufficiency	1 (0.8)
Low output syndrome	2 (1.6)
Multiple organ failure	2 (1.6)
Sepsis	2 (1.6)
Gastrointestinal bleeding	1 (0.8)
Arrhythmia	1 (0.8)
Renal failure	1 (0.8)
Late mortality	3 (2%)
Valve related	
Endocarditis	1 (1)
Non-cardiac	
Pneumonia	1 (1)
Respiratory insufficiency	1 (1)

RESULTS

Mortality and functional results

Hospital mortality was 8% (10/121). Causes of early death are listed in Table 3.

Of 101 patients available for the late follow-up analysis, there have been three late deaths, one valve-related due to bacterial endocarditis in the prosthetic valve and two non-valve related deaths due to pneumonia and respiratory insufficiency, respectively. Actuarial survival was 89% (95% CI: 81.9–93.3%) at 3 years.

Postoperatively most patients showed good relief of symptoms, with 80% (79/98) in functional class I/II.

Valve-related events

Thromboembolic complications and valve thrombosis. There were two episodes of cerebral thromboembolism (2/101, 1.9%), which occurred at 2 days and at 2 months postoperatively, respectively. The first case was a stroke with sequelae of permanent dysarthria due to cerebellar infarct and the other was a transient neurological deficit with complete recovery. Both patients presented chronic atrial fibrillation. The linearized incidence of thromboembolic events was 0.9%/100 patients/year. By the Kaplan–Meier method, 98% (95% CI: 93–99.2%) were free from thromboembolic complications at 3 years of follow-up (Fig. 3A).

There were no documented cases of valve thrombosis in this series.

Haemorrhagic complications

During the 4 years of follow-up, there were no haemorrhagic complications (Fig. 3B).

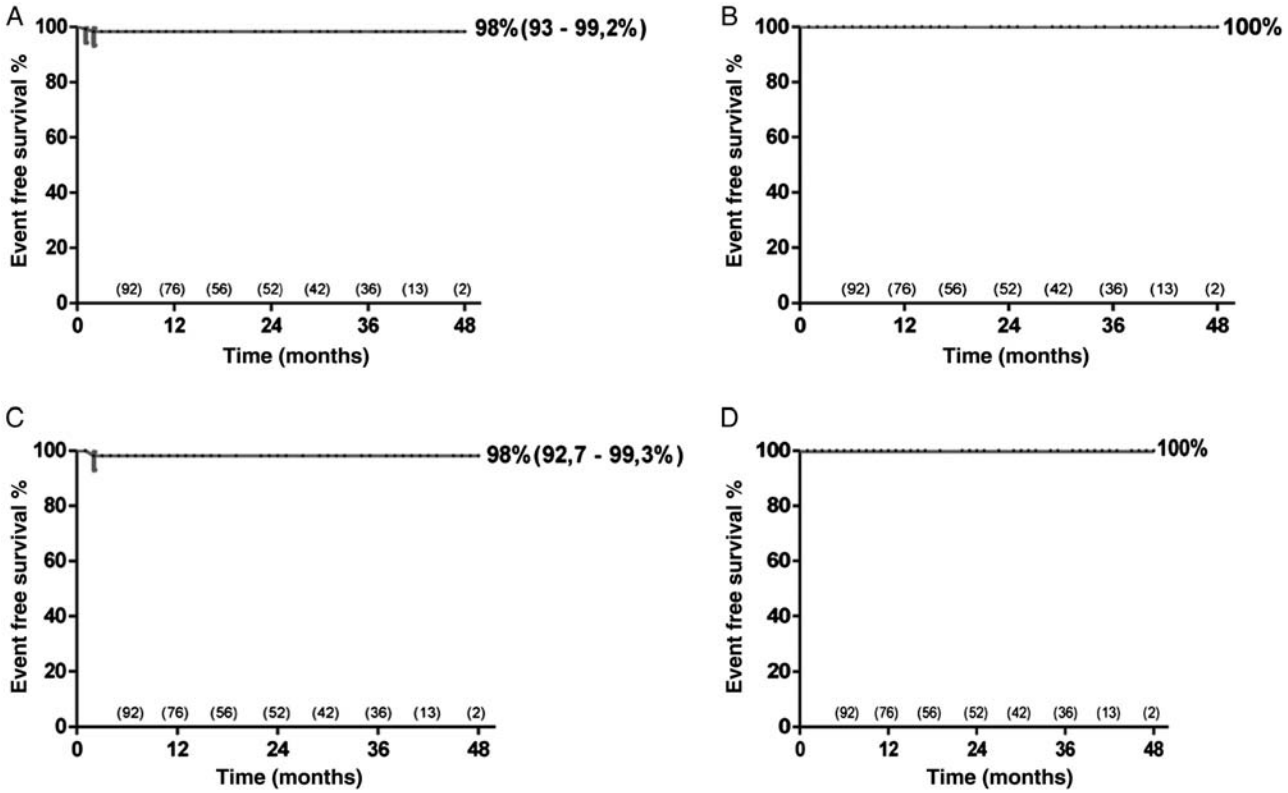

Figure 3: The Kaplan–Meier curves for the main valve related complications. (**A**) Freedom from thromboembolic complications. (**B**) Freedom from haemorrhagic complications. (**C**) Freedom from infective valve endocarditis. (**D**) Freedom from structural valve dysfunction.

Bacterial endocarditis

Two patients (2/101, 1.9%) developed bacterial endocarditis of the prosthetic valve that necessitated reoperations, both at 2 months of follow-up. One case was due to *Staphilococcus aureus* infection and in the second case, it was not possible to identify the responsible agent. Both patients were re-operated on and the prosthetic valves substituted for aortic homografts, but one did not survive. The linearized incidence of bacterial endocarditis was 0.9% per 100 patients/year and 98% (95% CI: 92.7–99.3%) were free from bacterial endocarditis at 3 years (Fig. 3C).

Structural and non-structural valve dysfunction

During the period of observation, there were no cases of both structural and non-structural valve dysfunction, and 100% of the patients are free from this complication at 3 years (Fig. 3D). There are two cases of mild paravalvular leaks, none necessitating re-intervention.

Echocardiographic analysis

Eighty-six patients had at least one echocardiogram during the follow-up; however, for this study we only included 51 patients in whom the echo studies were performed in our institution by the same observer, with consistent data for the analysis of the haemodynamic performance of the prosthetic valve.

The mean EOA for all valves analysed was 1.61 ± 0.45 cm^2, with $\Delta P_{mean} = 13 \pm 5$ mmHg and $\Delta P_{max} = 22 \pm 9$ mmHg. When EOAI ≤ 0.65 cm^2/m^2 was considered, the incidence of significant patient–prosthesis mismatch was 11%, mainly in small valve sizes. The details of the haemodynamic performance by valve size are listed in Table 4.

Haematological analysis

Haematological values were normal, with no evidence of haemolytic anaemia or platelet dysfunction in any patient. At 12 months of follow-up, the mean values for the globular volume were 41.6%, haemoglobin 13.9 g/dl, platelet count 176.960/mm^3, reticulocytes 1.04% and haptoglobin 129 mg/dl.

DISCUSSION

The present study represents the first clinical report of the Premium valve for AVR, analysing 121 patients with a follow-up of 4 years. Although this period of observation is too limited to draw any inference on long-term durability, the absence of primary valve structural deterioration, the maintenance of stable EOAs and the normal haematological results demonstrate the quality of the bioprosthesis and that its clinical use is safe. It is well documented that primary structural valve failure is related to patient's age and tends to occur after 8–12 years. However, the reports of Banbury *et al.* [4] with the Carpentier-Edwards

Table 4: Echocardiographic data

Prosthesis	EOA (cm^2)	EOAI (cm^2)	ΔP_{med} (mmHg)	ΔP_{max} (mmHg)	PPM (%)
19-mm ($n = 4$)	1.27 ± 0.10	0.74 ± 0.06	18 ± 6	32 ± 11	0
21-mm ($n = 13$)	1.41 ± 0.38	0.83 ± 0.30	14 ± 6	25 ± 11	30.8
23-mm ($n = 16$)	1.53 ± 0.27	0.88 ± 0.17	13 ± 5	23 ± 7	6.6
25-mm ($n = 9$)	1.57 ± 0.13	0.83 ± 0.13	12 ± 5	22 ± 10	11.1
27-mm ($n = 8$)	2.19 ± 0.61	1.19 ± 0.30	8 ± 3	16 ± 6	0
29-mm ($n = 1$)	2.67	1.40	7	12	0
Global (51)	1.61 ± 0.45	0.91 ± 0.26	13 ± 5	22 ± 9	11.2

EOA: effective orifice area; EOAI: effective orifice area index; ΔP_{med}: mean gradient; ΔP_{max}: instantaneous maximum gradient; PPM: patient–prosthesis mismatch.

Perimount valve and of Jamieson *et al.* [8] with the St Jude Epic valve have shown occasional cases of primary structural valve dysfunction due to either calcification or rupture before 4 years of follow-up.

The risk of thromboembolic complications with bioprosthetic AVR is relatively low; however, the incidence can vary depending on the patient population characteristics as well as on the methodology employed to detect the events. David *et al.* [9] analysed patients with the Hancock II valve for up to 25 years and found a linearized incidence of 1.2% per 100 patients/year. Two other extensive series have demonstrated incidences of 0.3% per 100 patients/year with the Carpentier-Edwards Perimount [3] and of 0.98% with the St Jude Epic [8]. A large meta-analysis performed by Puvimanasinghe *et al.* [10], comparing bovine pericardium with porcine bioprosthetic valves, has demonstrated linearized rates of 1.35% and 1.76% per 100 patients/year, respectively. In this context, our incidence of 0.9% per 100 patients/year with the Premium valve appears to compare favourably with other third-generation valves.

The anticoagulation management after bioprosthetic AVR is controversial and varies according to institutional protocols. We had no haemorrhagic complications in our patients, which compares favourably with other series [10].

The Premium valve has specific features that include, among other characteristics, a low-profile stent and a supra-annular configuration. In theory, positioning the valve in a supra-annular position would allow prosthetic oversizing, making its internal orifice to be similar to the diameter of the native annulus and thus, avoiding patient–prosthesis mismatch [11, 12]. However, as pointed out by Botzenhardt *et al.* [13], prosthetic EOA is dependent on other factors such as the compliance of the cusps, orientation and angle between the prosthesis and the left ventricular outflow tract and the ascending aorta.

As emphasized by Gerosa *et al.* [14], prosthetic valve function evaluation is more complex and might include other parameters, such as regurgitant volumes, leaking volumes and calculation of energy losses, which are not readily available clinically. For that reason, detailed knowledge of these parameters for each type of prosthetic valve with *in vitro* studies in pulse duplicators is fundamental. In this context, the Premium valve has been extensively studied and its energy losses were quite low, due to adequate EOAs and low regurgitant and leaking volumes [5].

It is recognized that a direct comparison of results obtained with different bioprosthesis implanted in different institutions is very limited. Notwithstanding these limitations, we could demonstrate that the Premium valves exhibited adequate EOAs and low gradients, which were comparable with other current commercially available bioprosthetic valves. Considered as a group, our mean EOA of 1.61 cm^2 for the Premium valve was similar to those reported by Borger *et al.* [15] with the Magna valve (1.40 cm^2) or the Hancock II valve (1.29 cm^2). In the same manner, Wagner *et al.* [12] studied four different bioprostheses (Magna, Perimount, Mosaic and Sorin Soprano) and obtained EOAs ranging from 1.31 cm^2 to 1.64 cm^2.

The mean gradient of 12 mmHg and the peak gradient of 22 mmHg observed in the Premium valve are also similar to those reported by others [11, 15]. The incidence of patient–prosthesis mismatch with pericardium and porcine valves has been reported to vary between 0 and 70% [12]. Our incidence of significant patient–prosthesis mismatch of 11% is also similar to that reported by Dalmau *et al.* [11] with the Magna valve.

CONCLUSIONS

The clinical and echocardiographic results obtained with the Premium aortic bioprosthesis demonstrated that it was associated with good functional recovery and a low incidence of adverse late valve-related events. The haemodynamic performance is comparable with other third-generation bioprosthetic valves and there has been no case of primary structural valve dysfunction up to 4 years of follow-up.

Conflict of interest: Francisco Diniz Affonso da Costa owns shares in the company that produces the Premium valve.

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