Transcatheter Bioprosthesis Implantation for the Treatment of Aortic Stenosis: Three-Year Experience

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Abstract

Background: Transcatheter aortic bioprosthesis implantation is a new treatment modality for patients with aortic stenosis who are inoperable or at high surgical risk.

Objective: To report the three-year experience with transcatheter CoreValve® bioprosthesis implantation.

Methods: From January 2008 to January 2011, 35 patients with aortic stenosis (33) or aortic valve bioprosthesis dysfunction (two) at high surgical risk underwent transcatheter CoreValve® bioprosthesis implantation.

Results: The patients' mean age was 81.5 ± 9 years, and 80% had heart failure functional class III or IV. The EuroScore was 18.4 ± 14.3% and the STS risk score was 14.5 ± 11.6%. Successful device implantation was achieved in 34 (97.1%) patients. After the intervention, a reduction in the transvalvular pressure gradient from 84.9 ± 22 to 22.5 ± 9.5 mm Hg was observed, and 87.1% of the patients progressed to functional class I or II. Thirty-day mortality and mortality in the follow-up of 400 ± 298 days were 11.4% and 31.4%, respectively. The occurrence of life-threatening hemorrhagic complications was the only independent predictor of cardiovascular mortality. Stroke occurred in 5.7% of the patients. Permanent pacemaker was required in 32.1% of the patients within the first month after the procedure.

Conclusion: Transcatheter aortic bioprosthesis implantation is a safe and effective procedure to be used in patients with aortic stenosis at high surgical risk. The CoreValve® prosthesis proved to have mid-term efficacy in a three-year follow-up. (Arq Bras Cardiol. 2012; [online].ahead print, PP.0-0)

Keywords: Aortic valve stenosis; balloon dilatation; heart valve prosthesis.

Introduction

Aortic stenosis is the most common heart valve disease. Its prevalence increases with age, affecting approximately 3% of the population over the age of 75 years[1]. In Brazil, with the increased life expectancy, it is estimated that by 2030 there will be 11 million Brazilians in that age group (http://www.ibge.gov.br), and, thus, approximately 350,000 patients with degenerative aortic stenosis[2].

For decades, surgical aortic valve replacement has been the treatment of choice for patients with symptomatic aortic stenosis, providing symptom relief and increasing survival. However, the surgical risk increases as age advances and comorbidities associate, determining that more than one third of the octogenarians with symptomatic aortic stenosis be denied surgery[3,4]. In this context, transcatheter implantation of aortic valve bioprosthesis, a new modality of treatment for patients considered inoperable or at high surgical risk, was introduced in clinical practice some years ago. The Edwards-Sapien® balloon-expandable transcatheter heart valve and the self-expandable Medtronic-CoreValve® system have proved to be safe and highly effective[5-15]. By the time this study was written, over 35,000 patients had already been treated with those devices worldwide. In Brazil, the experience with transcatheter aortic valve implantation began in January 2008, with the approval and availability of the CoreValve® system[16]. In this study, we report the experience accumulated over three years with that device at the medical center that initiated the use of that new therapeutic modality in Brazil.

Methods

Selection of patients

From January 2008 to January 2011, 35 consecutive patients with aortic valve stenosis (33 cases) or aortic valve bioprosthesis dysfunction (two cases) underwent percutaneous implantation of the CoreValve® bioprosthesis. Those patients were selected from a greater universe, where other cases were assessed and did not undergo the procedure due to either lack of compliance with the indication criteria, or administrative questions. The indication of the procedure was restricted to a

selected group of patients, who, because of advanced age or comorbidities, were at high risk or had contraindications for conventional surgical treatment. The EuroScore and the STS risk score were used to estimate the risk of surgical mortality of those patients[17,18]. In general, patients with an aortic valve area < 1 cm², aortic valve annulus ≥ 20 and ≤ 27 mm, ascending aorta ≤ 43 mm, and diameter of the common femoral artery ≥ 6 mm are considered fit for the percutaneous procedure.

The procedure

Patients undergoing percutaneous aortic valve replacement received aspirin (100 mg) and clopidogrel (attack dose of 300 mg, followed by 75 mg per day), starting on the day preceding the procedure and recommended to be maintained for three to six months. Antibiotic prophylaxis was performed with cefuroxime, 1.5 g one hour before and six hours after the procedure. During the procedure, heparin, at the dose of 100 U/kg, was administered aiming at reaching an activated coagulation time > 250 and < 300 seconds. The vascular approach, when performed through the femoral access, was totally percutaneous, using hemostatic devices (Perclose and Prostar XL). The subclavian access required surgical dissection. After obtaining vascular access, balloon aortic valvuloplasty was performed to pre-dilate the native valve for prosthesis implantation. Then, the CoreValve® bioprosthesis (CoreValve Revalving System, Medtronic, Inc.) was implanted and consisted of three porcine pericardial leaflets, mounted and sutured on a self-expandable 5-cm nitinol stent. Implantation was always performed by the same two surgeons, using an 18-F sheath (6 mm). For valvular annulus sizes between 20 and 23 mm, the 26-mm prosthesis was selected, and for valvular annulus sizes between 23 and 27 mm, the 29-mm prosthesis was selected. At the end of the procedure, transvenous pacemaker was maintained for 24 to 48 hours, as a protection if bradyarrhythmia occurred.

Definitions and endpoints

All complications and study endpoints were adjudicated in accordance with the Valve Academic Research Consortium Consensus on Event Definition[19].

CoreValve® device success was achieved when one single prosthesis could be positioned and properly implanted, with proper function, heart valve area > 1.2 cm², mean aortic transvalvular pressure gradient < 20 mm Hg or peak velocity < 3 m/s, and, at most, mild aortic regurgitation.

Data collection during follow-up

Clinical data and complementary test results during follow-up were collected on medical visits or via telephone.

Statistical analysis

The continuous variables are presented as mean and standard deviation, and the categorical variables as frequencies (number and percentage).

When analyses of subgroups were performed, the chi-square test, Fisher exact test or likelihood ratio test were used for categorical variables. For continuous variables, ANOVA was

used, or, when the variable did not have a normal distribution, the non-parametric Mann-Whitney test was used.

The McNemar test was used for the sequential analysis of categorical variables. For continuous variables with normal distribution in the same patient, ANOVA was used for repeated measures with Bonferroni multiple comparison test. When the variable did not have normal distribution, the non-parametric Friedman test was used, and, when a difference between times was detected, two-by-two comparisons were performed using the non-parametric paired Wilcoxon test, adjusted to the Bonferroni multiple comparison test.

To determine independent predictors of mortality, of cardiovascular mortality and of permanent pacemaker implantation, multivariate logistic regression was used, including variables whose p values were lower than or equal to 15% in the univariate model.

The Kaplan-Meier curve was used to build the mortality and cardiovascular mortality graphs.

The significance level adopted was 5% (p-valor ≤ 0.05).

Results

The demographic, clinical and echocardiographic characteristics of the 35 patients studied are shown in Tables 1 and 2. The patients' mean age was 81.5 ± 9 years (61 to 98 years), and 80% of them were in New York Heart Association heart failure functional class III or IV. The mean logistic EuroScore was 18.4% ± 14.3% (2.4% to 71.4%), and the mean STS risk score was 14.5 ± 11.6% (1.3% to 42.9%).

The mean follow-up time was 400 ± 298 days (0 to 1,105 days). The 1-month, 1-year- and 2-year follow-ups were available for 35 (100%), 25 (71.4%) and 11 (31.4%) patients, respectively. There was no loss to clinical follow-up.

The mean hospital length of stay was 11 ± 12.5 days (4 to 69 days).

Procedure

Procedural data are shown in Table 3. Only one patient, who had an abdominal aorta aneurysm, underwent the procedure through dissection of the subclavian artery. The others underwent puncture of the common femoral artery. Successful device implantation was achieved in 34 (97.1%) patients, and device success was achieved in 29 (82.8%). The failures were as follows: one patient had cardiac tamponade and died due to perforation of the left ventricle caused by the guidewire while guiding the prosthesis towards the valvular annulus, in which case, the prosthesis was not implanted; one prosthesis malpositioning, with embolization to the ascending aorta and need for implantation of a second prosthesis (valve-in-valve); and four cases of moderate periprosthetic regurgitation on echocardiographic evaluation, despite balloon post-dilation in two cases.

Complications

Four (11.4%) patients died in the procedure due to cardiovascular causes as follows: three patients due to hemorrhagic complications (abdominal aorta dissection,

Table 1 – Baseline demographic and clinical data

	(n = 35)
Age, years	81.5 (SD 9)
Male sex, n (%)	16 (45.7%)
STS,%	14.5 (SD 11.6)
Logistic EuroScore, %	18.4 (SD 14.3)
NYHA Functional Class	
I or II, n (%)	7 (20%)
III or IV, n (%)	28 (80%)
Diabetes, n (%)	10 (28.5%)
Renal Failure*, n (%)	21 (60%)
Coronary Artery Disease, n (%)	14 (40%)
Previous Percutaneous Intervention, n (%)	8 (22.8%)
CABG surgery, n (%)	5 (14.3%)
Aortic Valvuloplasty, n (%)	4 (11.4%)
Aortic Valve (Bioprosthesis) Replacement, n (%)	2 (5.7%)
Cerebrovascular Disease, n (%)	5 (14.3%)
Peripheral Vascular Disease, n (%)	6 (17.1%)
COPD, n (%)	8 (22.8%)
Atrial Fibrillation/Flutter, n (%)	2 (5.8%)
Permanent pacemaker, n (%)	3 (8.6%)
* Creatinine Clearance < 60 mL/min	
NYHA: New York Heart Association	
CABG: Coronary Artery Bypass Graft	
COPD: Chronic Obstructive Pulmonary Disease	

retroperitoneal hemorrhage, and tamponade due to left ventricular perforation with guidewire); and one patient with severe left ventricular dysfunction died because of refractory cardiogenic shock after balloon aortic valvuloplasty. Table 4 shows the complications that occurred in the first 30 days and during clinical follow-up.

During the procedure and within the first 24 hours, life-threatening or disabling hemorrhagic complications occurred in six (17.1%) patients, while major hemorrhages occurred in five (14.3%). Thus, major hemorrhages or life-threatening or disabling hemorrhagic complications were observed in 11 (31.4%) patients, three of whom died. Major vascular complications occurred in six (17.1%) patients, four of which caused associated hemorrhagic complications. The vascular and hemorrhagic complications were observed mainly in the beginning of our experience, and most of them might have been due to the lack of familiarity with the Prostar hemostastic device.

In the periprocedural period, neither stroke nor myocardial infarction was observed, and no emergency cardiac surgery was required.

Endpoints

In the period between 1 and 30 days after the procedure, no additional deaths were observed, and, thus, the all-cause mortality and cardiovascular mortality rates within 30 days after the procedure were 11.2%, similar to the intraprocedural mortality (Table 4). In the one-moth follow-up, the following were not observed: new myocardial infarctions; significant ischemic or hemorrhagic complications; acute renal failure; and need for cardiac surgery to fix problems related to the CoreValve® bioprosthesis. Two patients (5.7%) had stroke in that period, 4 and 12 days after the procedure, the latter being a patient with atrial fibrillation. Thus, at the end of 30 days, 26 (74.3%) patients had no major complication.

In the period between one month and one year, one non-ST-segment elevation myocardial infarction and four additional deaths were observed, two of which had a cardiovascular cause. Thus, at the end of 12 months, 21 (60%) patients had no major complication.

Three non-cardiovascular deaths occurred after one year of clinical follow-up. Thus, the survival estimates (Kaplan-Meier) free from the all-cause death and cardiovascular death events reached 54.3% and 82.7%, respectively, at 36 months. Figures 1 and 2 show the actuarial curves.

None of the variables assessed proved to be an independent predictor of all-cause mortality in the multivariate regression model. Regarding cardiovascular mortality, the only predictor identified on logistic regression was the occurrence of life-threatening hemorrhagic complication during the procedure (p=0.038).

The clinical follow-up of the patients identified a significant improvement in the clinical symptomatology of heart failure (Table 5), with 87.1% of the patients achieving functional class I or II already within the first 30 days. After that period, the clinical benefit persisted, with 93.5% of the patients with functional class I or II at 452 ± 277 days (45 to 1,105 days) of follow-up.

Echocardiographic and electrocardiographic endpoints

Regarding echocardiographic data (Table 2), an immediate drop in the mean and peak aortic transvalvular pressure gradients was identified after CoreValve® implantation. No significant difference was observed between the pressure gradients measured after the procedure and on echocardiographic follow-up.

Echocardiographic assessment after bioprosthesis implantation revealed moderate periprosthetic regurgitation in four (12.9%) of the 31 patients who survived the procedure; three of them maintained the same pattern on control echocardiogram and one showed a reduction in the intensity of the regurgitation. Only one patient had an increase in the intensity of perivalvular regurgitation (from mild to moderate) when comparing the tests performed after the procedure and during follow-up. Thus, on control echocardiography performed 319 ± 242 (16 to 981) days after bioprosthesis implantation, four (12.9%) patients were identified as having moderate regurgitation, two of whom required readmission due to heart failure. No other abnormality in the bioprostheses implanted was identified during the entire follow-up.

Regarding left ventricular function, a trend (p=0.057) towards an increase in the ejection fraction was detected during clinical follow-up (Table 2).

Table 2 - Echocardiographic evolution

	Baseline	Post-Procedure	Follow-up
			319 ± 242 (16-981) days
	(N 35)	(N 31)	(N 28)
Aortic Valve Area, cm²	0.7 (SD 0.2)	n/a	n/a
Peak Gradient, mmHg	84.9 (SD 22)	22.5 (SD 9.5)	20.5 (SD 10.5)
Mean Gradient, mmHg	51.8 (SD 16.3)	12.3 (SD 5.2)	12.2 (SD 6.2)
LV Ejection Fraction,%	58.1 (SD 14.1)	58.9 (SD 13.5)	63.3 (SD 14.9)
Aortic Regurgitation			
None/Mild, n (%)	29 (82.8%)	27 (87.1%)	24 (85.7%)
Moderate, n (%)	5 (14.3%)	4 (12.9%)	4 (14.3%)
Severe, n (%)	1 (2.9%)	0	0
Mitral Regurgitation			
None/Mild, n (%)	27 (77.1%)	22 (70.9%)	25 (89.3%)
Moderate, n (%)	8 (22.9%)	9 (29.1%)	3 (10.7%)
Severe, n (%)	0	0	0
n/a: not available LV: left ventricular			
Peak Gradient (Baseline X Post)		p< 0.001	
Peak Gradient (Baseline X Follow-up)		p< 0.001	
Peak Gradient (Post X Follow-up)		p=0.228	
Mean Gradient (Baseline X Post)		p< 0.001	
Mean Gradient (Baseline X Follow-up)		p< 0.001	
Mean Gradient (Post X Follow-up)		p=1.000	

Baseline Ejection Fraction vs. Post Ejection Fraction vs. Follow-up Ejection Fraction　　*p= 0.057*

Table 3 – Data from the procedure

	(n = 35)
Tutoring, n%	22 (62.8%)
Anesthesia	
General, n (%)	21 (60%)
Sedation, n (%)	14 (40%)
Access	
Femoral, n (%)	34 (97.1%)
Subclavian, n (%)	1 (2.9%)
Valvuloplasty, n%	35 (100%)
Valve-in-valve	2 (5.8%)
Bioprosthesis	
Size 26, n%	12 (35.3%)
Size 29, n%	22 (64.7%)
Post-dilation, n%	7 (20.6%)
Hemostatic device	34 (97.1%)
Implantation success, n% Device success, n%	34 (97.1%) 29 (82.8%)

In this series, excluding the patients who died during the procedure and those already having a pacemaker, ten (35.7%) of 28 underwent permanent pacemaker implantation (Table 4) and 17 (60.7%) developed a new left bundle branch block. Of those requiring pacemaker implantation, eight had it implanted while still hospitalized, one had the implantation indicated in the first month, and only one patient had the permanent pacemaker implanted 12 months after the procedure. In logistic regression analysis, no variable proved to be an independent predictor of the need for pacemaker implantation.

Discussion

This study, comprising the three-year follow-up of patients undergoing transcatheter CoreValve® bioprosthesis implantation for the treatment of symptomatic aortic valve stenosis, shows that this new modality of treatment is effective. It provides immediate enlargement of the valvular area and a reduction in the aortic transvalvular pressure gradient, with consequent relief of the congestive heart failure symptoms.

The CoreValve® prosthesis was effectively implanted in more than 95% of the patients and device success was

Table 4 - Cumulative adverse events

	30 days	Follow-up
	(N 35)	(N 35)
		400 ± 298 (0 to 1,105) days
Death		
All-cause, n (%)	4 (11.4%)	11 (31.4%)
Cardiovascular, n (%)	4 (11.4%)	6 (17.1%)
Myocardial Infarction	0	1 (2.8%)
Stroke	2 (5.7%)	2 (5.7%)
TIA, n (%)	0	0
Minor, n (%)	0	0
Major, n (%)	2 (5.7%)	2 (5.7%)
Acute Renal Failure*		
Stage 1, n (%)	5 (16.1%)	n/a
Stage 2, n (%)	0	n/a
Stage 3, n (%)	0	n/a
Hemorrhagic Complication, n (%)	11 (31.4%)	11 (31.4%)
Major, n (%)	5 (14.3%)	5 (14.3%)
Risk of Death, n (%)	6 (17.1%)	6 (17.1%)
Vascular Complications, n (%)	12 (31.4%)	n/a
Minor, n (%)	5 (14.3%)	n/a
Major, n (%)	6 (17.1%)	n/a
Cardiac Reintervention, n (%)*	0	0
Prosthesis Dysfunction	0	0
Endocarditis, n (%)*	0	0
Permanent Pacemaker, n (%)**	9 (32.1%)	10 (35.7%)
Readmission, n (%)*	0	3 (8.6%)

n/a: not applicable
TIA: transient ischemic attack

* Patient at risk = 31

** Patient at risk = 28

Free from complications: absence of all-cause death, stroke, life-threatening or disabling bleeding, stage 3 acute renal failure, periprocedural infarction, new percutaneous or surgical procedure to correct valvular dysfunction.

achieved in approximately 83%, indices systematically reported after overcoming the learning curve for both the balloon-expandable heart valve (Sapien®) and the self-expandable prosthesis (CoreValve®)[5,8,10-15]. The lack of success of the CoreValve® device was mainly due to the detection of moderate periprosthetic regurgitation on the echocardiography performed immediately after implantation. Usually, mild periprosthetic regurgitation, common after the implantation of CoreValve® and Sapien® devices[11,12,15], is clinically very well tolerated. However, the presence of moderate regurgitation is believed to have a negative impact on the clinical evolution of patients[14], and, according to the Valve Academic Research Consortium Consensus on Event Definition[19], that condition should be considered a device

failure. In fact, in our experience, two (50%) of four patients with moderate aortic regurgitation had no improvement in heart failure functional class, requiring hospital readmission to achieve compensation.

The 30-day mortality of 11.2% observed in the present study is in accordance with that reported in several series (ranging from 3.4% to 20%)[5,7-15,20,21], being lower than the mortality estimated for the conventional surgical treatment of the same patients, when using the EuroScore or STS risk score. One-year mortality, according to the Kaplan-Meier estimate, reached 23.6%, and the deaths within that period were mostly due to cardiovascular causes, most of them related to procedural complications. After one year of follow-up, no additional cardiovascular deaths occurred, all of them being
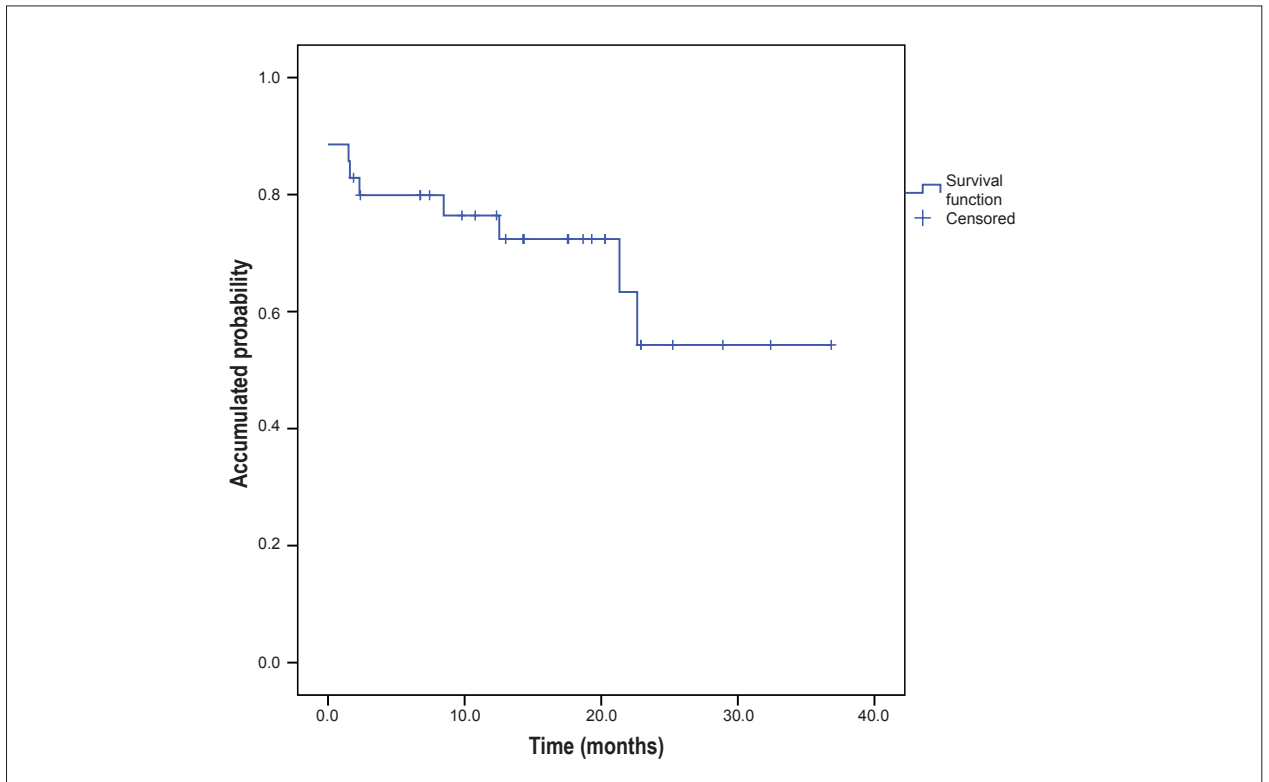
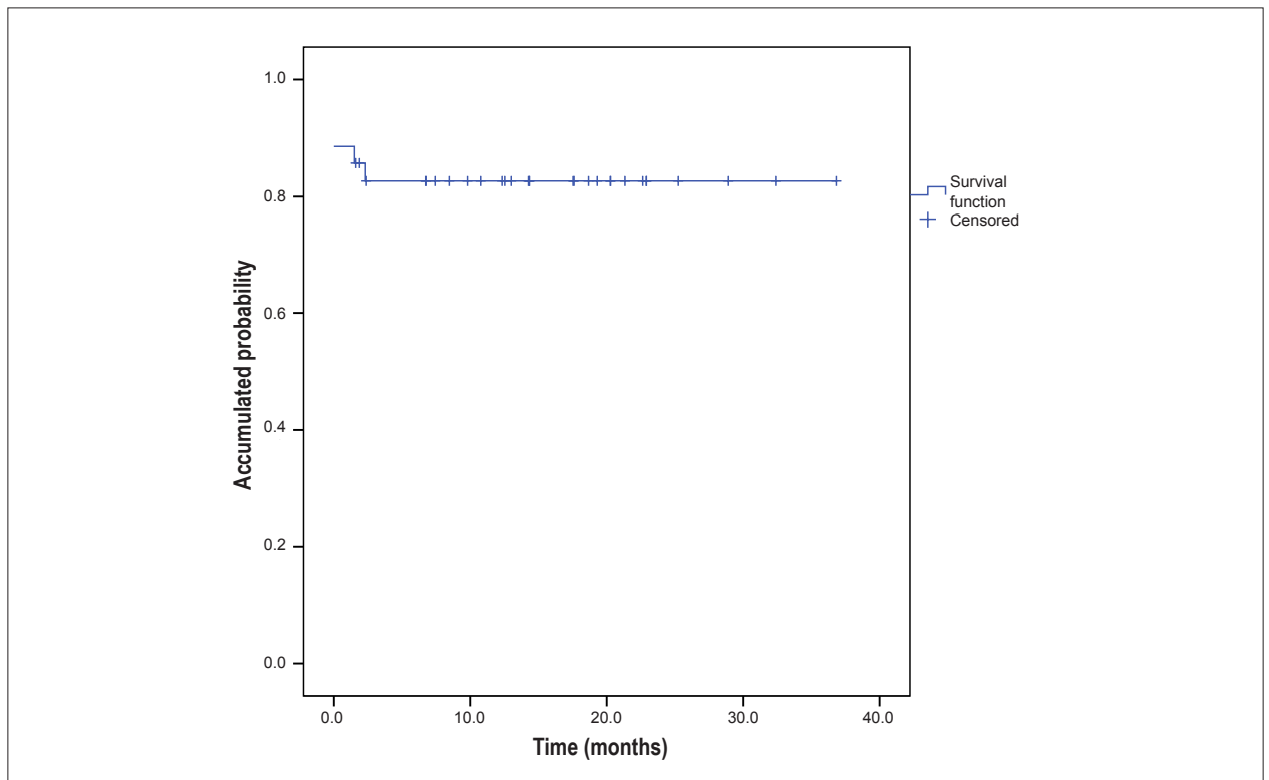**Figure 1 -** *Kaplan-Meier survival curve (all-cause death)*

Figure- 2 - *Kaplan-Meier survival curve (cardiovascular death)*

Table 5 – Progression of the heart failure functional class

	Baseline	30 days	Follow-up
			452 ± 276 (45-1,105) days
	(N 35)	(N 31)	(N 31)
FC I, n (%)	0	17 (54.8 %)	19 (61.3%)
FC II, n (%)	7 (20%)	10 (32.3 %)	10 (32.3%)
FC III, n (%)	19 (54.3%)	4 (12.9%)	2 (6.4%)
FC IV, n (%)	9 (25.7%)	0	0

FC: Functional Class

Baseline vs. 30 days (p<0.001)
Baseline vs. Follow-up (p<0.001)

due to the severe comorbidities inherent to that specific population, mostly composed of high-risk octogenarians. Such findings are in accordance with those reported by other studies on the mid-term follow-up of patients undergoing transcatheter aortic bioprosthesis implantation[5,8,10,12].

The present study identified one single independent predictor of cardiovascular mortality, which was the occurrence of life-threatening or disabling hemorrhagic complications during the procedure, which was also a mortality predictor in the study by Tamburino et al.[14]. In our initial experience, we detected an elevated incidence of vascular and hemorrhagic complications in the vascular access site, attributed to the learning curve and to the lack of familiarity in handling the Prostar hemostatic device. That fact determined a change in the hemostasis technique, with the use of two or three Proglide devices (Perclose), following the experience with the percutaneous implantation of endoprostheses for correcting aortic aneurysm, with sheaths of up to 24F[22]. After this change in technique, hemorrhagic and vascular complications became less frequent.

The incidence of stroke in our series is in accordance with that of the randomized PARTNER trial and of other published series[8,10,13,15,20], in which that complication occurred in 2.8% to 11% of the patients. In our experience, ischemic cerebral events did not occur during the procedure, but in the first weeks following the intervention. That complication might be related to atheroembolism of plaques in the ascending aorta and aortic arch, embolization of calcified debris of native aortic valve leaflets, thromboembolism originating from the valvular prosthesis, and the occasional occurrence of atrial fibrillation, as might have occurred in one of our patients. In the PARTNER trial, only approximately half of the cases of stroke occurred during the procedure, which, along with our findings, raise the question about the efficacy of protective devices against cerebral embolism when used only at the occasion of prosthesis implantation[8,10,23].

In our case series with the CoreValve® device, advanced atrioventricular conduction disorder was detected, requiring permanent pacemaker implantation in approximately one third of the patients. Complete left bundle branch block was identified in over half of the patients. These findings of the present study are in accordance with those of other studies in which permanent pacemaker was necessary in over 20% to 40% of the patients, and left bundle branch block occurred in approximately 60% of the patients[15,24-26]. Proximity of the aortic valve annulus to the atrioventricular node, to the bundle of His (membranous septum), and to the fascicles of the left bundle branch (muscular region of the interventricular septum) can explain why manipulation and trauma of the aortic valve annulus are associated with heart conduction system disorders[27]. Edema, inflammation and ischemia can result from the manipulation of the aortic valve annulus during surgery or from the mechanical stress caused by percutaneous aortic valve implantation. In surgical aortic valve replacement, one third of the patients has heart conduction system disorders, and around 5% of them require permanent pacemaker implantation[28,29]. These numbers are similar to those reported in studies with percutaneous or transapical implantation of the Sapien® prosthesis[8,10,30]. In the present study, independent predictors of the need to implant a permanent pacemaker were not identified. Other studies have reported that the deeper implantation of the CoreValve® bioprosthesis in left ventricle outflow tract, the over-dimensioning of the prosthesis regarding the valvular annulus, and the presence of complete right bundle branch block at baseline condition identify those with a higher tendency to develop advanced atrioventricular conduction disorders[24,26,30-32].

Late echocardiographic follow-up of this series showed persistence of the benefits obtained immediately after the intervention regarding valvular area and mean and peak aortic transvalvular pressure gradients, with the tendency towards a left ventricular function improvement during follow-up. CoreValve® bioprosthesis dysfunction was not detected in any patient during that period. Clinically, more than 90% of the patients being followed up had heart failure functional class I or II. Those clinical and echocardiographic findings of mid-term efficacy of the CoreValve® prosthesis are in accordance with those of other published studies[5,6,8,10,11,13].

The major limitation of the present study is the small number of patients included, especially when aiming at identifying independent predictors of adverse events. However, we believe this is a significant experience for the Brazilian reality

and its investigative character should motivate the performance of larger sample studies, such as the Brazilian Registry of Transcatheter Aortic Bioprosthesis Implantation conducted by the Brazilian Society of Interventionist Cardiology[33].

In conclusion: 1) transcatheter CoreValve® bioprosthesis implantation is a safe and effective procedure to be used for selected high-risk or inoperable patients; 2) hemorrhagic complications are predictors of cardiovascular mortality; 3) approximately one third of the patients require permanent pacemaker implantation, because of advanced atrioventricular conduction disorder following CoreValve® bioprosthesis implantation; and 4) clinical and echocardiographic results show that CoreValve® bioprosthesis has mid-term efficacy in a three-year follow-up.

Potential Conflict of Interest

Sources of Funding

Study Association

This study is not associated with any post-graduation program.

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