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Original article

Long-term Follow-up After Transcatheter Aortic Valve Implantation for Severe Aortic Stenosis

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ABSTRACT

Introduction and objectives: Transcatheter aortic valve implantation is used as an alternative to surgical valve replacement in patients with severe aortic stenosis who are considered high-surgical-risk or inoperable. Two of the main areas of uncertainty in this field are valve durability and long-term survival.
Methods: This prospective single-center registry study from a tertiary hospital included all consecutive patients who underwent percutaneous aortic valve implantation between 2008 and 2012. Clinical follow-up lasted a minimum of 2.5 years and a maximum of 6.5 years. Valve Academic Research Consortium-2 definitions were used.
Results: Seventy-nine patients were included, with an immediate success rate of 94.9%. The median survival was 47.6 months (95% confidence intervals, 37.4-57.9 months), ie, 4 years. One quarter of deaths occurred in the first month, and most were of cardiovascular cause. After the first month, most deaths were due to noncardiovascular causes. The mean values of valve gradients did not increase during follow-up. The cumulative rate of prosthetic valve dysfunction was 15.3%, with no cases of repeat valve replacement.
Conclusions: Half of the patients with aortic stenosis who underwent transcatheter aortic valve implantation were alive 4 years after the procedure. There was a 15.3% prosthetic valve dysfunction rate in cumulative follow-up, with no cases of repeat valve replacement.

Seguimiento a largo plazo tras implante percutáneo de válvula aórtica por estenosis aórtica grave

Palabras clave:
Implante percutáneo de válvula aórtica
Reemplazo percutáneo de válvula aórtica
Estenosis aórtica
Valvulopatía
Definiciones *Valve Academic Research Consortium*

RESUMEN

Introducción y objetivos: El implante percutáneo de válvula aórtica se utiliza como alternativa a la sustitución valvular quirúrgica para pacientes con estenosis aórtica grave de alto riesgo quirúrgico o inoperables. Dos de las principales áreas de incertidumbre son la durabilidad de la válvula y la supervivencia a largo plazo.
Métodos: Registro unicéntrico prospectivo de un hospital terciario que incluyó consecutivamente todos los implantes percutáneos de válvula aórtica entre 2008 y 2012. Se realizó seguimiento clínico durante un mínimo de 2,5 años y un máximo de 6,5 años. Se utilizaron definiciones *Valve Academic Research Consortium-2*.
Resultados: Se incluyó a 79 pacientes, con un éxito inmediato del 94,9%. La mediana de supervivencia fue de 47,6 (intervalo de confianza del 95%, 37,4-57,9) meses, es decir, 4 años. Un cuarto de las muertes sucedieron en el primer mes, la mayoría de causa cardiovascular. Después del primer mes, la causa más frecuente fue no cardiovascular. Los valores medios de gradientes valvulares no se incrementaron en el seguimiento. La tasa acumulada de disfunción protésica fue del 15,3%, sin ningún caso de resustitución valvular.
Conclusiones: La mitad de los pacientes con estenosis aórtica intervenidos mediante implante percutáneo de válvula aórtica sobreviven 4 años después del procedimiento. Se detectó un 15,3% de disfunción protésica en el seguimiento acumulado, sin casos de resustitución valvular.

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Abbreviations

AR: aortic regurgitation
AS: aortic stenosis
TAVI: transcatheter aortic valve implantation
VARC: Valve Academic Research Consortium

INTRODUCTION

Aortic stenosis (AS) is the most common acquired valvular heart disease, with a prevalence of up to 4.6% in patients older than 75 years, and is the primary reason for valve surgery in adults.[1] In developed countries, the most common cause is degenerative AS.[2] The natural history of the disease begins with a long subclinical period, which cannot be modified by medical treatment.[3] Symptoms appear when AS is hemodynamically severe, and from that point the survival rate rapidly falls if the valve is not replaced. Survival in patients with severe AS only began to improve with the introduction of surgical valve replacement.[4] However, despite 60 years of experience, it has been estimated that more than a third of eligible candidates do not undergo surgical valve replacement.[2,5] The main reason is their high surgical risk, assessed with scores such as EuroSCORE or the STS (Society of Thoracic Surgeons) score, although there are other limiting factors: advanced age, liver disease, porcelain aorta, coronary artery bypass graft, pulmonary hypertension, right ventricular dysfunction, and the condition known as hostile chest.[6]

It was with these circumstances in mind that transcatheter aortic valve implantation (TAVI) was developed, a procedure that has grown exponentially since its introduction little more than a decade ago. The current indication for TAVI is symptomatic severe AS in patients considered inoperable by a multidisciplinary team due to high surgical risk (class I-B recommendation). In patients who are operable but high-risk, the decision to operate should be made on an individual basis (class IIa-B recommendation).[7] These indications are primarily based on 2 randomized clinical trials, in which TAVI was shown to have similar outcomes to surgical valve replacement in patients with high surgical risk (PARTNER A),[8] and to improve survival and functional class more than medical treatment (including valvuloplasty) in inoperable patients (PARTNER B).[9]

Transcatheter aortic valve implantation is successfully performed in approximately 90% to 98% of patients.[10–13] Several registries have reported 30-day mortality of around 5% to 15%,[8,13,14] 1-year mortality of 15% to 30.7%,[9,14,15] and 2-year mortality of 26.3% to 43%.[12,16,17] However, data beyond 2 years postprocedure are scarce, especially in Spain. Among the areas of uncertainty relating to TAVI are long-term patient survival and valve durability.

METHODS

Aims

The primary aim of this study was to analyze long-term all-cause death-free survival in a cohort of consecutive patients with severe AS, indication for valve replacement, and high surgical risk who underwent TAVI. The secondary aims were to describe the cause and timing of deaths, adverse events, and valve function at follow-up.

Design and Sample Selection

This was a prospective observational study with follow-up of all consecutive patients (N = 79) who had a TAVI procedure in our center between June 2008 and June 2012.

All patients had a diagnosis of severe AS and indication for valve replacement according to the European Society of Cardiology guidelines on the management of valvular heart disease.[7] Patients were considered high-surgical-risk if predicted mortality was $\geq$ 15% on EuroSCORE, or $\geq$ 10% on the STS score and if they were considered to be inoperable based on Heart Team assessment of comorbidities and other factors.[6]

Procedure

Clinical assessment and diagnostic testing of patients with severe AS and high surgical risk were similar to published recommendations and have been previously described.[6,18–20] Informed consent was obtained from all patients. The procedures were performed in a cardiac catheterization laboratory under sterile conditions, according to the manufacturer's established protocols, under general anesthetic, and with continuous transesophageal echocardiographic monitoring.[19,20] If significant coronary artery disease was found, the patients underwent revascularization and TAVI was postponed for 1 month. Vascular access was obtained via surgical femoral cutdown, with the exception of the first 10 patients (percutaneous closure). Post-TAVI medical treatment consisted of acetylsalicylic acid 100 mg (indefinitely) and clopidogrel 75 mg (6 months). The implanted prosthesis was Edwards SAPIEN or the subsequent Edwards SAPIEN XT (from 2010), both from Edwards Lifesciences. In patients with adequate vascular access (iliofemoral diameter $<$ 7 mm, or $<$ 6 mm in XT model), transfemoral access was used, otherwise transapical access was used.

Study Parameters

The variables were entered in a specially-dedicated database. In October 2011, the first European consensus document on TAVI, called Valve Academic Research Consortium (VARC), was published and subsequently revised in the VARC-2 recommendations.[6] For our study, all variables were adapted to VARC-2 definitions, with the exception of postprocedure acute kidney injury (24-h diuresis not recorded) and the combined early safety endpoint (which included acute kidney injury). The following are definitions of the most relevant variables (definitions of all variables are available in the appended supplementary material):

- Mortality: all-cause mortality (primary endpoint), subclassified as cardiovascular or noncardiovascular (secondary endpoint); deaths of unknown cause were attributed to cardiovascular causes.
- Major adverse event: all-cause mortality, stroke, readmission for valve-related symptoms or for worsening heart failure, deterioration in functional class to class III-IV, or prosthetic valve dysfunction; equivalent to the VARC-2 composite endpoint of clinical efficacy after 30 days.
- Acute kidney injury postprocedure, not requiring hemodialysis: creatinine raised by $>$ 0.5 mg/dL or $>$ 50% of baseline value.
- Device success (VARC-2): post-procedure survival, correct positioning of a single prosthetic heart valve in the proper anatomical location and intended performance of the prosthetic heart valve (absence of mismatch, mean gradient $<$ 20 mmHg or peak velocity $<$ 3 m/s and absence of moderate or severe aortic regurgitation [AR]).

- Early safety at 30 days (modified from VARC-2): all-cause death, stroke, life-threatening bleeding, acute kidney injury post-procedure, coronary artery obstruction requiring intervention, major vascular complication, or prosthetic valve dysfunction requiring intervention (surgical valve replacement, repeat TAVI, or valvuloplasty).
- Prosthetic valve dysfunction (VARC-2): mean prosthetic gradient > 20 mmHg, effective orifice area < 0.9 cm^2 to 1.1 cm^2, Doppler velocity index < 0.35, or moderate or severe AR.

Follow-up

Prospective follow-up of adverse events was carried out during clinic visits or via telephone at 1 month, 6 months, and annually thereafter. The inclusion period was from June 2008 until June 2012. Clinical follow-up ended in January 2015, giving a minimum follow-up of 2.5 years and maximum of 6.5 years. No patients were lost to clinical follow-up and contact was maintained with all patients until their death or until end of follow-up. Four patients were lost to echocardiographic follow-up, because they moved out of the Community of Madrid (clinical follow-up was completed, but without echocardiographic data).

Statistical Analysis

The descriptive analysis used count and percentage for categorical variables, and mean ± standard deviation or median [interquartile range] for qualitative variables. Echocardiographic data were compared using a paired Student *t* test. Survival data was analyzed using the Kaplan-Meier method. In the adverse events analysis, only the first recorded event was included. A bilateral *P* value < 0.05 was considered significant. The programs SPSS 20 (SPSS Inc.) and Stata 11.1 (StataCorp LP) were used.

RESULTS

Population Characteristics

In total, 79 procedures were performed, all with approved indications, except for 7 cases with off-label indications: 2 cases with an aortic ring < 1.8 cm, 2 with a prosthetic mitral valve, 2 valve-in-valve implants in degenerative bioprotheses, and 1 with a bicuspid aortic valve.

The baseline clinical characteristics and echocardiographic data are shown in Table 1. All patients had symptomatic severe AS, indication for valve replacement, and high surgical risk, or were inoperable. Access was transfemoral in 64 procedures (81%) and transapical in 15 (19%). The Edwards SAPIEN valve was implanted in 14 patients (17.7%) and the Edwards SAPIEN XT was implanted in 65 patients (82.3%). The mean surgical risk scores were as follows: logistic EuroSCORE, 16.9% ± 9.1% (1.8% to 46.9%); EuroSCORE-2, 5.7% ± 3.8% (0.7% to 18.1%); STS score, 5.9% ± 2.9% (1.1% to 13.4%).

Procedure Outcomes

The prosthesis was successfully implanted in 75 patients (94.9%). There were 4 implant failures: 2 cases were cancelled because of major vascular complications during percutaneous access, and there were 2 cases of valve embolization. The VARC-2 composite endpoint of device success was achieved in 69 patients (87.3%). The patients without device success were the 4 implant failures, 5 patients with a mean gradient of > 20 mmHg and/or moderate AR after the procedure, and 1 death during the procedure; 6 of the 7 off-label procedures had device success according to VARC-2.

One patient died during the procedure (coronary occlusion with refractory shock). In-hospital mortality was 11.4% (9 patients, 2 of them with implant failure) and 30-day mortality was 12.7%. In-hospital complications are shown in Table 2. Of the 79 patients who underwent the procedure, 55 (69.6%) achieved the 30-day event-free modified early safety composite endpoint.

Table 1
Baseline Clinical Characteristics and Echocardiographic Parameters of the Study Population (N = 79)

Age, y	82.3 ± 6.1
Women	43 (54.4)
Body surface area, m^2	1.7 ± 0.2
BMI	27.3 ± 4.7
Patients with BMI < 18.5	1 (1.3)
Patients with BMI > 35	6 (7.6)
DM	33 (41.8)
Non-insulin-dependent DM	19 (24.1)
Insulin-dependent DM	14 (17.7)
Dyslipidemia	38 (48.1)
Smoking	
Smokers/ex-smokers	22 (27.8)
Nonsmokers	57 (72.2)
Chronic obstructive pulmonary disease	19 (24.1)
Hypertension	63 (79.7)
Chronic ischemic heart disease	35 (44.3)
Previous revascularization	
None	2 (2.5)
PCA	27 (34.2)
CABG	5 (6.3)
CABG + PCA	1 (1.3)
Previous myocardial infarction	9 (11.4)
Peripheral vascular disease	10 (12.7)
Previous stroke	13 (16.5)
Kidney injury	16 (20.3)
Creatinine clearance (mL/min)	49.3 ± 0.3
Hemodialysis	1 (1.3)
Pacemaker	12 (15.2)
Active neoplasia[*]	3 (3.8)
Previous atrial fibrillation	31 (39.2)
LVEF, %	55.4 ± 11.8
Patients with LVEF < 50%	16 (20.3)
Patients with LVEF < 35%	6 (7.6)
Effective orifice area (continuity), cm^2	0.7 ± 0.2
Indexed effective orifice area, cm^2/m^2	0.4 ± 0.1
Maximum gradient, mmHg	70.8 ± 20
Mean gradient, mmHg	42 ± 14.3
Pulmonary systolic pressure, mmHg	52.5 ± 15.2

BMI, body mass index; CABG, coronary artery bypass graft; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; PCA, percutaneous coronary angioplasty.
Data are expressed as No. (%) or mean ± standard deviation.
[*] The 3 neoplasms were low grade and did not limit life expectancy at the time of the procedure.

Long-term Survival

The primary endpoint of the study was all-cause death-free survival at follow-up, which was analyzed in all 79 patients who

Table 2
In-hospital Complications

All complications	39 (49.4)
In-hospital deaths	9 (11.4)
Immediate complications	
Tamponade requiring drainage	5 (6.4)
Primary implant failure	4 (5.0)
Prosthetic valve embolization	2 (2.6)
Acute myocardial infarction	2 (2.6)
Emergency cardiac surgery[a]	1 (1.3)
Respiratory complications	
Intubation > 24 h	5 (6.4)
Respiratory failure[b]	3 (3.8)
Renal complications	
Acute kidney injury not requiring hemodialysis	12 (15.2)
Acute kidney injury requiring hemodialysis	2 (2.6)
Bleeding and vascular complications	
Transfusion	17 (21.0)
All hemorrhages (BARC)	9 (11.4)
Minor vascular complication (VARC-2)[c]	9 (11.4)
Major vascular complication (VARC-2)[c]	3 (3.8)
Other complications	
New onset atrial fibrillation	7 (9.0)
Infection	6 (7.7)
Permanent pacemaker	3 (3.8)
Stroke	2 (2.6)
Endocarditis	0 (0.0)

BARC, Bleeding Academic Research Consortium; VARC, Valve Academic Research Consortium.
Values are expressed as No. (%).
[a] Emergency surgery for cardiac tamponade in one transapical case, which did not require valve replacement.
[b] Respiratory failure without heart failure.
[c] All major vascular complications and 7 of the 9 minor vascular complications occurred in the first 10 cases, in which percutaneous closure was used.

underwent TAVI, independent of procedural success. Mean follow-up was 34 months (18.3-42.4 months), ie, 2.8 years, with a cumulative follow-up of 2416.7 patient-months. Median survival was 47.6 months (95% confidence interval, 37.4-57.9 months) (almost 4 years). The Kaplan-Meier survival curve is shown in the Figure.

Cumulative survival at the end of years 1 to 5 was 79.7%, 70.9%, 58.9%, 49.5%, and 32%, respectively. If we selected only those patients who survived to hospital discharge (n = 70), the mean survival would be 50.3 months (95% confidence interval, 41.8-58.8 months), and survival at 1, 2, 3, 4, and 5 years would have been 90%, 80%, 66.5%, 55.9%, and 36.1%.

Stratified analysis by 50% and by quartiles of patient inclusion was performed, as well as by access via the transfemoral or transapical route, with no significant differences found.

Causes of Death

Of the 79 patients who underwent TAVI, 39 (49.4%) died during follow-up (Table 3). Slightly less than half of the deaths (43.6%) were of cardiovascular cause; the most common cardiovascular causes were heart failure and stroke. Infection was the most common noncardiovascular cause and also the most common absolute cause. A quarter of deaths (10 of 39) occurred within 1 month, when death was most commonly due to cardiovascular cause (70%). After the first month, deaths were distributed more evenly in time and were predominantly of nonvascular cause (65.5%).

Major Adverse Events During Follow-up

In the study population, 52 patients (65.8%) had a major adverse event during follow-up (VARC-2 composite endpoint of clinical efficacy). A quarter (25%) of adverse events occurred in the first month and approximately half (51.9%) in the first year. The median adverse event-free survival was 25.4 months (95% confidence interval, 13.9-36.9 months) (2.1 years).

Of 52 adverse events, 30 (57.7%) were fatal and 22 (42.3%) were nonfatal. The main cause of adverse events was worsening functional class or worsening heart failure (in 16 patients). These 16 patients had a concomitant diagnosis of respiratory tract infection and/or exacerbation of chronic obstructive pulmonary disease. An echocardiogram was performed in all 16, and none had evidence of new prosthetic valve dysfunction or deterioration in ejection fraction. Of the other 6 patients who had nonfatal adverse events, 4 patients had a stroke (2 strokes, 2 transient ischemic attacks), 1 required a pacemaker, and 1 required hospital admission for an unknown cause in another center (which was counted as an adverse event). The cumulative rate of stroke during follow-up was 11.4% (6.3% for stroke and 5.1% for transient ischaemic attack). The median time from procedure to stroke was 489 days.

Prosthesis Function at Follow-up

The following patients were excluded from echocardiographic follow-up: patients who died before discharge from hospital (n = 9) or before 12 months follow-up (n = 7), those with implant failure who were discharged (n = 2), and 2 patients who were lost to echocardiographic follow-up. Table 4 shows the parameters at baseline, postprocedure, and at the last available follow-up (n = 59). All parameters improved significantly after the procedure. The mean values obtained at the last echocardiographic follow-up were not significantly different from the mean postprocedure values. This highlights the stability of gradient and ejection fraction at follow-up. The ventricular mass and ventricular mass index were significantly reduced at follow-up compared with baseline values.

On post-TAVI echocardiogram, 94.9% of patients had mild or undetectable AR, and only 3 patients (5.1%) had moderate AR. At follow-up, 3 more patients (cumulative rate, 10.2%) had moderate AR. No cases of severe AR were detected. Regarding prosthetic valve stenosis, no patients had a post-TAVI gradient > 25 mmHg; 3 patients (5.1%) had gradients of 20 mmHg to 25 mmHg, which is defined in VARC-2 as "possible stenosis". This percentage did not increase throughout follow-up. There were no cases of "significant stenosis" (mean gradient > 35 mmHg).

The VARC-2 composite variable of prosthetic valve dysfunction increased from 10.2% post-procedure to 15.3% at follow-up (10.2% because of moderate AR and 5.1% because of a mean gradient > 20 mmHg). None of those patients needed repeat valve replacement. There were no documented cases of aortic complication, mitral valve lesions, endocarditis, or prosthetic valve thrombosis.

DISCUSSION

Study Population and Procedure Outcomes

In this study we have described the long-term follow-up and results of a prospective single-center registry that included consecutive patients who underwent TAVI. The study population included patients of advanced age (mean 82.3 years), with significant comorbidities and moderately elevated surgical risk

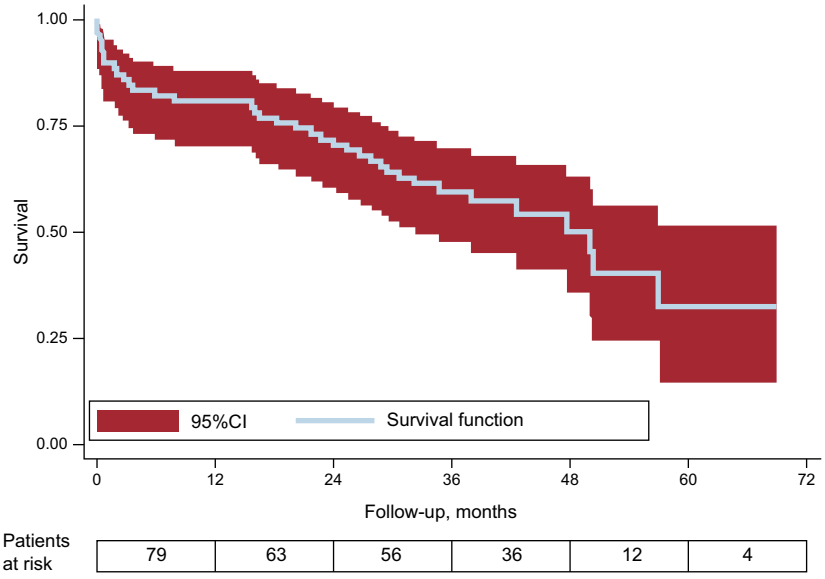

Figure. Kaplan-Meier curve of all-cause death-free survival with 95% confidence intervals and the patients at risk in each period. The longest follow-up of a living patient was 69 months. 95%CI, 95% confidence interval.

scores (EuroSCORE, 16.9%; STS score, 5.9%). The risk profile was similar to those in other series published in Spain, but was slightly lower than those in other international series.[12,14,21,22]

Our short-term study results were within the figures published in contemporary national and international series, which had success rates between 90% and 98%[10–13,21] and 30-day mortality between 7.4% and 14.5%.[12–14,22,23] More recent studies have reported 30-day survival rates > 95%,[24,25] which may be explained by the increased experience in those centers and technical advances in the devices.

In our study, the VARC-2 composite endpoint of device success was not achieved in 10 of the 79 patients (12.7%), a figure which was similar to or better than contemporary studies that used VARC-1 definitions (12.9%-20.0).[23,26] However, in the recent CHOICE study, the Edwards SAPIEN arm had an excellent device failure rate of 4.1% (according to VARC-1).[25]

Table 3
Causes and Timing of all Deaths in the Series (n = 39)

Cause of death	Patients, No. (%)	≤ 72 h	3-30 days[a]	2-12 moths	> 1 year
Cardiovascular	17 (43.6)	4	3	2	8
Heart failure	4 (10.3)		1		3
Stroke	3 (7.7)				3
Acute myocardial infarction	2 (5.1)	1			1
Cardiac tamponade	2 (5.1)	2			
Multiple complications post-TAVI[b]	2 (5.1)		2		
Prosthetic valve embolization to LV	1 (2.6)	1			
Sudden death	1 (2.6)			1	
Unknown	2 (5.1)			1	1
Noncardiovascular	22 (56.4)	—	3	4	15
Infection/sepsis[c]	10 (25.7)		1	3	6
Alzheimer disease/dementia	4 (10.3)				4
Complications following a fracture/fall	2 (5.1)				2
Liver disease[d]	2 (5.1)		1		1
Respiratory failure[e]	2 (6.7)		1		1
Other[f]	2 (6.7)			1	1

TAVI, transcatheter aortic valve implantation; LV, left ventricle; VARC, Valve Academic Research Consortium.

[a] Until 30 days or hospital discharge; as in the Valve Academic Research Consortium-2 definition of procedural mortality.

[b] One patient had a femoral artery dissection that required urgent vascular surgery and afterward had multiple complications; the other patient had multiple complications peri-transcatheter aortic valve implantation and post-transcatheter aortic valve implantation (coronary artery occlusion requiring urgent angioplasty, cardiac tamponade requiring pericardiocentesis and kidney injury requiring hemodialysis). Both patients had a long hospital stay post-transcatheter aortic valve implantation and died before discharge.

[c] The origin of infection/sepsis was respiratory in 7 patients; urinary in 1; gastrointestinal in 1; and of unknown origin in 1 after endocarditis was ruled out (negative blood cultures and imaging).

[d] One case of hepatic failure postoperatively; 1 case (> 1 year) due to hepatocarcinoma.

[e] One patient with pulmonary fibrosis and another with grade IV chronic obstructive pulmonary disease; heart failure was ruled out in both patients.

[f] One patient committed suicide 6 months after the procedure, another was admitted with lower limb ischemia with multiple complications.

Table 4
Mean Echocardiographic Data at Baseline, Postprocedure, and at the Last Available Follow-up

	Baseline	Post-TAVI[a]	Last follow-up	Mean difference	*P*
EOA (continuity), cm^2	0.68 ± 0.19	2.23 ± 0.83[a]	1.9 ± 0.56	–0.33[b]	.18[b]
indexed EOA, cm^2/m^2	0.38 ± 0.09	1.16 ± 0.46[a]	0.98 ± 0.32	–0.18[b]	.18[b]
Maximum gradient, mmHg	74.14 ± 18.3	18.74 ± 7.51[a]	19.22 ± 8.23	+0.47[b]	.73[b]
Mean gradient, mmHg	45.1 ± 13.2	8.99 ± 3.45[a]	9.23 ± 4.28	+0.24[b]	.74[b]
LVEF, %	56.03 ± 12.2	58.61 ± 9.9[a]	60.81 ± 11.67	+2.2[b]	.16[b]
Ventricular mass, g	271.76 ± 71.3	—	227.8 ± 86.94	–46.9[c]	.001[c]
Indexed ventricular mass, g/m^2	156.8 ± 40.1	—	130.8 ± 44.67	–27.2[c]	.001[c]
PSP, mmHg	50.45 ± 15.77	38.03 ± 5.24[a]	41.83 ± 7.55	+3.8[b]	.37[b]

EOA, effective orifice area; LVEF, left ventricular ejection fraction; PSP, pulmonary systolic pressure; TAVI, transcatheter aortic valve implantation.
Values at the last follow-up were compared with values on discharge, except for ventricular mass values, which were compared with baseline values. Data are expressed as mean ± standard deviation.
[a] Post-transcatheter aortic valve implantation echocardiograms were done between 24 hours post-procedure and discharge from hospital. The statistical comparison of parameters on discharge against baseline values was statistically significant for all variables ($P < 0.05$).
[b] The difference and *P* values represent the differences on echocardiogram at latest follow-up compared with post-transcatheter aortic valve implantation.
[c] The difference and *P* values represent the differences on echocardiogram at the last follow-up compared with baseline.

Long-term Survival

There are few series on Edwards SAPIEN valve with follow-up ≥ 3 years, and none of them are national studies. Their results are summarized in Table 5. The single-center series by Toggweiler et al[27] describes 5 complete years of follow-up for 88 selected patients (implant failure and deaths before 30 days were excluded), in which the first generations of valve and delivery systems were used. These authors obtained results similar to those of our unselected series. In an exhaustive study, Rodés-Cabau et al[28] published a follow-up of up to 4 years in a multicenter Canadian study with 339 consecutive patients (which probably included those of Toggweiler et al[27]); their results were also comparable to ours.

Two other series offer some data on 5 year mortality: Unbehaun et al[29] reported a mortality of 61.4% of 136 selected (alive at 30 days) patients from an administrative data source; the TAVI arm of PARTNER B recently reported a 5-year mortality of 71.8%.[30] D'Onofrio et al. reported a 3-year mortality of 32.4%[15]; in the TAVI arm of PARTNER A, 3-year mortality was 44.2%.[31]

In general, 5-year mortality after a TAVI procedure with the Edwards SAPIEN valve is around 60% to 70%, and is limited by a very old population with significant comorbidities (as a reference, the estimated 5-year mortality of American controls with no comorbidities would be 40.5%[30]). Currently, the reduction in peri-TAVI mortality (30-day survival > 95%[24,25]) and the shift toward lower-risk candidate characteristics enables us to predict that the long-term mortality of patients who undergo TAVI today will probably decrease further.

Causes of Death and Major Adverse Events

Regarding causes of death, the findings are in line with those of a high risk procedure, with high mortality in the first month (a third of all deaths), of predominantly cardiovascular cause, and mortality of predominantly noncardiovascular causes in the medium- and long-term. Among specific causes of death, infection was prominent, particularly when associated with respiratory disease, which, independently of TAVI, is a common cause of death in elderly patients.[32] The next most common cause of death was

Table 5
Long-term Mortality Data for Edwards Sapien Valve in This Study, Other International Studies, and 2 Clinical Trials

Series	Patients, No.	Implant period	Access	Mean survival, years	Maximum/mean follow-up, years	Mortality, %					Repeat VR, %
						1 year	2 year	3 years	4 years	5 years	
Hospital La Paz, all	79	2008-2012	64 TF-15 TA	3.97	5.70/2.80	20.3	29.1	41.1	50.5	68.0	0.0
Hospital La Paz (alive at discharge)	70	2008-2012	64 TF-15 TA	4.20	5.70/2.80	10.0	20.0	33.5	44.1	63.9	0.0
D'Onofrio et al[15]	774	2008-2012	TA	—	3.60/1.00	18.3	23.9	32.4	—	—	0.0
Rodés-Cabau et al[28]	339	2005-2009	163 TF-176 TA	—	4.00/3.50	24.0	33.0	49.0	57.0	—	0.6
Toggweiler et al[27,a]	88	2005-2007	64 TF-24 TA	3.40	—/5.00	17.0	26.0	47.0	58.0	65.0	1.1
Unbehaun et al[29]	136[b]	2008-2013	TA	—	5.23/1.56	18.4	33.1	42.8	51.8	61.4	3.0
PARTNER A (TAVI arm)[8,16,31,c]	348	2007-2009	244 TF-104 TA	—	—/3.00	24.2	33.7	44.2	—	—	0.0
PARTNER B (TAVI arm)[9,17,30,c]	179	2007-2009	TF	2.50	—/5.00	30.7	43.0	53.9	64.1	71.8	1.1

TA, transapical; TAVI, transcatheter aortic valve implantation; TF, transfemoral; VR, valve replacement.
[a] Patients from this single-center series are probably included in the series of Rodés-Cabau et al[28]; however, data are given by it being the only study with complete 5-year data. Toggweiler et al[27] reported a selected population from which they excluded patients with implant failure and deaths before 30 days. Five-year follow-up was obtained in 84 of 88 patients.
[b] Subgroup follow-up ≥ 4 years of 145 patients (from a series of 730), from whom the authors selected the 136 patients who were alive at 30 days. Duration of follow-up and rate of repeat valve replacement refers to the complete series of 730 patients, not to this subgroup.
[c] Intention-to-treat data analysis; patients who crossed over were censured from the time they crossed over. The data on repeat valve replacement come from 2-year follow-up data.

advanced dementia, requiring us to consider the relevance of cognitive function in patient prognosis. Importantly, residual cardiovascular mortality after the first year was 34.5%, similar to that of other series.[28,30]

Major adverse events were concentrated in the first year post-TAVI and occurred in two thirds of patients in the long-term (65.8%). This information is difficult to compare with that of other series, because of differences in definitions and follow-up times. In the series reported by Gurvitch et al,[33] the composite endpoint of death, infarction, stroke, or aortic valve replacement was reached in 48.6% at 3 years. Heart failure not associated with prosthetic valve dysfunction was the primary cause of nonfatal adverse events, which, together with the relevant residual cardiovascular mortality data, indicates the need for more investigation in this field.

Prosthetic Function at Follow-up

A notable finding was the durability of the prosthetic valve used in this study at follow-up: a 15.3% prosthetic valve dysfunction rate according to VARC-2 (moderate AR and/or mean gradient of 20 mmHg to 25 mmHg) without need for repeat valve replacement. Long-term prosthetic valve dysfunction has been reported in a heterogeneous manner, focusing on moderate or severe AR, which in the long-term is very low (2.3%, 0.0%, and 0.0% at 4-5 years in the series reported by Toggweiler et al,[27] Rodés-Cabau et al,[28] and PARTNER B,[30] respectively), although there may be a bias, as the patients in these studies had higher mortality. The need for repeat valve replacement was minimal (Table 5).

Limitations

The number of patients in this registry was smaller than in other multicenter registries, but reflects the normal practice of a Spanish tertiary center, and the inclusion of consecutive patients makes the results more representative of clinical practice. In our center, a mean of 19.8 procedures were performed each year during the study period, whereas in Spain the average was 15.8 per center in 2012.[34] The number of patients may have limited the capacity to find differences regarding the experience of the center or between different access routes. The follow-up time was not the same for all patients, but this was the method used in many similar studies.[15,28] The study was designed with a minimum follow-up of 2.5 years for living patients, and no patients were lost to clinical follow-up.

CONCLUSIONS

In this unselected population of 79 consecutive patients with severe AS, indication for valve replacement, and high surgical risk who underwent TAVI, the median all-cause death-free survival was 47.6 months (4 years). If we selected the 70 patients who survived to discharge, the median survival would be 50.3 months (4.2 years).

A third of deaths occurred in the first 30 days, most of which were from cardiovascular causes (70%). The other deaths were evenly distributed in time, and were most commonly due to noncardiovascular causes (65.5%), particularly infection associated with respiratory disease. However, there was a residual cardiovascular morbidity and mortality that was not associated with prosthetic valve dysfunction, which was not insignificant.

The improvement in hemodynamic parameters post-TAVI was maintained throughout follow-up, and although 15.3% of patients met VARC-2 criteria of prosthetic valve dysfunction at follow-up, no patients required subsequent valve replacement.

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CONFLICTS OF INTEREST

None declared.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found in the online version available at doi:10.1016/j.rec.2015.03.017.

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