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Original Article

Impact of Transcatheter Aortic Valve Implantation Learning Curve on Patient Selection and Clinical Outcomes

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ABSTRACT

Background: Transcatheter aortic valve implantation (TAVI) is an alternative treatment for high-risk or inoperable patients with aortic stenosis. The multidisciplinary team must undergo specific training and accumulate experience to achieve optimal results. However, its learning curve is not well established. Our objective was to investigate the impact of learning curve on patient selection, technical aspects and clinical outcomes of TAVI. **Methods**: Observational, prospective analysis of the first 150 patients undergoing transfemoral TAVI between January 2009 and December 2013. Patients were divided into tertiles (n = 50), according to the procedure date. Outcomes were defined according to Valve Academic Research Consortium-2 (VARC-2) criteria. **Results**: Mean age was 82.5 ± 6.7 years, 44% were male and 75% were in NYHA class III/IV. EuroSCORE (24.2 ± 13% vs. 21.2 ± 10.8% vs. 23.4 ± 14.3%) and STS Score (5.9 ± 2.9% vs. 6.7 ± 4.3% vs. 5.8 ± 3.1%) were similar between groups. A gradual decrease was observed in procedure times (107.2 ± 48.1 minutes vs. 90.3 ± 42.2 minutes vs. 76.6 ± 37.7 minutes; $p < 0.01$), fluoroscopy times (31.3 ± 9,6 minutes vs. 25.4 ± 8.7 minutes vs. 17.2 ± 6.2 minutes; $p = 0.01$) and contrast volume (145.5 ± 70.9 mL vs. 123.2 ± 87.8 mL vs. 101.1 ± 50 mL; $p = 0.01$). Mortality decreased gradually (20% vs. 10% vs. 4%; $p = 0,047$), and lower bleeding and moderate-to-severe aortic regurgitation were observed in the third tertile (14% and 4%, respectively). There were no cases of reintervention, stroke or other clinical events between hospital discharge and 30-day follow-up. **Conclusions**: The competence in performing TAVI improved progressively as the number of patients treated increased and was associated with better clinical outcomes.

DESCRIPTORS: Aortic valve stenosis. Heart valve prosthesis. Heart valve prosthesis implantation.

RESUMO

Impacto da Curva de Aprendizado na Seleção de Pacientes e nos Resultados Clínicos do Implante por Cateter de Prótese Aórtica

Introdução: O implante por cateter de prótese aórtica (TAVI, do inglês *transcatheter aortic valve implantation*) constitui tratamento alternativo para pacientes com estenose aórtica de alto risco cirúrgico ou inoperáveis. Para adquirir competência, o grupo multidisciplinar deve receber treinamento especifico e acumular experiência na execução do TAVI. Contudo, sua curva de aprendizado não está bem estabelecida. Nosso objetivo foi analisar o impacto da curva de aprendizado na seleção de pacientes, nos aspectos técnicos e nos resultados clínicos do TAVI. **Métodos**: Estudo observacional e prospectivo dos primeiros 150 pacientes submetidos a TAVI por via femoral, entre janeiro de 2009 e dezembro de 2013 divididos em tercis (n = 50) de acordo com a data do procedimento. Os desfechos foram definidos conforme os critérios *Valve Academic Research Consortium-2* (VARC-2). **Resultados**: A idade foi de 82,5 ± 6,7 anos, sendo 44% homens e 75% em classe NYHA III/IV. O EuroSCORE (24,2 ± 13% vs. 21,2 ± 10,8% vs. 23,4 ± 14,3%) e o STS Score (5,9 ± 2,9% vs. 6,7 ± 4,3% vs. 5,8 ± 3,1%) foram similares entre os grupos. Observou-se redução gradativa nos tempos do procedimento (107,2 ± 48,1 minutos vs. 90,3 ± 42,2 minutos vs. 76,6 ± 37,7 minutos; $p < 0,01$) e de fluoroscopia (31,3 ± 9,6 minutos vs. 25,4 ± 8,7 minutos vs. 17,2 ± 6,2 minutos; p = 0,01), e no volume de contraste (145,5 ± 70,9 mL vs. 123,2 ± 87,8 mL vs. 101,1 ± 50 mL; $p = 0,01$). A mortalidade reduziu-se de forma progressiva (20% vs. 10% vs. 4%; $p = 0,047$), e menores taxas de sangramentos e de refluxo paraprotético de grau moderado/grave foram observadas no terceiro tercil (14% e 4%, respectivamente). Não ocorreram casos de reintervenção, acidente vascular cerebral e nem outros eventos clínicos entre a alta hospitalar e o 30º dia pós-implante. **Conclusões**: A competência para o TAVI aumentou progressivamente com o número de pacientes tratados, associando-se a melhores desfechos clínicos.

DESCRITORES: Estenose da valva aórtica. Próteses valvulares cardíacas. Implante de prótese de valva cardíaca.

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Justified by the continuous accumulation of scientific evidence from large registries[1-4] and randomized trials,[5-7] the indication for transcatheter aortic valve implantation (TAVI) has already been established in Brazilian and international guidelines for treatment of valve diseases.[8-10] TAVI is recommended as the treatment of choice for patients with severe aortic stenosis considered inoperable (class I, level of evidence B), and an alternative strategy to valve replacement surgery should be considered in individuals at high surgical risk (class IIa, level of evidence B). Estimates indicate that over 100,000 patients have been treated worldwide, and current results in centers with broad experience demonstrate high rates of procedural success (> 95%), with rates of mortality at 30 days < 5%.[11,12]

TAVI must be developed within a program for the treatment of aortic stenosis, and not merely seen as a procedure. The creation of a multidisciplinary group (ideally consisting of clinical cardiologists, interventional cardiologists, surgeons, anesthesiologists, and specialists in cardiovascular imaging) is essential for an appropriate patient assessment, resulting in an adequate environment dedicated to the choice and promotion of a safer, more effective and definitive treatment of patients with this valvular heart disease. It is postulated that the multidisciplinary team involved in patient selection and performance of procedures should receive specific theoretical and practical training to acquire competence.[13,14] Supplementary teaching methods, which include the use of simulators, practice using animal models, courses, and symposia are recommended, while the supervision of more experienced surgeons (proctors) is essential at the beginning of the learning curve. In turn, the number of patients to be treated at this stage in order to attain the desired clinical outcomes is yet to be established. The present study aimed to analyze the impact of the learning curve on patient selection, technical aspects, and clinical outcomes of TAVI.

METHODS

Patient selection

The first 150 patients undergoing TAVI procedure through femoral artery access in Instituto Dante Pazzanese de Cardiologia and Hospital do Coração, institutions where the same multidisciplinary team works, both located in the city of São Paulo, Brazil, were included in this study. These patients were treated between January 2009 and December 2013, due to a picture of severe and symptomatic aortic stenosis, and high or prohibitive surgical risk, according to risk estimate models (Society of Thoracic Surgeons – STS Score – and logistic EuroSCORE) and team consensus. To investigate the anatomical feasibility of TAVI, stringent assessment was performed by imaging methods, which consisted of transthoracic echocardiography, coronary angiography, and multidetector angio-computed tomography (CT) of the aortic complex, descending aorta, and iliac and femoral arteries. All patients were informed of the objectives of the intervention to be performed and the need for late assessment, as well as the risks inherent to the procedures, and signed an informed consent form.

Patient preparation and used prostheses

All patients were pretreated with acetylsalicylic acid 100 mg and clopidogrel 300 mg on the day prior to implantation. In individuals with renal dysfunction, intravenous hydration with 0.9% saline solution, at a dose of 0.3 to 0.5 mL/kg/h, was initiated 12 hours before the procedure. Also aiming at the prevention of contrast-induced nephropathy, the angiograms required during the procedure were obtained with low-osmolarity contrast media, with a 50% dilution.

Three transcatheter implantation systems were used: CoreValve® (Medtronic Minneapolis, United States), Edwards SAPIEN XT (Edwards Lifesciences, Irvine, United States) and Acurate TF® (Symetis Inc., Geneva, Switzerland). As they have a distinct learning curve, subjects submitted to valve implantation through alternative access routes (transapical, transaortic, and subclavian) were excluded from the study.

Group division and data collection

Patients were divided into tertiles (n = 50), allocated consecutively according to the date of procedural completion. The cases were entered into a specific database, prospectively created to record TAVI at the two institutions. Baseline characteristics of patients, imaging results, hemodynamic data, procedural aspects, complications, and in-hospital clinical outcomes were collected. Clinical data and information from supplementary tests at the 30 day follow-up were obtained through medical visits or phone contact. Patients were also submitted to clinical and echocardiographic assessment at 6 and 12 months post-procedure and to annual consultations after the first year of intervention.

Definitions

Complications and clinical outcomes of the study followed the criteria established by the Valve Academic Research Consortium-2 (VARC-2).[15] The following were considered as successful device implantation: single prosthesis implanted in the right place, with the absence of prosthesis-patient mismatch, mean aortic transvalvular gradient < 20 mmHg or peak velocity < 3 m/s, and absence of aortic regurgitation ≥ moderate, according to the definitions of the transesophageal or transthoracic echocardiography.

Procedural safety at 30 days was assessed by mortality from all causes, cardiovascular mortality, and the occurrence of complications. Stroke was determined by the onset of focal or global neurological

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deficit lasting > 24 h, or the presence of a new area of cerebral infarction or bleeding in neuroimaging methods, regardless of symptom duration. Bleeding complications were divided into: (1) life-threatening bleeding, when fatal or overt bleeding occurred in a vital organ (intracranial, intraocular, and pericardial) or bleeding that resulted in hypovolemic shock or severe hypotension requiring vasopressors or surgery; or overt bleeding with a decrease in hemoglobin ≥ 5 g/dL or need for transfusion of four or more bags of packed red blood cells; (2) major bleeding: overt bleeding with a decrease in hemoglobin ≥ 3 g/dL or need for transfusion of two or three bags of packed red blood cells, or bleeding that required hospitalization or surgery; (3) minor bleeding: any bleeding worth mentioning (e.g., hematoma at the puncture site) that did not meet the criteria for life-threatening or major bleeding.

Vascular complications were categorized as major according to the following criteria: occurrence of aortic dissection, aortic or aortic annulus rupture, or left ventricular perforation; diagnosis of vascular injury at the femoral puncture site that resulted in death, major bleeding, or life-threatening bleeding; vascular injury that caused visceral ischemia or neurological impairment; non-cerebral distal embolization that required surgery; need for surgical or percutaneous intervention that led to death, major bleeding, visceral ischemia, or neurological impairment; or any documented ipsilateral ischemia. Chronic renal failure was determined by the presence of creatinine clearance < 50 mL/min. In turn, the post-procedure acute kidney injury that occurred was classified according to the Acute Kidney Injury (AKIN) score,[16] assessed until the seventh day after implantation. After the measurement of serum creatinine levels and quantification of urinary volume, kidney injury was categorized as: (a) Stage 1: increase of 0.3 mg/dL in serum creatinine or increase of 150% to 200% from baseline, or urinary output < 0.5 mL/kg/h for 6 hours post-procedure; (b) Stage 2: increase > 200-300% of baseline serum creatinine or urinary output < 0.5 mL/kg/h for > 12 hours; c) Stage 3: increase > 300% of baseline serum creatinine or serum creatinine ≥ 4.0 mg/dL, associated with an increase of at least 0.5 mg/dL from baseline; urinary output < 0.3 mL/kg/h for 24 hours anuria for more than 12 hours. The presence of pulmonary hypertension was determined by the systolic pulmonary artery pressure (measured by transthoracic echocardiography) > 55 mmHg.

Statistical analysis

Continuous variables were expressed as means and standard deviations; categorical variables were expressed as absolute numbers and percentages. The analysis of differences between categorical variables was assessed by Pearson's chi-squared or Fisher's exact test, as appropriate. Differences between continuous variables were determined by analysis of variance (ANOVA). For all tests, p-values ≤ 0.05 were considered statistically significant. Data were analyzed using SPSS, version 20 (Chicago, United States).

RESULTS

Clinical and echocardiographic features

Table 1 depicts patients' clinical characteristics, both as a whole and in accordance with the group to which they were allocated. The mean age of patients was 82.5 ± 6.7 years; 44% were males, 32% were diabetics, 61.3% had chronic renal failure, and 30% had pulmonary artery hypertension. Before the intervention, patients were symptomatic (75% were in New York Heart Association [NYHA] functional class III or IV), and the risk of surgical mortality was estimated at 6.1 ± 3.5% by STS and 22.9 ± 12.7% by logistic EuroSCORE.

Patients in group 1 were treated from January 2009 to April 2011; those belonging to group 2 had the procedure performed between May 2011 and January 2013; finally, individuals placed in group 3 underwent TAVI between February 2013 and December 2013. There were no statistically significant differences between groups in relation to the assessed clinical variables, except for NYHA functional class, chronic renal failure (66% vs. 72% vs. 46%; $p = 0.02$), and pulmonary hypertension (48% vs. 14% vs. 28%; $p < 0.01$).

Table 2 presents the results of the echocardiographic assessment performed before and after the procedure. The mean pre-implantation left-ventricle (LV) ejection fraction (EF) was 57.4 ± 13.1%, and 19 patients (12.6%) had left ventricular dysfunction (EF < 40%). The mean transvalvular gradient was 54.3 ± 15.1 mmHg, with an estimated aortic valve area of 0.7 ± 0.2 cm.^{2} After treatment, there was a significant reduction in the mean transvalvular gradient to 11.2 ± 4.7 mmHg and increase in valve area to 1.8 ± 0.3 cm^2 ($p < 0.01$ for both variables, when comparing pre- and post-TAVI). Sixteen patients (10.6%) had moderate or severe periprosthetic leakage after valve implant, with an incidence of 16% in the initial group and 4% in the third tertile. The evolution of patients treated in the second and third tertiles showed larger valve areas (1.7 ± 0.2 cm^2 vs. 1.9 ± 0.3 cm^2 vs. 1.9 ± 0.3 cm^2; $p < 0.01$).

Characteristics of the procedure

Technical aspects related to TAVI are shown in Table 3. Most patients underwent implantation under general anesthesia, aimed at monitoring by transesophageal echocardiography. In the first 20 cases, the femoral access was obtained by dissection and was subsequently replaced by percutaneous technique with the use of vascular repair devices (Prostar® or Perclose ProGlide®; Abbott Vascular, Redwood City, United States). In the

TABLE 1
Clinical data of patients submitted to Transcatheter Aortic Valve Implantation

Characteristics	Total (n = 150)	First tertile (n = 50)	Second tertile (n = 50)	Third tertile (n = 50)	*p*-value
Age, years	82.5 ± 6.7	81.8 ± 7.4	83.3 ± 5.6	82.3 ± 7.0	0.55
Age range	59-93	62-92	68-93	59-93	
Weight, kg	68.3 ± 11.9	66.7 ± 10.9	68.4 ± 12.1	69.9 ± 12.7	0.40
Height, m	1.61 ± 0.1	1.61 ± 0.1	1.62 ± 0.1	1.60 ± 0.1	0.87
Male gender, n (%)	66 (44)	17 (34)	23 (46)	26 (52)	0.18
STS Score, %	6.1 ± 3.5	5.9 ± 2.9	6.7 ± 4.3	5.8 ± 3.1	0.22
Logistic EuroSCORE, %	22.9 ± 12.7	24.2 ± 13.0	21.2 ± 10.8	23.4 ± 14.3	0.48
Symptoms/NYHA functional class, n (%)					0.02
I-II	37 (24.7)	10 (20)	8 (16)	19 (38)	
III-IV	113 (75.3)	40 (80)	42 (84)	31 (62)	
Comorbidities, n (%)					
Arterial hypertension	121 (80.7)	38 (76)	42 (84)	41 (82)	0.57
Diabetes mellitus	48 (32)	16 (32)	20 (40)	12 (24)	0.23
Chronic renal failure*	92 (61.3)	33 (66)	36 (72)	23 (46)	0.02
COPD	15 (10)	6 (12)	3 (6)	6 (12)	0.51
Peripheral artery disease	26 (17.3)	11 (22)	11 (22)	4 (8)	0.10
Pulmonary artery hypertension#	45 (30)	24 (48)	7 (14)	14 (28)	< 0.01
Previous cardiovascular events, n (%)					
Myocardial infarction	31 (20.7)	10 (20)	12 (24)	9 (18)	0.75
Stroke	8 (5.3)	5 (10)	2 (4)	1 (2)	0.28
Previous cardiac procedures, n (%)					
Percutaneous coronary intervention	41 (27.3)	8 (16)	17 (34)	16 (32)	0.09
CABG	36 (24)	11 (22)	10 (20)	15 (30)	0.46
CABG ≥ 2 times	5 (3.3)	2 (4)		2 (4)	> 0.99
Aortic-valve replacement	2 (1.3)	0	1 (2)	1 (2)	> 0.99
Aortic-balloon valvuloplasty	5 (3.3)	1 (2)	2 (4)	2 (4)	> 0.99
Definitive pacemaker /ICD	17 (11.3)	5 (10)	4 (8)	8 (16)	0.14
LV dysfunction (EF ≤ 40%), n (%)	19 (12.6)	5 (10)	7 (14)	6 (12)	0.83
Porcelain aorta, n (%)	7 (4.7)	5 (10)	1 (2)	1 (2)	0.22

*Creatinine clearance < 50 mL/min; #pulmonary-artery systolic blood pressure > 55 mmHg.
STS Score: Society of Thoracic Surgeons Score; NYHA: New York Heart Association; COPD: chronic obstructive pulmonary disease; CABG: coronary-artery bypass graft surgery; ICD: implantable cardioverter defibrillator; LV: left ventricle; EF: ejection fraction.

transition between the second and third tertiles, the procedures started to be performed preferably at the hybrid room. The beginning of this experience with TAVI occurred with the self-expanding Core Valve® system, and 40% of the implants performed in the first tertile occurred without pre-dilation. When the balloon-expandable prosthesis Edwards SAPIEN XT® became available in Brazil, the first procedure by this group was performed in September 2011. The first implantation of the self-expandable prosthesis Acurate TF® occurred in January 2012. In general, post-dilation was required in 35% of cases.

In the comparison between tertiles, a significant reduction was observed in procedure duration (107.2 ± 48.1 min vs. 90.3 ± 42.2 min vs. 76.6 ± 37.7 min; $p < 0.01$) in fluoroscopy time (31.3 ± 9.6 min vs. 25.4

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TABLE 2
Pre- and post-procedural echocardiographic findings

Variables	Total (n = 150)	First tertile (n = 50)	Second tertile (n = 50)	Third tertile (n = 50)	*p*-value
Pre-procedure					
Left-ventricular ejection fraction, %	57.4 ± 13.1	57.4 ± 14.2	58.0 ± 12.4	56.8 ± 12.9	0.90
Minimum-maximum values	25-75	25-74	27-75	30-72	
Mean gradient, mmHg	54.3 ± 15.1	56.6 ± 15.6	53.3 ± 14.2	52.5 ± 15.7	0.36
Aortic-valve area, cm^2	0.7 ± 0.2	0.6 ± 0.1	0.7 ± 0.2	0.7 ± 0.2	0.23
Pulmonary-artery systolic pressure, mmHg	51.1 ± 12.4	53.9 ± 13.1	52.8 ± 11.6	47.1 ± 11.6	0.02
Moderate/severe aortic regurgitation, n (%)	13 (8.7)	5 (10)	5 (10)	3 (6)	0.81
Moderate/severe mitral regurgitation, n (%)	27 (18)	6 (12)	12 (24)	9 (18)	0.30
Post-procedure					
Left-ventricular ejection fraction, %	58.5 ± 12.5	57.9 ± 13.1	59.2 ± 11.5	58.5 ± 13.0	0.89
Mean gradient, mmHg	11.2 ± 4.7	11.4 ± 4.6	12.0 ± 4.4	10.4 ± 4.9	0.23
Aortic-valve area, cm^2	1.8 ± 0.3	1.7 ± 0.2	1.9 ± 0.3	1.9 ± 0.3	< 0.01
Pulmonary-artery systolic pressure, mmHg	48.5 ± 14.5	54.8 ± 19.2	46.1 ± 12.2	45.3 ± 9.2	< 0.01
Moderate/severe aortic regurgitation, n (%)	16 (10.6)	8 (16)	6 (12)	2 (4)	0.13
Moderate/severe mitral regurgitation, n (%)	30 (20)	9 (18)	9 (18)	12 (24)	0.69

TABLE 3
Procedural data

Characteristics	Total (n = 150)	First tertile (n = 50)	Second tertile (n = 50)	Third tertile (n = 50)	*p*-value
Local, n (%)					< 0.01
Catheterization room	93	50 (100)	30 (60)	13 (26)	
Hybrid room	57	0	20 (40)	37 (74)	
Type of anesthesia, n (%)					> 0.99
General	147 (98)	49 (98)	49 (98)	49 (98)	
Sedation	3 (6)	1 (2)	1 (2)	1 (2)	
Vascular access/repair, n (%)					< 0.001
Surgical dissection	30 (20)	30 (60)	0	0	
Percutaneous (Prostar®/ProGlide®)	120 (80)	20 (40)	50	50	
Pre-dilation, n (%)	118 (78.7)	30 (60)	40 (80)	48 (96)	< 0.01
Type of prosthesis, n (%)					< 0.01
Core Valve®	81 (54)	50 (100)	23 (46)	8 (16)	
Edwards SAPIEN XT®	41 (27.3)	0	13 (26)	28 (56)	
Acurate TF®	28 (18.7)	0	14 (28)	14 (28)	
Post-dilation, n (%)	52 (34.7)	15 (30)	17 (34)	20 (40)	0.57
Second prosthesis implantation, n (%)	6 (4)	5 (10)	1 (2)	0	0.048
Support-with extracorporeal circulation, n (%)	2 (1.3)	0	2 (4)	0	0.33
Time of procedure, minutes	94.7 ± 43.4	107.2 ± 48.1	90.3 ± 42.2	76.6 ± 37.7	< 0.01
Contrast volume, mL	132.1 ± 67	145.5 ± 70.9	123.2 ± 87.8	101.1 ± 50.0	0.01
Fluoroscopy, minutes	27.4 ± 9.2	31.3 ± 9.6	25.4 ± 8.7	17.2 ± 6.2	0.01
Procedural success, n (%)	131 (87)	41 (82)	44 (88)	48 (96)	< 0.01

± 8.7 min vs. 17.2 ± 6.2 min; $p = 0.01$) and the contrast volume used for valve implantation (145.5 ± 70.9 mL vs. 123.2 ± 87.8 mL vs. 101.1 ± 50 mL; $p = 0.01$; Figure). Six patients (4%) required the implantation of a second prosthesis, and most of these cases occurred in the beginning of the study (10% vs. 2% vs. 0%; $p = 0.048$). Procedural success was achieved in 133 (88.6%) patients, of whom 41 patients were in the first tertile (82%), 44 (88%) patients in the second, and 48 (96%) patients in the third tertile ($p = 0.085$).

In-hospital and 30 day results

The overall mortality at 30 days decreased from 20% (n = 10) in the first tertile to 10% (n = 5) in the second, and to 4% (n = 2) in the third tertile ($p = 0.047$; Table 4). Stroke and major vascular complications occurred in 2% and 8.7% of cases, respectively (with no differences between groups). Overall lower rates of bleeding were observed over the period (46% vs. 34% vs. 14%; $p = 0.03$), and this difference was attributed to the decrease in minor bleeding episodes.

There was a significant reduction in the time of intensive care unit hospitalization (3.2 ± 4.6 days vs. 2.7 ± 1.5 days vs. 1.8 ± 1.2 days; $p = 0.04$) and hospital length of stay (9.6 ± 6.7 days vs. 8.6 ± 9.2 days vs. 6.8 ± 3.3 days; $P = 0.03$). After 30 days post-procedure, all survivors were submitted to clinical, laboratory, and electrocardiographic evaluations; when patients could not come to the hospital, information was obtained by telephone contact. There were no reintervention cases, stroke, or other clinical events during the interval between hospital discharge and 30 days post-implantation.

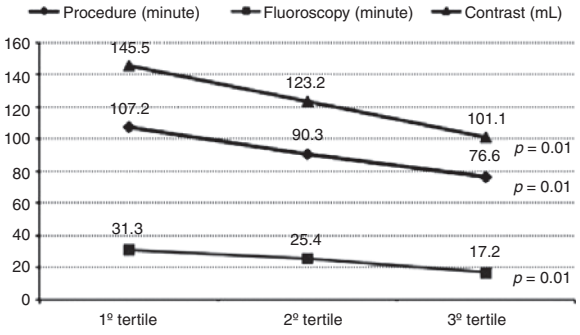

Figure – Technical parameters in the different tertiles.

DISCUSSION

In this study, which described the initial experience of a multidisciplinary group with TAVI, the learning curve in patient selection and implementation of the procedure was progressively associated with better clinical outcomes. As a greater number of patients was assessed, selected, and treated, there was a significant reduction in overall mortality at 30 days and bleeding episodes caused by the procedure, as well as numerically lower rates of moderate/severe periprosthetic leakage.

Among the several aspects related to the clinical success of TAVI, the factors related to patients, the technique, and the devices used are noteworthy. Adequate patient selection for TAVI should be based on specific clinical and anatomical criteria, being crucial for procedural success. In this study, the multidisciplinary group reviewed all relevant clinical aspects and results of imaging methods, interpreting and unifying them into a consensual decision-making, which defined the best

TABLE 4
In hospital and 30 day clinical outcome

	1º tertile (n = 50)	2º tertile (n = 50)	3º tertile (n = 50)	*p*-value
Death	10 (20)	5 (10)	2 (4)	0.047
Cardiovascular	9 (18)	3 (6)	2 (4)	0.06
Stroke/TIA, n (%)	1 (2)	1 (2)	1 (2)	> 0.99
Major vascular complications, n(%)	5 (10)	5 (10)	3 (6)	0.82
Bleedings, n (%)	23 (46)	17 (34)	7 (14)	0.03
Life-threatening bleeding	2 (4)	3 (6)	1 (2)	0.87
Major bleeding	10 (20)	6 (12)	4 (8)	0.20
Minor bleeding	11 (22)	8 (16)	2 (4)	0,03
Acute kidney injury, n (%)				0.49
AKIN 1	5 (10)	7 (14)	6 (12)	
AKIN 2	2 (4)	2 (4)	2 (4)	
AKIN 3	7 (14)	2 (4)	2 (4)	
Permanent pacemaker, n (%)	10 (20)	5 (10)	6 (12)	0.31
Urgency surgery, n (%)	1 (2)	1 (2)	0	> 0.99
Time at ICU, days	3.2 ± 4.6	2.7 ± 1.5	1.8 ± 1.2	0.04
Hospital stay, days	9.6 ± 6.7	8.6 ± 9.2	6.8 ± 3.3	0.03

TIA: transient ischemic attack; AKIN: Acute Kidney Injury Score; ICU: intensive care unit.

strategy for each patient. Along the learning curve, no change was observed in the risk profile of the selected patients: both the mean age and estimates of surgical mortality according to the STS score and EuroSCORE were similar among the groups. According to these algorithms, these individuals could be categorized as moderate (mean STS score of 6.1 ± 3.5%) to high surgical risk (mean EuroSCORE of 22.9 ± 12.7%). This clinical profile is similar to that of patients included in recent studies that suggested that individuals with aortic stenosis and progressively lower surgical risk have been progressively referred to TAVI. Lange et al.[17] observed, over three years, a change in the clinical characteristics of patients undergoing the procedure, with a tendency toward the selection of younger patients, those with progressively lower STS, and lower prevalence of associated diseases: the mean STS score was 7.1 ± 5.4% in the first quartile of treated patients, decreasing to 4.8 ± 2.6% in the last quartile. The propensity to indicate TAVI for patients with lower surgical risk is further corroborated by data from the UK TAVI Registry Investigators,[4]from the United Kingdom, with a mean reported EuroSCORE of 18.5%, and from the randomized clinical trials US Core-Valve[7] (comparing with surgical valve replacement, with mean STS score of 7.3 ± 3.0%) and CHOICE (STS score between 5 and 6.9%).[18] In the present study, some patients showed clinical and anatomical factors known to be associated with increased surgical morbidity and mortality: 14 patients were diagnosed as having fragile and seven as having "porcelain" aorta. As these factors are not included in current models of operative risk stratification, the estimated mortality provided by these scores represented just one more fact to guide – not to define – decision-making. Also related to patient selection, it was observed that in the first 50 cases, there was a higher prevalence of individuals with chronic renal failure on hemodialysis (n = 3) or severe pulmonary arterial hypertension (pulmonary artery pressure > 70 mmHg, n = 7);[19] these had worse post-TAVI evolution. Therefore, the indication for the procedure to patients with these comorbidities became more stringent and such conditions were less common in the third tertile.

The improvement in parameters that express the technique employed in valve implantation reflects the progressive acquisition of proficiency for the procedure. By implementing specific imaging protocols, a significant decrease in the volume of contrast used in implants was observed. At the beginning of the series, for instance, two or more aortographies were usually required to find the ideal angiographic projection for prosthesis release. This process has been simplified by routine determination of this angulation by CT angiography, which allows for aperfect alignment of the three aortic cusps on the same plane. When it is impossible to perform the pre-procedure angiography, tomographic image reconstruction using the rotational acquisition program (DynaCT Aortic Valve Guide, Siemens AG; Munich, Germany), was also shown to be useful in determining the best view for the implantation.[20] Although the sequence of steps required for TAVI (attaining the access route, valvuloplasty, positioning, and release of the prosthesis) has not changed during the study period, there was significant reduction in the duration of the procedure and fluoroscopy time, a result of the greater skill and safety to cross the stenotic aortic valve, insert the rigid guide wire in the left ventricular cavity, and finally, to position and implant the prosthesis.

When analyzing the above-mentioned parameters, Alli et al.[21] observed that achieving competence in TAVI performance can be attained with a smaller number of patients (n = 44). The present study goes further regarding this question by demonstrating that other important technical aspects, such as the need for a second prosthesis and procedural success (both with prognostic significance) are related to the accumulated experience. Therefore, in the third tertile, procedural success (defined as the implantation of a single prosthesis in the correct anatomic position without significant gradient or leakage and without operative mortality) occurred in 96% of patients – similar to the rate found in the CHOICE study, which compared the Sapien XT® and Core Valve® prostheses.[18] In that randomized clinical trial, the procedure was successfully performed in 95.9% of patients treated with a balloon-expandable system and in 77.5% of those who underwent implantation of the self-expandable prosthesis. In the present, the most frequent use of the Edwards SAPIEN® prosthesis in the third tertile may also explain the improvement in success rates of the device.

The presence of moderate or severe periprosthetic aortic regurgitation was less frequent in the last group treated (reduction from 16 to 4%). Several studies have indicated that the occurrence of periprosthetic regurgitation has a negative impact on the outcome of patients undergoing TAVI.[22,23] In a recent meta-analysis, Athappan et al.[24] demonstrated that the presence of moderate or severe periprosthetic leakage is common (11.7 %), and is an independent predictor of early mortality (odds ratio – OR = 2.95; 95% confidence interval – 95% CI: 1.73 to 5.02) and longer-term mortality (hazard ratio – HR = 2.27; 95% CI: 1.84 to 2.81). Although multifactorial, the occurrence of periprosthetic leakage is fundamentally related to the anatomical characteristics of the aortic annulus-complex (elliptical configuration and asymmetric calcification), and the disproportion between the valve annulus and the prosthesis of choice. At the beginning of the present study, the reference used to determine the size of the prosthesis to be implanted was the annulus diameter, obtained by transthoracic echocardiography, as recommended by the manufacturers at the time. However, recent evidence suggests that multi-detector CT angiography provides more valuable information for the choice of prosthesis and that such assessment can influence the clinical results of the procedure.[25] Based on this new

Box
Clinical outcomes at 30 days observed in recent studies.

	Partner B (n=179)[5]	US CoreValve®* (n=390)[7]	CHOICE (n=241)[18]	France-2 (n=2,361)[2]	UK-TAVI† (n=599)[4]	TVT Registry†,‡ (n=4,972)[30]	Third tertile (n=50)
Death, %	5	3.3	4.6	8.5	5.5	4.9	4
Stroke, %	6.7	4.9	4.2	3.7	4	2.6	2
Major vascular complications, %	16.2	5.9	10.5	5.5	8.4	6.5	6
Life-threatening bleeding, %	16.8	13.6	10.1	1.2	NA	3.3	2
Permanent pacemaker, %	3.4	19.8	27	15.2	16.3	6	12
Moderate/severe periprosthetic leakage. %	11.8	10	3.7	18.6	15.6	8.5	4

*17% of the patients were not treated by transfemoral access; † cohort of patients treated via femoral artery; ‡ registry with balloon-expandable Edwards SAPIEN® prosthesis. NA, Information not available.

knowledge obtained during the learning curve, the area and perimeter measurements (defined by angiotomography or by three-dimensional echocardiography) started to be used for the choice of prosthesis size. In general, the aim was that the CoreValve® prosthesis were 10 to 25% oversize in relation to the valve annulus, and that the Edwards SAPIEN XT® prosthesis were 5 to 15% oversize; obviously, certain characteristics, such as the degree and pattern of calcification of the annulus, and the outflow-tract and sinotubular-junction diameter were also considered in that decision. Thus, the choice of larger prosthesis (and the most appropriate for the valve annulus of each patient) would explain the lower incidence of periprosthetic leakage found in the last group. In fact, valve areas obtained in the second and third tertiles were greater than those observed in the first tertile.

The best clinical results were obtained in the last tertile of the learning curve. During this period, the observed outcomes were comparable to those reported in major international series and randomized trials (Box). A great deal of evidence shows the remarkable association between the volume of procedures and the occurrence of clinical outcomes after percutaneous cardiovascular procedures, such as percutaneous coronary intervention,[26] carotid angioplasty with stent,[27] or mitral valvuloplasty.[28] This association, however, has not been well established for TAVI.[29] The previously published consensuses controversially indicate that the number of procedures required for certification and maintenance of competence in TAVI ranges from 10 cases (no established interval between cases)[13] to 2 cases/month or 20 cases/year.[14] According to the data of this study, the minimum number of cases recommended by these consensuses is much lower than that required to achieve the desired clinical results. In this experience, the last 50 patients were treated at an interval of 11 months, constituting a mean of approximately 4.5 patients/month – a significantly higher rate than that observed in the first and second tertiles (1.85 and 2.5 patients/month, respectively). Therefore, it is justified that not only the total number of cases exerts a crucial role: the regularity with which they are performed can have an influence on the learning curve.

CONCLUSIONS

In this experiment, the learning curve had a significant impact on the technical aspects and clinical results of TAVI, and was associated with a reduction in rates of mortality, bleeding, and moderate/severe periprosthetic leakage.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES

1. Chieffo A, Buchanan GL, Van Mieghem NM, Tchetche D, Dumonteil N, Latib A, et al. Transcatheter aortic valve implantation with the Edwards SAPIEN versus the Medtronic Core Valve Revalving system devices: a multicenter collaborative study: the PRAGMATIC Plus Initiative (Pooled-Rotterd Am-Milano-Toulouse In Collaboration). J Am Coll Cardiol. 2013;61(8):830-6.
2. Gilard M, Eltchaninoff H, Iung B, Donzeau-Gouge P, Chevreul K, Fajadet J, et al; FRANCE 2 Investigators. Registry of transcatheter aortic-valve implantation in high-risk patients. N Engl J Med. 2012;366(18):1705-15.
3. Zahn R, Gerckens U, Linke A, Sievert H, Kahlert P, Hambrecht R, et al; German Transcatheter Aortic Valve Interventions-Registry Investigators. Predictors of one-year mortality after transcatheter aortic valve implantation for severe symptomatic aortic stenosis. Am J Cardiol. 2013;112(2):272-9.

4. Moat NE, Ludman P, de Belder MA, Bridgewater B, Cunningham AD, Young CP, et al. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K.TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. J Am Coll Cardiol. 2011;58(20):2130-8.
5. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al; PARTNER Trial Investigators. Transcatheter aorticvalve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010;363(17):1597-607.
6. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011;364(23):2187-98.
7. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med. 2014;370(19):1790-8.
8. Tarasoutchi F, Montera MW, Grinberg M, Barbosa MR, Piñeiro DJ, Sánchez CR, et al. Diretriz Brasileira de Valvopatias – SBC 2011/I Diretriz Interamericana de Valvopatias – SIAC 2011. Arq Bras Cardiol. 2011;97(5 Supl. 1):1-67.
9. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(22):e57-e185.
10. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, et al. Guidelines on the management of valvular heart disease (version 2012): the joint task force on the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2012;33(19):2451-96.
11. Popma JJ, Adams DH, Reardon MJ, Yakubov SJ, Kleiman NS, Heimansohn D, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol.2014;63(19):1972-81.
12. Thomas M, Schymik G, Walther T, Himbert D, Levèfre T, Treede H, et al. One-year outcomes of cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. Circulation.2011;124(4):425-33.
13. Brito Junior FS, Lemos PA, Siqueira D, Sarmento-Leite R, Mangione JA, Carvalho LA, et al. Consenso de Especialistas sobre o implante por cateter de biopróteses valvares para o tratamento da estenose aórtica de alto risco cirúrgico: relato da Sociedade Brasileira de Hemodinâmica e Cardiologia Intervencionista. Rev Bras Cardiol Invasiva. 2011;19(2):200-7.
14. Holmes DR Jr, Mack MJ, Kaul S, Agnihotri A, Alexander KP, Bailey SR, et al. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement. J Am Coll Cardiol. 2012;59(13):1200-54.
15. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. Eur Heart J. 2012;33(19):2403-18.
16. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al; Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31.
17. Lange R, Bleiziffer S, Mazzitelli D, Elhmidi Y, Opitz A, Krane M, et al. Improvements in transcatheter aortic valve implantation outcomes in lower surgical risk patients: a glimpse into the future. J Am Coll Cardiol. 2012;59(3):280-7.
18. Abdel-Wahab M, Mehilli J, Frerker C, Neumann FJ, Kurz T, Tölg R, et al. Comparison of balloon-expandable vs self-expandable valves in patients undergoing transcatheter aortic valve replacement: the CHOICE randomized clinical trial. JAMA. 2014;311(15):1503-14.
19. Rodés-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Osten M, et al. Long-term outcomes after transcatheter aortic valve implantation: insights on prognostic factors and valve durability from the Canadian multicenter experience. J Am Coll Cardiol.2012;60(19):1864-75.
20. Kempfert J, Noettling A, John M, Rastan A, Mohr FW, Walther T. Automatically segmented DynaCT: enhanced imaging during transcatheter aortic valve implantation. J Am Coll Cardiol.2011;58(25):e211.
21. Alli OO, Booker JD, Lennon RJ, Greason KL, Rihal CS, Holmes DR Jr. Transcatheter aortic valve implantation: assessing the learning curve. JACC Cardiovasc Interv. 2012;5(1):72-9.
22. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, et al; PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med. 2012;366(18):1686-95.
23. Tamburino C, Capodanno D, Ramondo A, Petronio AS, Ettori F, Santoro G, et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. Circulation. 2011;123(3):299-308.
24. Athappan G, Patvardhan E, Tuzcu EM, Svensson LG, Lemos PA, Fraccaro C, et al. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. J Am Coll Cardiol. 2013;61(15):1585-95.
25. Wilson AB, Webb JG, Labounty TM, Achenbach S, Moss R, Wheeler M, et al. 3-dimensional aortic annular assessment by multidetector computed tomography predicts moderate or severe paravalvular regurgitation after transcatheter aortic valve replacement: a multicenter retrospective analysis. J Am Coll Cardiol. 2012;59(14):1287-94.
26. Minges KE, Wang Y, Dodson JA, Normand SLT, Rathore SS, Ting HH, et al. Physician annual volume and in-hospital mortality following percutaneous coronary intervention [abstract]. American Heart Association 2011 Annual Scientific Sessions. Circulation. 2011;124:A16550.
27. Ahmadi R, Willfort A, Lang W, Schillinger M, Alt E, Gschwandtner ME, et al. Carotid artery stenting: effect of learning curve and intermediate-term morphological outcome. J Endovasc Ther. 2001;8(6):539-46.
28. Rihal CS, Nishimura RA, Holmes DR Jr. Percutaneous balloon mitral valvuloplasty: the learning curve. Am Heart J. 1991;122(6):1750-6.
29. Gurvitch R, Tay EL, Wijesinghe N, Ye J, Nietlispach F, Wood DA, et al. Transcatheter aortic valve implantation: lessons from the learning curve of the first 270 high-risk patients. Catheter Cardiovasc Interv. 2011;78(7):977-84.
30. Mack MJ, Brennan JM, Brindis R, Carroll J, Edwards F, Grover F, et al; STS/ACC TVT Registry. Outcomes following transcatheter aortic valve replacement in the United States. JAMA.2013;310(19):2069-77.