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Sutureless bioprosthesis for aortic valve replacement: surgical and clinical results

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Dedicatória

Para o Nuno do futuro, inspirado pela Mafalda do presente.

Agradecimentos

“Quem caminha sozinho pode até chegar mais rápido, mas aquele que vai acompanhado, com certeza vai mais longe.”

Clarice Lispector

Com este mantra em mente, quero agradecer ao Dr. Ricardo Ferreira pela disponibilidade, pela ética de trabalho e pela orientação desta dissertação de mestrado.

Aos meus pais e avós, pelo apoio incondicional.

À Sofia, à Mafalda, à Cristiana, ao Diogo, à Helena, à Catarina e à Beatriz, pela amizade, inspiração e presença constantes.

Resumo

Introdução: A estenose valvular aórtica é a doença valvular mais comum em adultos em países desenvolvidos. O envelhecimento da população e o aumento das comorbilidades, incita o desenvolvimento de alternativas terapêuticas mais seguras. As próteses sem suturas têm demonstrado resultados promissores, especialmente em procedimentos tecnicamente complexos e à medida que mais pacientes necessitam de cirurgias concomitantes.
Objetivos: Avaliar o desempenho clínico e hemodinâmico e durabilidade da válvula Perceval em substituição isolada da válvula aórtica e em procedimentos concomitantes.

Métodos: Neste estudo de coorte longitudinal retrospetivo recolhemos dados de todos os pacientes adultos com doença da válvula aórtica submetidos a substituição da válvula com uma válvula Perceval entre Fevereiro de 2015 e Outubro de 2020. Dos 196 pacientes (idade média 77,20±5,08 anos; 45,4% mulheres; EuroSCORE II logístico médio 2,91±2,20%), a maioria tinha estenose aórtica. Os pacientes foram posteriormente divididos em dois grupos e comparados: um incluiu pacientes submetidos a substituição isolada (n=132) e o outro, pacientes com cirurgia concomitante (n=49). O seguimento destes pacientes foi efetuado até 5 anos.

Resultados: Os tempos médios de clampagem da aorta e de circulação extracorporal foram de 33,31±14,08 e 45,50±19,04 minutos, respetivamente. Os tempos médios de internamento total e na unidade de cuidados intensivos foram 7,70±5,82 e 3,32±3,20 dias, respetivamente. 4 válvulas foram reimplantadas devido a mau posicionamento. Os gradientes transvalvulares médios foram 7,82±3,62 mmHg. Implante de *pacemaker* foi necessário em 12,8% dos pacientes, fibrilhação auricular *de novo* ocorreu em 21,9% e suporte de substituição renal foi necessário em 3,1%. A mortalidade foi de 2,0%. Não houve deterioração estrutural da válvula, AVC ou endocardite nos 5 anos de seguimento. Houve uma trombose da válvula. Comparativamente, pacientes com procedimentos concomitantes tinham pior função ventricular esquerda (66.7 vs 86.1%; p=0,030), maiores tempos de clampagem da aorta (43,33±11,60 vs 27,30±8,10 minutos; p<0,001) e de circulação extracorporal (59,98±17,60 vs 37,45±11,30 minutos; p<0,001). Adicionalmente, a estadia na unidade de cuidados intensivos foi mais longa (3,96±3,20 vs 2,80±2,70 dias; p=0,016). Não houve diferenças significativas em complicações pós-operatórias e sobrevivência.

Conclusões: Este estudo confirma o excelente desempenho clínico e hemodinâmico e a segurança da válvula Perceval, mesmo ao fim de 5 anos, com resultados consistentes em intervenções isoladas e concomitantes, solidificando-a como uma opção viável para o tratamento de doenças isoladas da válvula aórtica, e agora também para pacientes que necessitam de procedimentos concomitantes.

Palavras-chave

Prótese sem suturas; substituição de válvula aórtica; válvula Perceval; estenose valvular aórtica; doença valvular aórtica.

Abstract

Background: Aortic valve stenosis is the most common adult valve disease in industrialized countries. The ageing population and the rising in comorbidities urges the development of safer alternatives to the current surgical treatment. Sutureless bioprosthesis have shown promising results, especially in technically difficult procedures and as more patients need concomitant surgeries.

Objectives: Assess the clinical and hemodynamic performance, safety, and durability of the Perceval valve in isolated aortic valve replacement surgery and in concomitant procedures.

Methods: This single center retrospective longitudinal cohort study collected data of all adult patients with aortic valve disease who underwent aortic valve replacement with a Perceval bioprosthesis between February 2015 and October 2020. Of the 196 patients analyzed (mean age 77.20±5.08 years; 45.4% female; mean logistic EuroSCORE II 2.91±2.20%), the majority had aortic stenosis. Patients were further divided into two groups and compared: one group comprised patients who underwent isolated valve implantation (n=132) and the other patients who had concomitant coronary artery bypass grafting (n=49). Follow-up of these patients lasted up to 5 years.

Results: Overall mean cross-clamp and cardiopulmonary bypass times were 33.31±14.09 and 45.55±19.04 minutes, respectively. Mean intensive care unit and total hospital stay were 3.32±3.24 and 7.70±5.82 days, respectively. Procedural success was 98,99%, as two explants occurred. 4 valves were reimplanted due to misplacement/paravalvular leaks. Mean transvalvular gradients were 7.82±3.62 mmHg. Pacemaker implantation occurred in 12.8% of patients, new-onset atrial fibrillation in 21.9% and renal replacement support was necessary in 3.1%. Early mortality was 2.0%. We report no structural valve deterioration endocarditis and one successfully treated valve thrombosis during the 5-year follow-up period. In comparison, patients with concomitant procedures had worse left ventricular function (66.7 vs 86.1%; $p=0.030$), longer aortic cross-clamping (43.33±11.56 vs 27.30±8.14 minutes; $p<0.001$) and cardiopulmonary bypass times (59.98±17.53 vs 37.45±11.32 minutes; $p<0.001$), as expected. Intensive care unit stay after surgery was also longer (3.96±3.87 vs 2.85±2.09 days; $p=0.016$). There were no other significant differences in postoperative complications and survival.

Conclusions: Our study confirms the excellent clinical and hemodynamic performance and safety of a truly sutureless aortic valve, even up to the 5-year follow-up. These results were consistent in isolated and concomitant interventions, solidifying this device as a viable option for treatment of isolated aortic valve disease, and now also in patients needing concomitant procedures.

Keywords

Sutureless bioprosthesis; Aortic valve replacement; Perceval valve; Aortic valve stenosis; Aortic valve disease.

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Lista de Acrónimos

AVR	Aortic Valve Replacement
LV	Left Ventricle
CPB	Cardiopulmonary Bypass
PPI	Permanent Pacemaker Implantation
TAVI	Transapical or trans-femoral transcatheter Aortic Valve Implantation
ICU	Intensive Care Unit
STJ	Sinotubular Junction
CABG	Coronary Artery Bypass Graft
MIS	Minimally Invasive Surgery

Chapter 1

Introduction

Aortic valve stenosis is the most frequent form of adult valvular heart disease in industrialized countries (1). Its prevalence increases with age, averaging 0.2% in people aged 50–59 and up to 9.8% in the 80–89 year cohort (2), with 75% of people aged 85 to 86 showing at least some degree of valvular calcification (3). It can be caused by rheumatic disease or, more commonly in high-income countries, by calcification of a congenitally bicuspid or trileaflet valve. Early recognition and management of aortic stenosis is crucial as untreated symptomatic severe disease is fatal (2).

Conventional aortic valve replacement (AVR) through median sternotomy is the established gold-standard for the treatment of severe and/or symptomatic cases (4). However, the continuous increase in patients' age (5) and comorbidities, the growing percentage of patients who need concomitant surgical procedures, coupled to the fact that the duration of aortic cross-clamping and cardiopulmonary bypass (CPB) are independent predictors of survival (6), with aortic cross-clamping time increasing the risk of severe cardiovascular morbidity by 1.4% per minute (7), have created the need for interventions that minimize operative times, hence reducing its inherent risks.

Transapical or trans-femoral transcatheter aortic valve implantation (TAVI) has been introduced as an alternative to conventional AVR, initially only for patients deemed inoperable, and more recently, driven by PARTNER trials and other randomized trials, in high and intermediate-risk patients. Still, the inability to excise the calcified aortic valve and annulus translates to higher rates of paravalvular leaks, major vascular complications and need for permanent pacemaker implantation (PPI) rates when compared to conventional AVR (4).

Sutureless bioprosthesis has surfaced as a viable alternative merging the best of both worlds. By avoiding sutures, it allows for reduced aortic cross-clamping, CPB and global surgical times, as well as the possibility of complete excision of the native aortic valve and complete annular decalcification, helping prevent paravalvular leaks, which is particularly useful in patients with severe aortic stenosis and an intermediate to high operative risk (8,9). Sutureless bioprostheses are especially beneficial in patients who are more sensitive to ischemia, in technically difficult procedures (such as small and/or highly calcified aortic roots, reoperations and in patients who require concomitant procedures) (10), patients with a high risk of patient-prosthesis mismatch (PPM), and patients who require faster recovery. Furthermore, by avoiding stitching through the annulus and suture knotting, the risk of tearing the aortic annulus and wall or embolizing foreign material is reduced (11). However, these advantages must be weighed against the apparent increased risk of PPI when compared to conventional AVR (12).

The Perceval valve (Sorin Group, Saluggia, Italy) is currently the only truly sutureless valve available, with extensive research supporting its excellent hemodynamic performance, safety, and versatility of use. However, several questions remain unanswered, namely long-term survival and valve durability, risk of endocarditis, the impact of the apparent increased need for postoperative PPI and safety of concomitant valvular procedures (13).

Our study aims to analyze the clinical and hemodynamic performance, safety and durability of the Perceval valves implanted in patients with aortic valve disease, both in isolated AVR as well as in patients who underwent concomitant procedures, over a period of 5 years in a single European center.

Chapter 2

Materials and Methods

Study design

In this retrospective longitudinal cohort study, data of all adult patients with aortic valve disease who underwent AVR with a Perceval valve between February 2015 and October 2020 in Hospital de Santa Maria (Lisbon, Portugal) was retrospectively collected from an available hospital database. Approval of the study and access to the data was granted by the ethical committee of the hospital involved (identification number: 510/18).

Patients

The data collected included demographics and preoperative characteristics, such as comorbidities, EuroSCORE II, presence of atrial fibrillation or pacemaker, left ventricular (LV) function and history of previous cardiac surgery. We also collected intraoperative data, such as the aortic cross-clamping and CPB times, size of the valves implanted and transvalvular gradients, as well as in-hospital stay and postoperative complications. Follow-up of these patients lasted up to 5 years.

Primary endpoints were the clinical and hemodynamic performance, safety and durability of the Perceval valve in AVR, evaluated through the following criteria: mortality and overall long-term survival, structural valve deterioration, operatory times (aortic clamping and CPB times), mean ICU and total hospital stay, postoperative complications - including PPI and infection rates (respiratory, urinary and/or in the bloodstream), endocarditis, stroke, early mortality (defined as in-hospital or up to 30 days after surgery), abnormal bleeding (defined as > 2ml/kg/h in first 2-3 hours, > 1ml/kg/h in the next 3 hours and/or > 0.5ml/kg/h in 12 hours), new-onset atrial fibrillation (paroxysmal, persistent or permanent), significant renal dysfunction (defined as KDIGO stages 2 and 3) and need for intra-aortic balloon pump, surgical exploration for bleeding, renal replacement support (performed through continuous veno-venous hemodiafiltration) or aminergic support >24h (performed with at least one of the following: epinephrine, norepinephrine, dobutamine) - and postoperative echocardiographic findings.

The secondary endpoint was analyzing and comparing patients who underwent isolated AVR with the Perceval valve with those who had additional concomitant procedures. To assess the comparative risk of adding concomitant procedures, patients were divided into two groups and compared: group A comprised patients who underwent isolated AVR with a Perceval valve plus those who had Morrow procedure, as it was considered this procedure did not add any significant additional difficulty or time length to the overall intervention (n=132). Group B comprised patients who had concomitant single, double or triple coronary artery bypass graft (CABG) surgery (n=49). Patients who underwent ascending aorta replacement, mitral and/or tricuspid valvuloplasties or replacements or Dor procedure (n=15) were too heterogeneous and were therefore not considered in this comparison.

The Perceval valve

The Perceval valve (Sorin Group, Saluggia, Italy) consists in 3 bovine pericardial cusps mounted on a self-expanding nitinol stent comprising two rings, allowing for stabilization simultaneously at the aortic annulus and at the sinotubular junction (STJ), and nine vertical struts covered by a thin coating of Carbofilm™, to improve biocompatibility. The stent holds the valve in place without any permanent suture, by exerting radial force on the patient's aortic annulus and aortic root. It is also flexible, allowing it to adapt to the anatomy of the aorta and its movements, thus relieving the stress on the leaflets. The valve is collapsed by collapsing the inflow and outflow rings with an atraumatic compression device, allowing the pericardial leaflets not to be crimped and remain mobile, ensuring they are not damaged (14) - in contrast to the necessary crimping of the TAVI, in which the leaflet's collagen fibers are damaged (10). The Perceval valve is currently available in four sizes: S, to be implanted in annular sizes from 19 to 21 mm, M from 21 to 23 mm, L from 23 to 25 mm and XL for patients with annular sizes from 25 to 27 mm (6).

Although the concept of sutureless bioprosthesis exists for over 40 years (15), the first reports evaluating implantation feasibility and valve safety in humans came out in 2007. It was CE approved in 2011 and FDA approved in 2016 (16).

Surgical technique

Indications for AVR were in agreement with the ESC/EACTS Guidelines for the management of valvular heart disease at the time of the interventions (17). The patients were operated on either through a standard median sternotomy or upper ministernotomy. All patients were operated on or supervised by an experienced surgeon in this procedure. Anesthetic and surgical techniques were standardized. A high transverse aortotomy near the epiaortic fat pad was performed, leaving a free edge for closure after implantation of the device. The native calcified aortic valve was excised, and the aortic annulus completely decalcified. Sizing of the annulus was done using dedicated sizers.

Concomitant procedures were performed in line with current department practices and always with the goal of minimizing aortic cross-clamping and CPB times. For instance, aortic graft anastomosis, when needed, was performed prior to cannulation using tangential aortic cross-clamping. The coronary anastomosis was performed during the time when the valve was being collapsed.

After the closure of the aortotomy in the usual fashion, thorough de-airing with CO_2, release of the aortic cross-clamp and weaning from CPB were performed. Valve function was investigated by intraoperative transesophageal echocardiography in all patients. Following the procedure, patients received antiplatelet treatment according to the standard protocol in use and were transferred to the ICU and managed according to the unit's protocol (18).

Statistical analysis

Statistical analysis was performed on all patients successfully implanted with a Perceval valve using IBM SPSS Statistics v27.1. Categorical variables are reported as absolute and relative frequencies. For continuous data, means and standard deviations were calculated. Cumulative survival and freedom from events were estimated using the Kaplan–Meier method, with 95% confidence intervals. A p-value under 0.05 was considered statistically significant. Continuous variables were treated as mean and standard deviation and compared with Student's t-test. Categorical variables were summarized as the number and/or percentage of subjects in each category and compared with Chi-square/Fisher's exact tests, as appropriate.

Chapter 3

Results

Overall cohort

Preoperative characteristics

Between February 2015 and October 2020, 198 patients underwent AVR with a Perceval valve in Hospital de Santa Maria (Lisbon, Portugal). We excluded 2 patients from the study due to immediate valvular explantation, resulting in a total of 196 patients analyzed. Aortic stenosis was the indication for surgery in most patients (96.4%), followed by aortic regurgitation (1.53%), native valve endocarditis (1.02%), prosthetic valve endocarditis (0.51%) and mechanic valve dysfunction (0.51%).

Preoperative baseline characteristics of the entire cohort are shown in table 1. The mean overall age was 77.20±5.08 and 45.4% of patients were female. EuroSCORE II predicted an in-hospital mortality risk of 2.91 ± 2.20%. The most prevalent preoperative risk factors were impaired renal function (85.2%), high blood pressure (88.3%), being overweight or obese (75.8%) and dyslipidemia (71.9%). Coronary disease was present in 34.7% of the cohort, atrial fibrillation in 17.9% and 8.7% had a history of stroke or transient ischemic attack. Most patients (69.4%) had preserved left ventricular function, defined as an ejection fraction higher than 55%.

Table 1 - Preoperative baseline characteristics and risk factors (mean ± Standard Deviation)

Patients	% (± SD)
Demographics	
Sex (female)	45.4
Age (in years)	77.20±5.08
EuroSCORE II	2.91±2.20
Preserved LV function	69.4
Risk Factors	
Impaired renal function[1]	85.2
High Blood Pressure	88.3
Overweight/obesity[2]	75.8
Dyslipidemia	71.9
Diabetes Mellitus	41.8
Insulin treated	2.6
Coronary disease	34.7
Atrial fibrillation	17.9
Smoking history[3]	18.9
Respiratory disease	14.3
Peripheral artery disease	4,6
Previous stroke or transient ischemic attack	8,7
Preoperative PPI	3.1
Previous cardiac surgery	2.0

[1] Impaired renal function was defined as glomerular filtration rate <85%

[2] Overweight/obesity was defined as a body mass index >25.

[3] Former or active.

Intraoperative outcomes

Intraoperative outcomes of the cohort are shown in table 2. Overall mean total surgery time was 131.67±56.71 minutes, with mean aortic cross-clamping and CPB times of 33.31±14.09 minutes and 45.55±19.04 minutes, respectively. Of all surgeries, 15 (7.65%) were minimally invasive, via upper ministernotomy.

The Perceval valve in size M was the most frequently implanted, accounting for 69 patients of the entire cohort (35.6%), followed by the L in 64 patients (33.0%), the XL in 35 (17.0%) and the S in 28 (14.4%).

Isolated AVR was performed in 122 (62.24%) patients. Concomitant CABG surgery was performed in 22 (11.22%) patients, double CABG surgery in 23 (11.73%) and triple CABG surgery in 4 (2.04%). Other concomitant procedures included mitral and/or tricuspid valvuloplasties/replacements in 12 patients (6.12%), Morrow procedure in 10 (5.10%), ascending aorta replacement in 2 (1.02%) and Dor procedure in 1 (0.51%) patient. 2 patients (1.02%) had already undergone previous cardiac surgery.

The Perceval valve was successfully implanted in 196 patients (98.98%), whereas in 2 cases (2/198 = 1.01%), conversion to conventional bioprosthesis was required after valve explantation due to severe displacement. In 4 cases (2/196 = 2.04%) reimplantation was necessary to readjust the valve, due to misplacement/paravalvular leaks.

Table 2 - Intraoperative outcomes (mean ± SD)

Patients		n = 196	%
Operatory data			
Total surgery (minutes)		131.67±56.71	
Cardiopulmonary bypass (minutes)		45.55±19.04	
Aorta cross-clamping (minutes)		33.31±14.09	
Valve size			
	S (*n*)	28	14.4
	M (*n*)	69	35.6
	L (*n*)	64	33.0
	XL (*n*)	35	17.0
Intra-operative valve complications			
Reimplantation		4	2.0
Significant paravalvular leaks[1]		0	0.0
Operation Details			
Isolated aortic valve replacement		122	62.24
+CABG 1		22	11.22
+CABG2		23	11.73
+CABG3		4	2.04
+Mitral/Tricuspid		12	6.12
+Morrow		10	5.10
+Ascending aorta replacement		2	1.02
+Dor procedure		1	0.51
Previous cardiac surgery		2	1.02
Minimally Invasive		15	7.65
Mean transvalvular gradients (mmHg)		7.82±3.62	

[1] Paravalvular leaks were considered significant if grade 2 or 3

Postoperative outcomes

Postoperative results of the cohort are shown in table 3. The average ICU stay was 3.32±3.24 days and the average hospital stay 7.70±5.82 days. Mean transvalvular gradients were 7.82±3.62 mmHg. 4 patients (2.04%) died, two as a consequence of uncontrolled septic shock following native valve endocarditis, one as a consequence of neurologic complications related to an underlying type A aortic dissection and the last was a case of low-flow low-gradient aortic stenosis in cardiogenic shock.

The most common immediate postoperative complications over the entire cohort were the need for aminergic support for over 24 hours (45.1%), new-onset atrial fibrillation (21.9%), PPI (12.8%) and significant renal dysfunction (10.5%). Less prevalent postoperative complications included infections (10.2%), abnormal bleeding (9.2%), renal replacement support (3.1%), early mortality (2.0%), intra-aortic balloon pump (2.0%) and the need for surgical exploration for bleeding (1.0%).

We report no structural valve deterioration, strokes, or cases of endocarditis and one case of valve thrombosis (0.5%), which was successfully treated with oral anticoagulants. Figure 1 shows the overall Kaplan-Meier cumulative survival curve throughout 5 years. The survival rate at the end of 1 year was 94%, at 3 years 86% and 5 years 71%.

Table 3 – Postoperative outcomes (mean ± SD)

Patients	%
In-hospital stay	
ICU stay (days)	3.32±3.24
Hospital stay (days)	7.70±5.82
Post-operative complications	
Aminergic support >24h	45.1
New-onset Atrial fibrillation	21.9
PPI	12.8
Significant renal dysfunction	10.5
Infection	10.2
Abnormal bleeding	9.2
Renal replacement support	3.1
Early mortality	2.0
Intra-aortic balloon pump	2.0
Surgical exploration for bleeding	1.0
Valve thrombosis	0.5
Stroke	0.0
Endocarditis	0.0

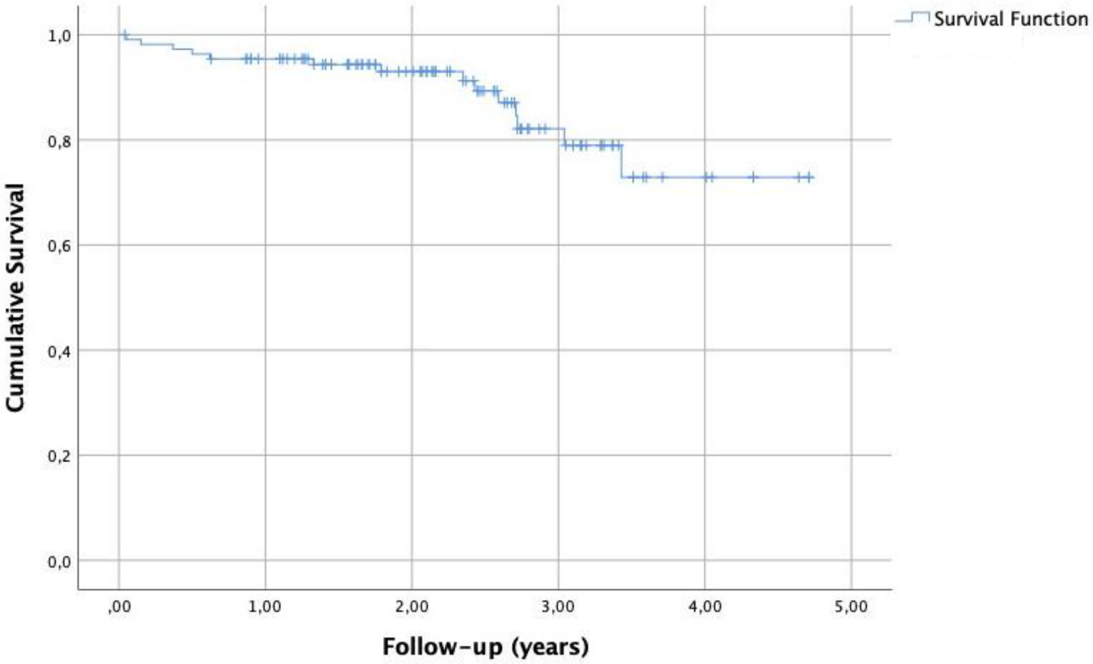

Figure 1 – Follow-up overall mortality (Kaplan–Meier survival curve)

Comparison analysis

Preoperative characteristics

Preoperative baseline characteristics of group A and B are shown in table 4. In comparison, group B had worse mean LV function (66.7 vs 86.1%; p=0.030). No other statistically significant differences in baseline characteristics were found between the two groups, apart from the expected difference in coronary disease incidence.

Table 4 - Preoperative baseline characteristics (mean ± SD). Comparison between group A and B.

	A (n=132) In %	B (n=49) In %	p-value
Demographics			
Sex (female)	47.0	38.8	0.401
Age (years)	77.15±4.95	77.64±5.32	0.900
EuroSCORE II (%)	2.71±2.11	3.26±2.45	0.492
Preserved LV function	86.1	66.7	0.030
Risk Factors			
High Blood Pressure	91.7	87.8	0.404
Impaired renal function	86.2	80.0	0.426
Overweight/obesity	77.3	73.9	0.688
Dyslipidemia	75.8	67.3	0.261
Diabetes Mellitus	40.9	40.8	1.000
Insulin treated	3.8	0.0	0.326
Coronary disease	21.2	100.0	N/A
Smoking history	20.5	12,2	0,279
Atrial fibrillation	19.7	12.2	0.280
Respiratory disease	14.4	12.2	0.812
Previous stroke or transient ischemic attack	9.1	8.2	1.000
Peripheral artery disease	3.8	6.1	0.448
PPI	3.0	4.1	0.663

Intraoperative outcomes

Intraoperative outcomes of group A and B are shown in table 5. As expected, group B showed longer mean aortic cross-clamping (43.33±11.56 vs 27.30±8.14 minutes; $p<0.001$) and CPB times (59.98±17.53 vs 37.45±11.32 minutes; $p<0.001$). No other statistically significant differences in intraoperative outcomes were found between the two groups.

Table 5 - Intraoperative outcomes (mean ± SD). Comparison between group A and B.

	A (n=132)	B (n=49)	p-value
Operatory data			
Cardiopulmonary bypass (minutes)	37.45±11.32	59.98±17.53	<0.001
Aorta cross-clamping (minutes)	27.30±8.14	43.33±11.56	<0.001
Valve size			
S (*n*)	19	6	
M (*n*)	46	20	
L (*n*)	43	15	
XL (*n*)	24	8	
Significant paravalvular leaks	0	0	
Mean transvalvular gradients (mmHg)	7.95±1.52	7.33±1.52	0.663

Postoperative outcomes

Postoperative outcomes of group A and B are shown in table 6. Group B had a significantly longer mean ICU stay after surgery (3.96±3.87 vs 2.85±2.09 days; $p=0.016$). Apart from this, there were no other significant differences in postoperative complications and survival, even up to 5 years. Figure 2 compares the Kaplan-Meier cumulative survival curves of group A (line in blue) and group B (line in red) throughout 5 years. The survival rate at the end of 1 year was 94%, at 3 years 83% and 5 years 69% for group A and 91%, 67% and 67% for group B, respectively. There seems to be no significant difference in survival at 5 years between the two groups.

Table 6 – Postoperative outcomes (mean ± SD). Comparison between group A and B.

	A (n=132) In %	B (n=49) In %	p-value
In-hospital stay			
ICU stay (days)	2.85±2.09	3.96±3.87	0.016
Hospital stay (days)	7.17±5.04	8.77±6.70	0.141
Post-operative complications			
Aminergic support >24h	39.5	53.7	0.147
New-onset Atrial fibrillation	19.7	10.2	0.183
PPI	12.1	14.3	0.802
Significant renal dysfunction	9.2	13.5	0.573
Infection	7.6	10.2	0.554
Abnormal bleeding	11.4	4.1	0.163
Renal replacement support	2.3	4.1	0.613
Early mortality	2.3	0.0	1.000
Intra-aortic balloon pump	1.5	2.0	1.000
Surgical exploration for bleeding	0.8	2.0	0.469
Stroke	0.0	0.0	N/A

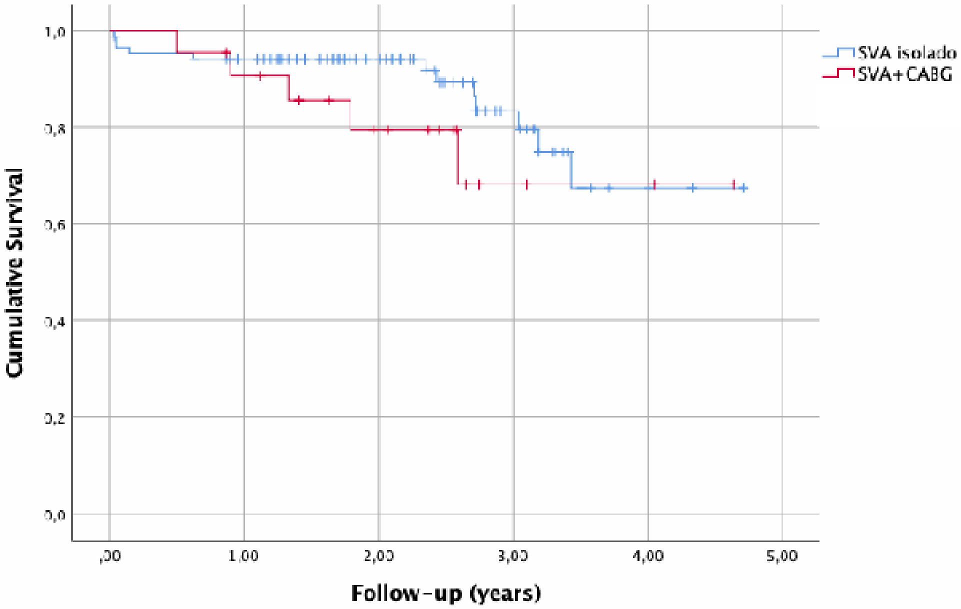

Figure 2 – Group A vs B follow-up mortality (Kaplan–Meier survival curve)

Chapter 4

Discussion

The Perceval valve (Sorin Group, Saluggia, Italy) has been increasingly used in European cardiac surgery centers for treatment of aortic valve disease since its first reports in 2007. As a truly sutureless bioprosthesis with proven excellent hemodynamic outcomes, safety and marked reduction in aortic cross-clamping and CPB times, it has been shown to allow for reduced postoperative morbidity and mortality as well as cost reduction of up to 25% when compared to conventional biological heart valves (8,19), especially when treating older patients and in those with comorbidities. However, several questions are yet unanswered, especially regarding long-term durability, risk for endocarditis, and the need for postoperative PPI.

In our retrospective study, we sought out to assess the clinical and hemodynamic performance, safety, and durability of the Perceval valve for AVR both in isolated and in concomitant procedures.

Our cohort is composed of mostly older people, with an average overall age of over 77 years and a small standard deviation of about 5 years. Additionally, most patients had one or more preoperative risk factors and/or comorbidity, with an average in-hospital mortality risk measured by an EuroSCORE II of 2.91 ± 2.20%, despite the majority having preserved LV function.

The overall total surgical time, mean aorta cross-clamping and CPB times of 131.67±56.71, 33.31±14.09 and 45.55±19.04 minutes, respectively, took into consideration the surgeries where reimplantation of the valve was necessary, the mini-invasive approach in 15 patients via upper ministernotomy, the 2 patients who had undergone previous cardiac surgery and the 64 patients who had concomitant procedures. Of the two patients who were previously operated on, indication for reoperation in one was prosthetic valve endocarditis and the other mechanical valve dysfunction. The times obtained represent a significant reduction in comparison to the mean aorta cross-clamping and CPB times of 78 and 106 min reported in conventional AVR, according to the Society of Thoracic Surgeons database. This major reduction of over 50% in both times could translate into improved clinical results, especially in patients with significant comorbidities (7) or in a medium-high surgical risk profile, as aortic clamping and CPB times are considered independent predictors of morbidity and mortality in heart surgery (10).

The Perceval valve was successfully implanted in 196 out of the 198 patients initially selected (98.99%) as in 2 cases (2/198 = 1.01%) conversion to conventional bioprosthesis was required after valve explantation caused by valve migration. One way of possibly reducing the likelihood of these events is by strictly obliging the manufacturer's preoperative echo-doppler aortic root evaluation recommendations (a patient is suitable if the ratio between the diameter of the STJ and the annular diameter is ≤ 1,3) (20).

In 4 cases (2.04%) reimplantation was necessary to readjust the valve, due to minor misplacement and/or paravalvular leaks found in the intraoperative transesophageal echocardiography, which is paramount to assure correct placement and function. Reimplantation through the "x-movement" technique, allowed for save removal of the bioprosthesis, collapsing and easy reimplantation (21). In one of the cases, migration followed and was assigned to cardiac manual manipulation and thorough manual de-airing. From this case onwards, de-airing with CO2 was performed instead, as it is shown to be a safe alternative (22).

In our study, we report no significant paravalvular leaks, a result below the already low 1-2% commonly observed in trials with the Perceval valve (6). In comparison, TAVI causes a greater number of moderate-to-severe paravalvular leaks (7-12%), followed by conventional AVR (1,9%), which at 2 years have been shown to be independent predictors of mortality (10,23). Consequently, correct measurement, placement and final visual confirmation of correct valve placement could help avoid these complications.

The most common immediate postoperative complications were the need for aminergic support for over 24 hours (45.1%), new-onset atrial fibrillation (21.9%), PPI (12.8%), significant renal dysfunction (10.5%), abnormal bleeding (9.2%), renal replacement support (3.1%) and need for surgical exploration for bleeding (1.02%) and were in line with the expected for a major cardiac procedure. The relatively high rate of postoperative aminergic support might be related to the fluid restriction protocol used in our department. New-onset atrial fibrillation is usually multifactorial and is the most common arrhythmic complication occurring after any cardiac surgery, affecting typically between 30% and 50% of the patients, more than in our study (24). Although the incidence of acute renal injury is relatively high, only a reduced number of patients required renal replacement technique.

The overall incidence rate for PPI of 12.8% is within the interval incidence described in the literature, of 3.1% (25) to 17% (26) although it is above rates for conventional bioprosthesis reported of 3.0 to 11.8% (27) and comparable to the ones reported for TAVI (28). Current best available evidence suggests baseline conducting system disease is the most powerful independent predictor of PPI requirement following AVR. Other patient-related predictors are advanced age, annular calcification, reoperations and longer perioperative CPB time (27). Operative-related factors such as incomplete decalcification of the aortic ring, valve oversizing and valve and guiding sutures position, the specific protocol for pacemaker implantation of each center and procedural implanting steps and sizing's learning curve effect are also important (13). In our center, all patients were operated on or supervised by an experienced surgeon in this procedure. That said, standardizing the implantation technique and careful patient selection could offer benefits in reducing the PPI incidence.

We report one case of valvular thrombosis (0.51%), which was successfully treated with oral anticoagulants. Following the procedure, all patients received antiplatelet treatment according to the standard protocol in use in our center, consisting of lifelong acetylsalicylic acid or clopidogrel when sinus rhythm was present. Antiplatelet and anticoagulation management after sutureless valve placement is not standardized, as no specific recommendations have been made in recent guidelines (17). Anticoagulation is indicated when specific baseline pathologies are present, such as atrial fibrillation.

We found no structural valve deterioration or cases of endocarditis up to the 5-year follow-up, presumably because the Perceval valve allows for less manipulation of the aortic root and annulus, zero permanent contact with foreign material such as sutures (13) and it has been shown to present high resistance against endocarditis in comparison with conventional prostheses. Nevertheless, 5 years of follow-up is still a short time compared to the data available for conventional prostheses of up to 25 years (29).

The mean postoperative transvalvular gradients after surgery confirm the excellent hemodynamic performance of the Perceval valve, coherent with other studies (6) and significantly lower when compared to the ones provided by conventional prostheses (27) and TAVIs (28).

ICU and total in-hospital stay were markedly lower when compared to conventional bioprostheses (30) and similar when compared to TAVIs (28).

Early overall mortality (in-hospital or up to 30 days after surgery) was 2.0%, a number below the one predicted by the initial EuroSCORE, in line with the 2.8% reported for conventional prostheses and significantly lower than with TAVIs (10,29,31,32). Of the four patients who died, two were a consequence of uncontrolled septic shock following native valve endocarditis, one as a consequence of neurologic complications related to an underlying type A aortic dissection and the last was a case of low-flow low-gradient aortic stenosis in cardiogenic shock. Importantly, the risk profile of these patients is not one of the typical patients usually submitted to these interventions, which might justify this relatively unexpected mortality rate. Otherwise, these results show good short-term clinical outcomes despite the risk profile and advanced age of the cohort.

Overall cumulative survival at 1, 3 and 5 years and the correspondent Kaplan-Meier curve are the ones expected taking into consideration our cohort's age, comorbidities, and type of interventions. It is up to par with the mean corresponding cumulative survival of conventional AVR (33) and better than with TAVIs up to 2 years (28), showing safety of use and good mid-term durability, with no structural valve deterioration.

Additionally, the Perceval valve enables standardization, simplification and MIS approaches in a way conventional prostheses have not yet made possible, as in these MIS is associated with greater technical difficulty due to reduced visualization leading to increased aortic cross-clamping and CPB time and a difficult and longer learning curve (10). Both MIS and the conventional approaches have similar clinical outcomes. However, MIS has numerous advantages over conventional approaches such as reduced postoperative pain, earlier mobilization, shorter hospital stays, improved aesthetics, lower incidence of surgical wound infection and lower requirements for transfusions.

To assess the comparative risk of adding concomitant procedures, patients were divided in two groups and compared. In our comparison, group A comprised patients who underwent isolated AVR with a Perceval valve plus those who had Morrow procedure, as it was considered this procedure did not add any significant additional difficulty or time length to the overall intervention. Group B comprised patients who had concomitant coronary artery bypass graft (CABG), double or triple bypass surgery. We did not include those who had other concomitant procedures, as they were too heterogeneous to be able to compare (n=15).

The number of patients who underwent isolated AVR with a Perceval valve (n=132; 67,35%) was higher than those who also had concomitant valvular interventions (n=49; 25%). Although we are comparing patients with isolated procedures with patients who underwent different concomitant operations, our goal was not to compare the risks and outcomes of the individual concomitant interventions themselves, but the risks of adding any concomitant intervention to AVR with a Perceval valve.

In comparison, group B had worse mean LV function (66.7 vs 86.1%; p=0.030) and no other significant differences in baseline characteristics, apart from the expected difference in coronary disease incidence (21,2% vs 100%). This difference explains the need for concomitant surgery, which consequently lead to longer mean aortic cross-clamping and CPB times (43.33±11.56 vs 27.30±8.14 minutes; p<0.001) and cardiopulmonary bypass times (59.98±17.53 vs 37.45±11.32 minutes; p<0.001) and longer mean ICU stay after surgery (3.96±3.87 vs 2.85±2.09 days; p=0.016). Importantly, these results are significantly lower than the ones obtained with conventional bioprostheses or TAVI both in isolated and in concomitant procedures (31). The 21,2% of patients in group A who had coronary disease were not submitted to concomitant CABG for different reasons, including the non-treatable nature of their condition at the time of the AVR or the decision of treating them with a different method posteriorly. There were no other significant differences in outcomes and survival, even up to 5 years. These results show that even with worse mean LV function and longer surgical and ICU times, adding concomitant interventions to AVR with a Perceval valve comes with no statistically significant impact on the procedural outcomes and complications, being considered therefore safe.

The possibility of performing simultaneous procedures with the Perceval valve, in particular CABG, represents a great advantage when compared with other interventional techniques, such as TAVI. This is significant because, according to the society of thoracic surgeons (STS) database, the proportion of candidates requiring concomitant CABG has risen from 5 to 25% over the past 20 years (34).

Conclusions

All patients with indication for AVR with a biological bioprosthesis could potentially benefit from a shorter and easily reproducible treatment. This seems to be especially beneficial in patients more sensitive to ischemia, technically difficult procedures, patients with a high risk of PPM, and patients who require faster recovery.

Our study further confirms the excellent clinical and hemodynamic performance and safety of the Perceval valve, a truly sutureless aortic valve, in a moderately large cohort of patients, even up to the 5-year follow-up. Consistent with current literature, the Perceval valve allowed for reduced aortic cross-clamping, CPB and surgical times due to its easy and rapid implantation technique as well as low rates of mortality, complications, or dysfunctions early and up to 5 years, even in our cohort of mostly older patients with comorbidities. Additionally, it has been proven to facilitate the reproducibility and resurgence of minimally invasive approaches, reducing additional postoperative complications and to be cost-effective.

These results were consistent both in isolated and concomitant interventions, solidifying this device as a viable treatment for isolated aortic valve disease, and now also in patients who need concomitant procedures.

Adequately sized prospective randomized controlled trials comparing the Perceval valve with the conventional aortic bioprosthesis and/or with TAVIs are necessary in the near future to confirm the findings described in this study, as well as to adequately assess long-term durability and complications.

Study limitations

This study carries all the limitations that a retrospective single center design implies. The main limitations are the lack of a control group of patients receiving conventional valves and randomization in its design. Our database only allowed for patient follow-up of a relatively small number of patients in terms of mortality and major cardiac events directly related to the valve, such as endocarditis, valvular thrombosis, or structural valve deterioration. Furthermore, the EuroSCORE may overestimate the risk of mortality. Additional limiting factors to consider were the proportion of isolated AVR to concomitant procedures, the number of patients with concomitant procedures which were too heterogeneous to compare, and possible bias introduced by surgical approach and the experience of the surgeons. Finally, as the indication for surgery in most patients was aortic valve stenosis, it is difficult to extrapolate the outcomes of this intervention to patients with other aortic valve diseases.

Conflicts of interest statement

The authors have no conflicts of interest to declare.

Bibliography

1. Carrel T, Heinisch PP. History, development and clinical perspectives of sutureless and rapid deployment surgical aortic valve replacement. Ann Cardiothorac Surg. 2020 Sep;9(5):375–85.

2. Joseph J, Naqvi SY, Giri J, Goldberg S. Aortic Stenosis: Pathophysiology, Diagnosis, and Therapy. Am J Med. 2017 Mar 1;130(3):253–63.

3. Kanwar A, Thaden JJ, Nkomo VT. Management of Patients With Aortic Valve Stenosis. Mayo Clin Proc. 2018 Apr;93(4):488–508.

4. Bilkhu R, Borger MA, Briffa NP, Jahangiri M. Sutureless aortic valve prostheses. Heart Br Card Soc. 2019 Mar;105(Suppl 2):s16–20.

5. Barnhart GR, Shrestha ML. Current Clinical Evidence on Rapid Deployment Aortic Valve Replacement. Innov Phila Pa. 2016 Jan;11(1):7–14.

6. Shrestha M, Fischlein T, Meuris B, Flameng W, Carrel T, Madonna F, et al. European multicentre experience with the sutureless Perceval valve: clinical and haemodynamic outcomes up to 5 years in over 700 patients. Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg. 2016 Jan;49(1):234–41.

7. Ranucci M, Frigiola A, Menicanti L, Castelvecchio S, de Vincentiis C, Pistuddi V. Aortic cross-clamp time, new prostheses, and outcome in aortic valve replacement. J Heart Valve Dis. 2012 Nov;21(6):732–9.

8. Desser AS, Arentz-Hansen H, Fagerlund BF, Harboe I, Lauvrak V. Sutureless Aortic Valve Replacement for Treatment of Severe Aortic Stenosis: A Single Technology Assessment of Perceval Sutureless Aortic Valve.

9. Mazine A, Bonneau C, Karangelis D, Yanagawa B, Verma S, Bonneau D. Sutureless aortic valves: who is the right patient? Curr Opin Cardiol. 2017 Mar;32(2):130–6.

10. Martínez-Comendador J, Castaño M, Gualis J, Martín E, Maiorano P, Otero J. Sutureless aortic bioprosthesis. Interact Cardiovasc Thorac Surg. 2017 Jul 1;25(1):114–21.

11. Folliguet TA, Laborde F, Zannis K, Ghorayeb G, Haverich A, Shrestha M. Sutureless Perceval Aortic Valve Replacement: Results of Two European Centers. Ann Thorac Surg. 2012 May 1;93(5):1483–8.

12. Flynn CD, Williams ML, Chakos A, Hirst L, Muston B, Tian DH. Sutureless valve and rapid deployment valves: a systematic review and meta-analysis of comparative studies. Ann Cardiothorac Surg. 2020 Sep;9(5):36474–36374.

13. Pfeiffer S, Fischlein T, Santarpino G. Sutureless Sorin Perceval Aortic Valve Implantation. Semin Thorac Cardiovasc Surg. 2017 Spring;29(1):1–7.

14. Sangani NK, Suri RM. Sutureless Aortic Valve Implantation. Oper Tech Thorac Cardiovasc Surg. 2013;18(4):288–304.

15. Totaro P, Nicolardi S, Zattera G, Viganò M. Old prosthesis with a modern concept: 41-year survival with a sutureless Magovern-Cromie aortic valve prosthesis. Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg. 2011 May;39(5):789.

16. Sian K, Li S, Selvakumar D, Mejia R. Early results of the Sorin® Perceval S sutureless valve: systematic review and meta-analysis. J Thorac Dis. 2017 Mar;9(3):711–24.

17. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017 Sep 21;38(36):2739–91.

18. Heimansohn D, Moainie S. Aortic Valve Replacement Using a Perceval Sutureless Aortic Bioprosthesis. Oper Tech Thorac Cardiovasc Surg. 2016 Dec 1;21(4):282–305.

19. Pollari F, Santarpino G, Dell'Aquila AM, Gazdag L, Alnahas H, Vogt F, et al. Better short-term outcome by using sutureless valves: a propensity-matched score analysis. Ann Thorac Surg. 2014 Aug;98(2):611–6; discussion 616-617.

20. LisaNova Ø. PERCEVAL® and PERCEVAL® PLUS Pre-operative Echo-Doppler AORTIC ROOT HEIGHT EVALUATION.

21. Di Bacco L, Pfeiffer S, Fischlein TJM, Santarpino G. Rapid Explantation of Rapid-Deployment Sutureless Valve in Case of Acute Endocarditis: How to Remove Safely Sutureless Perceval S Prostheses. Innovations. 2017 Nov 1;12(6):483–5.

22. Svenarud P, Persson M, van der Linden J. Effect of CO_2 Insufflation on the Number and Behavior of Air Microemboli in Open-Heart Surgery: A Randomized Clinical Trial. Circulation. 2004 Mar 9;109(9):1127–32.

23. Kodali SK, Svensson LG, Fontana GP, Pichard AD, Lim S, Malaisrie SC, et al. Two-Year Outcomes after Transcatheter or Surgical Aortic-Valve Replacement. N Engl J Med. 2012;10.

24. Chivasso P, Marsico R, Domenico V. Atrial Fibrillation after Cardiac Surgery: Where are we Now? 2018;4.

25. Flameng W, Herregods M-C, Hermans H, Van der Mieren G, Vercalsteren M, Poortmans G, et al. Effect of sutureless implantation of the Perceval S aortic valve bioprosthesis on intraoperative and early postoperative outcomes. J Thorac Cardiovasc Surg. 2011 Dec;142(6):1453–7.

26. Mazine A, Teoh K, Bouhout I, Bhatnagar G, Pelletier M, Voisine P, et al. Sutureless aortic valve replacement: a Canadian multicentre study. Can J Cardiol. 2015 Jan;31(1):63–8.

27. Thalji NM, Suri RM, Michelena HI, Greason KL, Dearani JA, Daly RC, et al. Do differences in early hemodynamic performance of current generation biologic aortic valves predict outcomes 1 year following surgery? J Thorac Cardiovasc Surg. 2015 Jan;149(1):163-173.e2.

28. Meco M, Miceli A, Montisci A, Donatelli F, Cirri S, Ferrarini M, et al. Sutureless aortic valve replacement versus transcatheter aortic valve implantation: a meta-analysis of comparative matched studies using propensity score matching. Interact Cardiovasc Thorac Surg. 2018 Feb 1;26(2):202–9.
29. Bourguignon T, Bouquiaux-Stablo A-L, Candolfi P, Mirza A, Loardi C, May M-A, et al. Very long-term outcomes of the Carpentier-Edwards Perimount valve in aortic position. Ann Thorac Surg. 2015 Mar;99(3):831–7.
30. Mujtaba SS, Ledingham SM, Shah AR, Pillay T, Schueler S, Clark S. Aortic Valve Replacement with a Conventional Stented Bioprosthesis versus Sutureless Bioprosthesis: a Study of 763 Patients. Braz J Cardiovasc Surg [Internet]. 2018 [cited 2021 May 4];33(2). Available from: https://bjcvs.org/pdf/2859/v33n2a04.pdf
31. Hamm CW, Möllmann H, Holzhey D, Beckmann A, Veit C, Figulla H-R, et al. The German Aortic Valve Registry (GARY): in-hospital outcome. Eur Heart J. 2014 Jun 21;35(24):1588–98.
32. Brown JM, O'Brien SM, Wu C, Sikora JAH, Griffith BP, Gammie JS. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. J Thorac Cardiovasc Surg. 2009 Jan;137(1):82–90.
33. Schwarz F, Baumann P, Manthey J, Hoffmann M, Schuler G, Mehmel HC, et al. The effect of aortic valve replacement on survival. Circulation. 1982 Nov;66(5):1105–10.
34. Shrestha M, Folliguet TA, Pfeiffer S, Meuris B, Carrel T, Bechtel M, et al. Aortic valve replacement and concomitant procedures with the Perceval valve: results of European trials. Ann Thorac Surg. 2014 Oct;98(4):1294–300.