Long-Term Outcomes and Valve Performance in Patients Undergoing Transcatheter Aortic Valve Implantation

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Transcatheter aortic valve implantation (TAVI) is an established method for treating patients with aortic valve stenosis. We sought to determine the long-term clinical outcomes and performance of a self-expanding bioprosthesis beyond 5 years. Consecutive patients scheduled for TAVI were included in the analysis. Primary end points were all-cause and cardiovascular mortality, structural valve deterioration (SVD) and bioprosthetic valve failure (BVF), based on the VARC-2 criteria and consensus statement by ESC/EAPCI. The study prospectively evaluated 273 patients (80.61 ± 7.00 years old, 47% females) who underwent TAVI with CoreValve/Evolut-R (Medtronic Inc.). The median follow-up duration was 5 years (interquartile range: 2.9 to 6; longest: 8 years). At 1, 5, and 8 years, estimated survival rates were 89.0%, 61.1%, and 56.0%, respectively, while cardiovascular mortality was 8% at the end of follow-up. Regarding valve performance, 5% of patients had early BVF and 1% had late BVF. Concerning SVD, 16 patients (6% of the total population) had moderate SVD (91% had an increase in mean gradient), with no severe SVD cases. Five patients with SVD died during follow-up. Actual analysis of the 8-year cumulative incidence of function of moderate SVD was 5.9% (2.5% to 16.2%). At multivariate analysis, the factor that emerged as an independent predictor for future SVD, was smaller bioprosthetic valve size (HR 0.58, 95% CI 0.41 to 0.82, p = 0.002). Long-term evaluation beyond 5 years after TAVI with a self-expanding bioprosthesis demonstrated low rates of cardiovascular mortality and structural valve deterioration. Valve size was an independent predictor for SVD. **(Am J Cardiol 2021;147:80−87)**

Transcatheter aortic valve implantation (TAVI) is an equal therapeutic strategy to surgery in patients with symptomatic severe aortic valve stenosis (AS) at low, medium and high surgical risk.[1−4] One of the few remaining issues with transcatheter heart valves is the long-term durability and valve performance. The aim of this study was to determine the long-term clinical outcomes and valve performance beyond 5 years with the first and second generation of a self-expanding bioprosthesis.

Methods

Between January 2012 and June 2015 consecutive patients with severe symptomatic AS, examined by the Heart Team and deemed appropriate for TAVI, were included in the analysis. All procedures were performed by experienced teams in three tertiary hospitals with active on-site cardiothoracic department. Patients with true bicuspid aortic valve as detected by multislice computed tomography (MSCT) and previous aortic valve replacement (surgical or TAVI) were excluded from the study. Patients with a follow-up period ≥5 years after TAVI were analyzed. Primary events were prospectively recorded over the study period. The last available echocardiographic evaluation was considered for the analysis. The study conforms to the principles outlined in the Declaration of Helsinki and each hospital's ethics committee approved the study. All patients provided informed consent regarding the procedure as well as storage and process of their personal medical data.

Transthoracic echocardiography was performed in all patients as part of the screening process. Severe AS was defined as an effective orifice area (EOA) <1 cm^2 or EOAi

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(EOA indexed to the body surface area) <0.6 cm^2/m^2 by the continuity equation and mean gradient >40 mm Hg or maximal aortic valve velocity >4.0 m/s on resting echocardiography (or after dobutamine infusion if the subject had a left ventricular ejection ventricular fraction <50%). All patients had an echocardiogram prior to discharge, at 1 month and yearly thereafter. Post-procedural echocardiographic data relate to the last available echocardiographic scan, performed either at the study hospitals or from referring physicians. Qualitative grading of aortic regurgitation (AR) severity (none, mild, moderate, severe) was based on integrating the available valve academic research consortium criteria-II (VARC-II).[5,6] The MSCT examination protocol used has already been described.[7,8] A commercially available and dedicated post processing software was used for all measurements (3mensio, Pie Medical Imaging, The Netherlands).

The TAVI procedure has been described previously.[9–11] All procedures were performed in the catheterization laboratory, with stand-by echocardiography. The participating institutions opt for the minimal TAVI approach, aiming for local anesthesia and mild sedation whenever possible.[12] All patients received 100 mg acetylsalicylic acid pre TAVI and lifelong thereafter and clopidogrel (300 mg as a bolus and 75 mg per day thereafter for 6 months, unless chronic use was deemed more appropriate). If chronic anticoagulation was in order, then dual therapy with clopidogrel and an oral anticoagulant was prescribed for 3 months and afterwards only the anticoagulant was preferred.

The TAVI prostheses used were the CoreValve/Evolut-R family (Medtronic Inc., Dublin, Ireland) with four available sizes at that time (23 mm, 26 mm, 29 mm, and 31 mm). The vascular access and size of the bioprosthesis was based at the operators' discretion and on the available MSCT data.

All definitions, measured outcomes and endpoints were designated according to the Valve Academic Research Consortium criteria – second update (VARC-II)[5] and the recently published consensus statement by the ESC/EAPCI for structural valve deterioration (SVD) and bioprosthetic valve failure (BVF).[13] In detail and based on echocardiographic data, moderate SVD was defined as mean transprosthetic gradient ≥20 mm Hg and <40 mm Hg, and/or ≥10 mm Hg and <20 mm Hg change from baseline, and/or moderate new or worsening intraprosthetic AR, as assessed by imaging modalities. Severe SVD was defined as mean gradient ≥40 mm Hg, and/or ≥20 mm Hg change from baseline, and/or severe intraprosthetic AR. BVF was defined as severe SVD accompanied by the consequent clinical manifestations. Pathophysiological processes, such as thrombosis, endocarditis or nonstructural valve dysfunction resulting in symptomatic valve failure were also included under this term. Moreover, depending on timing of onset after valve implantation, BVF was considered early (<30 days) or late (>30 days). In addition, BVF included autopsy findings of bioprosthetic valve dysfunction, likely related to the cause of death, or valve-related death. Primary end points were all-cause and cardiovascular mortality, SVD and BVF rates. Secondary endpoints were echocardiographic changes of mean gradient (MG), paravalvular leakage (PVL) and overall changes in New York Heart Association (NYHA) functional status.

This is a prospective observational research. Continuous variables are presented as mean values ± one standard deviation and compared with the Student's *t* test. The normality of distribution was assessed using the Shapiro-Wilk test and normality diagrams. Categorical variables are presented as frequencies and percentages and were tested by the chi-square test. Paired analysis was used for calculating echocardiographic differences in mean gradient changes. Differences in paired samples were tested using Wilcoxon signed-rank test or paired Student's *t* test. All-cause mortality was reported by the use of Kaplan-Meier estimates and the respective confidence intervals. Multivariate regression analysis was performed to detect predictors of SVD. pvalues <0.05 were considered statistically significant. These analyses were performed with SPSS 25 statistical software (SPSS Inc., Armonk, NY). Cumulative incidence function was used for calculating the risk for SVD and BVF, competing for death risk analysis (these calculations were done by XLSTAT, Addinsoft, Paris, France).

Results

A total number of 273 high-risk patients (Figure 1) underwent TAVI in three tertiary centers between January 2012 to June 2015 (center 1: 121 patients; center 2: 110 patients; center 3: 42 patients). Baseline clinical and echocardiographic parameters are presented in Tables 1 and 2. No significant clinical or echocardiographic baseline differences were observed in patients presenting with SVD/BVF compared with the population with no SVD/BVF. Clinical follow-up was achieved in all the patients, with a median duration of 5 years (interquartile range: 2.9 to 6) and with the longest clinical follow-up being 8 years.

All the TAVI procedural data and clinical events are shown in Tables 3 and 4 respectively. The first generation CoreValve was implanted in 156 patients (57%) and the second generation Evolut-R was implanted in the remaining 117 patients (43%). Transfemoral access was the preferred route in 84% of the patients.

Vascular complications occurred in 31 patients (11% of total population) and bleeding events were observed in 86 patients (31% of total population). A new pacemaker was implanted in 73 patients (27%) and 7 patients (2%) suffered from stroke or transient ischemic attack.

During the study period, 120 patients (44%) died. At 1, 5, and 8 years, estimated survival rates were 89.0%, 61.1%, and 56.0%, respectively. Cardiovascular causes of death were reported in 23 patients (8%). Kaplan-Meier actuarial survival analysis curves for all-cause mortality and cardiovascular mortality are presented in Figures 2 and 3 respectively.

A dramatic improvement in NYHA class functional status was seen at 30 days, which remained thereafter (Supplement/Figure 1).

At 5 years, 167 patients (61.1%) were alive and echocardiographic data were available for 55% of patients. At 8 years, available echocardiographic data were available for 20 patients, since they were patients from 2012 that have survived and reached the study's 8-year milestone of clinical and echocardiographic follow-up. By use of paired analysis, there was a significant drop in mean gradient after

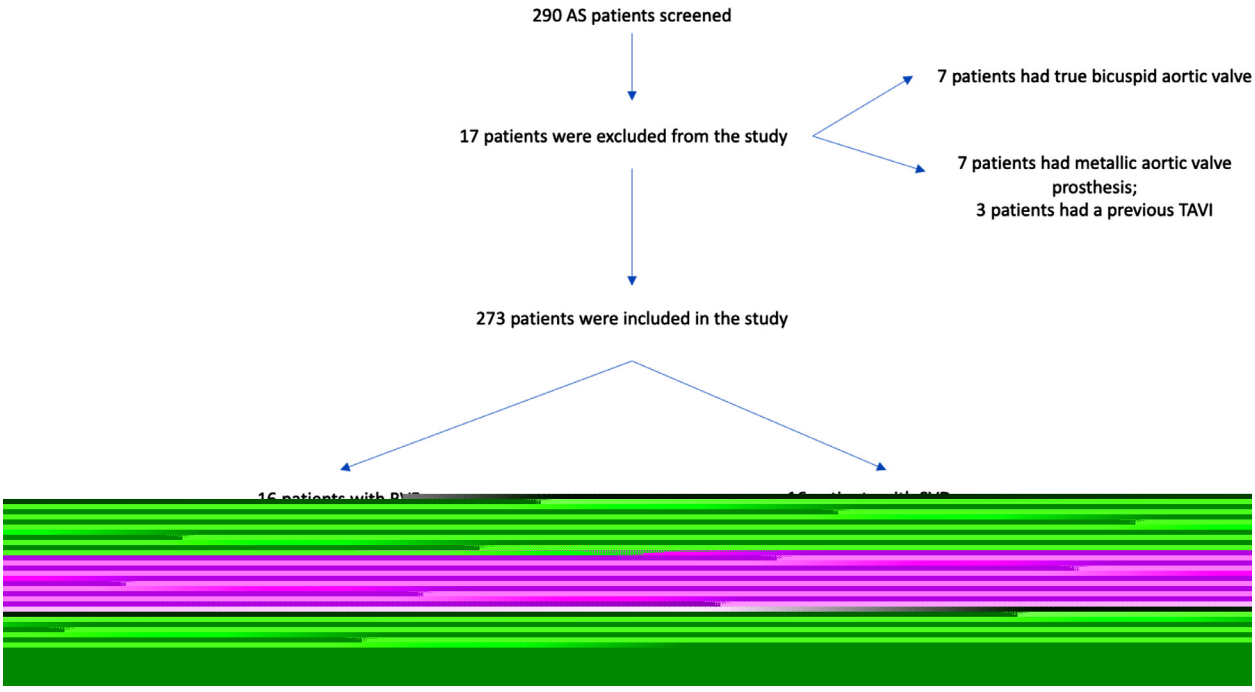


Figure 1. Flowchart of the study.

Table 1
Baseline clinical parameters (n = 273 patients)

Age, (years)	80.61 ± 7.00
Women	129 (47%)
Body mass index, (kg/m^2)	26.44±3.96
Hypertension	220 (80%)
Diabetes mellitus	65 (24%)
Smokers	69 (25%)
Coronary artery disease	123 (45%)
Previous PCI	32 (11%)
Previous CABG	31 (11%)
Prior stroke/TIA	23 (8%)
Chronic lung disease	56 (20%)
Chronic renal failure	85 (31%)
Creatinine level, (mg/dL)	1.30±0.97
Previous pacemaker	26 (9%)
Log EuroScore, (%)	25.21±8.01
NYHA Class III/IV	211 (77%)

CABG = coronary artery bypass graft; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

Table 2
Baseline echocardiographic parameters (n = 273 patients)

Ejection fraction, (%)	49.47 ± 9.32
AV peak gradient, (mmHg)	79.07 ± 20.12
AV mean gradient, (mmHg)	48.46 ± 13.98
AVA, (cm^2)	0.65 ± 0.15
AV regurgitation (≥moderate)	42 (15%)
MV regurgitation (≥moderate)	74 (27%)
TV regurgitation (≥moderate)	93 (34%)
PASP, (mmHg)	45.21 ± 10.41

AV = aortic valve; AVA = aortic valve area; MV = mitral valve; PASP = pulmonary artery systolic pressure; TV = tricuspid valve.

TAVI and at discharge (48.50 ± 14.12 mm Hg pre TAVI vs 8.43 ± 4.36 mm Hg at discharge, $p < 0.001$). During the duration of follow-up, the mean gradient remained at low levels, but without any significant change compared with discharge (Supplement/Figure 2). After TAVI, the majority of patients (n = 158; 58%) had mild PVL, 33 patients (12%) had moderate PVL and 2 patients had severe PVL. During the follow-up period, the majority of patients had no or minimal PVL (Supplement/Figure 3).

Table 3
Procedural characteristics (n = 273 patients)

Type of valve	
• CoreValve	156 (57%)
• Evolut R	117 (43%)
Access site	
• Transfemoral	229 (84%)
• Subclavian	42 (15%)
• Transaortic	2 (1%)
Surgical cut-down	72 (26%)
Bioprosthesis size	
• 23 mm	19 (7%)
• 26 mm	98 (36%)
• 29 mm	128 (47%)
• 31 mm	28 (10%)
Type of anesthesia	
• Local	215 (79%)
• General	58 (21%)
Predilation	65 (24%)
Postdilation	40 (15%)
Procedure time, (min)	131.72 ± 43.26
Fluoroscopy time, (min)	28.53 ± 10.01
Contrast use, (mL)	156.66 ± 61.79
Valve-in-valve	13 (5%)

Table 4
Procedural outcomes and 30-day clinical events based on VARC-2 criteria (n = 273 patients)

Vascular complications	
• Major	26 (9%)
• Minor	5 (2%)
Bleeding	
• Life-threatening bleeding	13 (5%)
• Major bleeding	29 (10%)
• Minor bleeding	44 (16%)
Mean hemoglobin drop, (%)	2.36±1.09
≥2 RBC transfusion units, (%)	56 (20%)
Mean creatinine level at 48 hours, (mg/dL)	1.29±0.72
New pacemaker insertion	73 (27%)
Stroke/TIA	7 (2%)

RBC = red blood cells; TIA = transient ischemic attack.

Regarding BVF, there were 13 cases (5%) of early BVF (<30 days), all due to valve-in-valve procedures that were performed in the index TAVI procedure and no patient died. In total, there were 3 (1%) late BVF cases observed >30 days post TAVI. Two of them were endocarditis cases diagnosed at days 157 and 357, respectively post TAVI and were treated with a redo TAVI procedure. The third case was a 77-year-old patient diagnosed with bioprosthetic valve thrombosis due to dual antiplatelet interruption following an upper gastrointestinal bleeding 1-year post TAVI. The patient received low molecular weight heparin for 7 days and clopidogrel 75 mg thereafter and at 6 months after this event, the patient remained stable, asymptomatic without signs of valve thrombosis during echocardiography. All 3 patients with late BVF were still alive at the last follow-up.

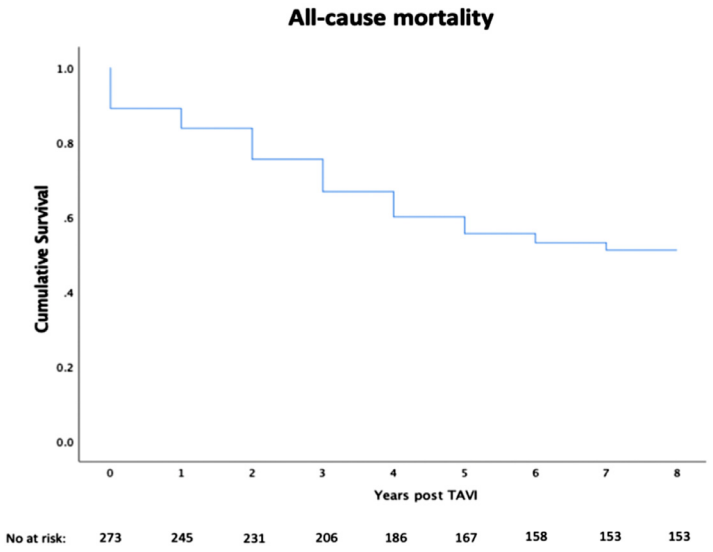


Figure 2. Cumulative incidence of all-cause mortality (44% in an 8-year period with 95% CI: 4.97 − 5.72) based on Kaplan-Meier actuarial analysis.

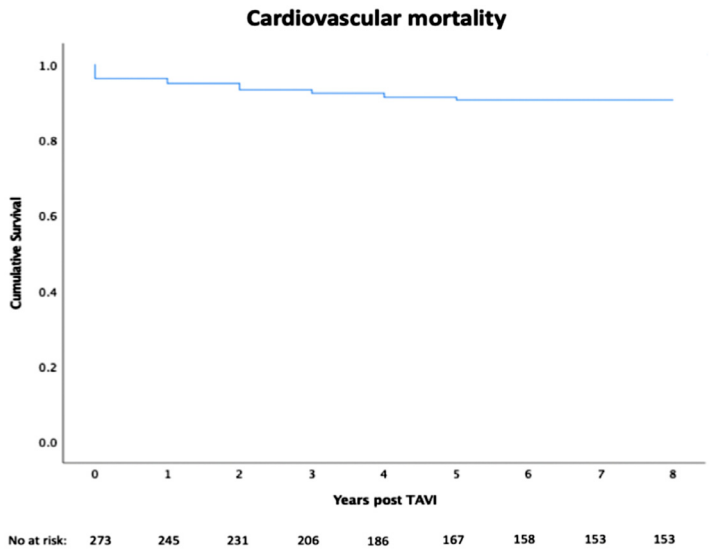
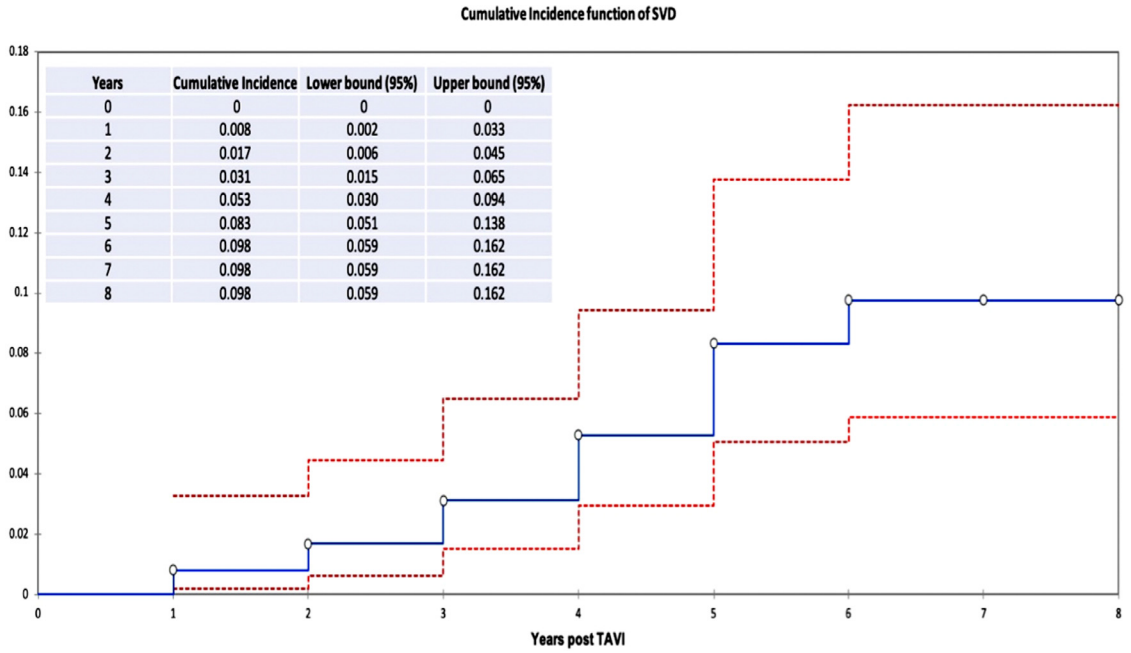


Figure 3. Cumulative incidence of cardiovascular mortality (8% in the study period with 95% CI: 7.15 − 7.64) based on Kaplan-Meier actuarial analysis.



Years	Cumulative Incidence	Lower bound (95%)	Upper bound (95%)
0	0	0	0
1	0.008	0.002	0.033
2	0.017	0.006	0.045
3	0.031	0.015	0.065
4	0.053	0.030	0.094
5	0.083	0.051	0.138
6	0.098	0.059	0.162
7	0.098	0.059	0.162
8	0.098	0.059	0.162

Figure 4/central illustration. Cumulative incidence function of structural valve deterioration (SVD) according to the competing risk analysis including the risk of death (actual analysis). 95% confidence intervals seen as red lines.

Concerning SVD, 16 (6% of total population) cases of moderate SVD were observed, with no severe SVD cases (Supplement/Figure 4). The majority of the moderate SVD cases (15 out of 16 [94% of moderate SVD cases]) were due to an increase in mean gradient and the remaining one case due to moderate intra-prosthetic AR. Regarding mortality, 5 patients (31% in the SVD subgroup; 4% in the total cohort, p = 0.43 for all measurements) died during follow-up. Based on the TAVI date, the first patient died 994 days post TAVI due to an upper gastrointestinal bleeding, the second patient died 1,857 days after TAVI due to lung infection, the third patient died 1,697 days after TAVI due to a lung infection, the fourth patient died 1,359 days post TAVI due to hematological cancer and the fifth patient died 1,468 days post TAVI due to a ruptured abdominal aorta aneurysm. Regarding the remaining SVD cases, 2 patients were in NYHA Class III; 5 patients were in NYHA Class II and 4 patients remained asymptomatic. Assuming death as a competing risk that can prevent SVD to happen, actual analysis resulted in an 8-year cumulative incidence of function of moderate SVD of 5.9% (2.5% to 16.2%; Figure 4/central illustration).

In a univariate model analysis for SVD predictors, multiple clinical and procedural factors were included in the analysis (Table 5). At multivariate analysis, smaller bioprosthetic valve size emerged as an independent predictor for SVD (HR 0.58, 95% CI 0.41 to 0.82, p = 0.002).

Discussion

The primary aim of this study was to record the long-term clinical outcomes and valve performance beyond 5 years in patients undergoing TAVI with a self-expanding transcatheter aortic valve using standardized definitions of SVD and BVF. The study's main findings are:

- The long-term all-cause mortality of this high-risk population is 44% and cardiovascular mortality is 8%.
- The long-term function of a self-expanding transcatheter bioprosthesis, as evidenced by the mean gradient and PVL, is reassuring.
- The rates of late BVF (1%) and SVD (6%) are low.

The mortality rate observed in the study fares equally with other studies.[14–18] It should be considered, that this study took place between January 2012 and June 2015, after the initial learning curve for TAVI, so the operators were experienced. Recently, Testa and colleagues reported 8-year mortality of 78.3% in 990 high-risk inoperable patients that were treated during the initial TAVI procedures (2007 to 2011).[19] A 5-year analysis of 4201 patients from the FRANCE-2 registry receiving both the self-expanding and balloon-expandable bioprostheses, showed a 60.8% all-cause mortality.[20] The UK TAVI registry that included 241

Table 5
Univariate analysis for predictors of structural valve deterioration

	Univariate analysis		
Factors	P	HR	95% CI
Age, years	0.29	1.08	0.93-1.26
Body mass index, (kg/m^2)	0.57	1.05	0.87-1.27
Hypertension	0.09	0.21	0.03-1.29
Diabetes mellitus	0.45	1.91	0.35-10.41
CAD	0.72	1.35	0.24-7.46
CABG	0.58	1.74	0.23-12.86
Gender, (male)	0.06	5.93	0.90-39.00
Logistic Euroscore, (%)	0.36	0.94	0.83-1.07
Procedure time, (min)	0.06	0.96	0.93-1.00
Valve size, (mm)	0.003	0.55	0.37-0.81

CABG = coronary artery bypass graft; CAD = coronary artery disease.

patients from 2007 to 2011 who received both types of bioprostheses, noted a 53.1% mortality rate at 5 years.[21]

The change in NYHA class functional status was evident at discharge and at 1-month. In addition, beyond 5 years of follow-up, the improved clinical status was also evident, even though the population was high risk and with a lot of comorbidities.

The percentage of available follow-up echocardiographic data are similar with other published studies.[19,20] The mean gradient decreased significantly post TAVI and remained low for the duration of the study. Studies with the Medtronic family of valves show persistently low levels of mean gradient, both with the first generation and the newer valve generation.[22,23]

Regarding valve performance, the recently published criteria that specify SVD and BVF provide a means for uniform comparison among studies.[13] The FRANCE-2 TAVI registry showed at 5 years that severe and moderate SVD rates were 2.5% and 13.3%, respectively,[20] with no association between SVD and mortality. Likewise, the UK TAVI registry with 5.8 years of follow-up had 8.7% of moderate SVD and 0.4% of severe SVD.[21] In a propensity-score matched analysis comparing TAVI and surgical aortic valves, both groups fared similarly in terms of SVD (HR 2.5, 95% CI 0.7 to 8.3, $p = 0.159$)[24] in a 6-year period. Furthermore, the 5-year outcomes from PARTNER 3 showed that the third-generation SAPIEN 3 (Edwards Lifesciences) had similar rates of SVD compared to the surgical arm and better SVD rates compared to the previous balloon-expandable valve (SAPIEN XT; Edwards Lifesciences) and that the BVF rates were higher for the TAVI arm (mainly due to PVL) compared to the surgical arm (mainly due to endocarditis).[25,26] Recently, 10-year data showed a total cumulative incidence of 6.5% for SVD/BVF in patients undergoing TAVI with mainly the balloon-expandable bioprostheses.[27] Other studies have shown similar rates of SVD and BVF.[14–18] The present study depicts the clinical outcomes and valve performance status of patients undergoing TAVI between January 2012 and June 2015 and confirms the already good results that previous trials have shown. Herein we present long-term outcomes beyond 5 years post TAVI with both generations of a self-expanding bioprosthesis, adding data regarding the long-term durability of these valves.

In the present analysis, the factor that predicted moderate SVD was smaller valve size, signifying that procedural factors do not seem to have an impact in bioprostheses function. In an analysis of 450 patients receiving both self-expandable and balloon-expandable devices, smaller valve size was an independent predictor of BVF, due to higher mean gradients.[15] In addition, a recent randomized trial comparing the use or not of predilation during TAVI, showed that direct TAVI was equal to nondirect regarding procedural success,[28] hence further supporting the fact that procedural factors have no influence on valve performance.

The strength of this study is thealmost complete clinical and echocardiographic follow-up achieved for the population alive during the study period. Although the number of patients and event rates are small, important conclusions are drawn regarding valve durability.

This is a prospective 3-center observational study that included patients undergoing TAVI with the first 2 generations of the self-expanding valve of the Medtronic family. There was not a central adjudication committee nor a core lab to review events and echocardiographic data and each center was responsible for data acquisition and representation. The echocardiographic follow-up data were available only for alive patients who had a standard echocardiogram. Patients receiving TAVI during the later stages of the study period, have yet to reach an 8-year clinical follow-up milestone. Furthermore, valve technology and operator experience have been progressing since the inception of TAVI and this may have positively impacted the results. During the study period the logistic Euroscore was calculated, which could have overestimated the risk of the TAVI population. Although the study population is small, the results are noteworthy and add to the already published articles regarding long-term valve performance. Finally, this study does not aim to extrapolate findings in younger population or lower surgical risk candidates for aortic valve replacement.

In conclusion, long-term valve performance beyond 5 years of a self-expanding transcatheter aortic valve bioprosthesis is excellent, with stable mean gradients and low SVD rates.

Author contributions

Konstantinos Stathogiannis: Data curation; Formal analysis; Investigation; Roles/Writing - original draft; Andreas Synetos: Supervision; Roles/Writing - original draft; George Latsios: Supervision; Validation; Antonios Karanasos: Methodology; Validation; George Trantalis: Methodology; Validation; Pantelis Toskas: Methodology; Validation; Maria Drakopoulou: Supervision; Writing - review & editing; Maria Xanthopoulou: Methodology; Data curation; Maria Karmpalioti: Methodology; Chryssa Simopoulou: Methodology; Stergios Soulaidopoulos: Software; Validation; George Oikonomou: Formal analysis; Georgios Benetos: Formal analysis; Sotirios Tsalamandris: Formal analysis; Ilias Kosmas: Data curation; Formal analysis; Vasilis Voudris: Supervision; Antonios Mastrokostopoulos: Data curation; Formal analysis; George Katsimagklis: Supervision; Panos Halvatsiotis: Supervision; Spyridon Deftereos: Supervision; Costas Tsioufis: Supervision; Validation; Konstantinos Toutouzas: Conceptualization; Supervision; Writing - review & editing.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.02.006.

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