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Seven-Year Clinical and Durability Outcomes of Balloon-Expandable Transcatheter Aortic Valve Implantation in a Turkish Single-Center Cohort

ABSTRACT

Background: Long-term durability data for early-generation balloon-expandable transcatheter aortic valve implantation (TAVI) in Turkish populations remain limited. The authors evaluated 7-year clinical outcomes and valve durability according to the Valve Academic Research Consortium (VARC-3) criteria.

Methods: In this single-center registry, 270 consecutive patients with symptomatic severe aortic stenosis treated with the early-generation balloon-expandable SAPIEN XT valve (January 2012-March 2017) were included. Clinical and echocardiographic outcomes were assessed up to 7 years. The primary endpoint was all-cause mortality. Structural valve deterioration (SVD) and bioprosthetic valve failure (BVF) were defined according to the VARC-3 criteria. Cumulative incidence was estimated using competing-risk analysis, with death from any cause treated as a competing event. Predictors of mortality were evaluated using Cox regression.

Results: At 7 years, cumulative survival was 29.6%. Cardiovascular and non-cardiovascular mortality occurred at comparable rates. In multivariable analysis, higher Katz index, reflecting better functional status, and higher body mass index were inversely associated with all-cause mortality, whereas eGFR <30 mL/min/1.73 m^2 was associated with increased mortality risk. The 5- and 7-year cumulative incidences of combined Stage 2-3 SVD were 0.74% and 3.72%, respectively; BVF rates were 1.11% and 2.23%, respectively.

Conclusion: In this Turkish single-center cohort treated during the early TAVI era, long-term outcomes reflected the advanced age and comorbidity burden of the study population. Using a competing-risk framework, the observed cumulative incidence of SVD and BVF was low at 5 and 7 years; however, these findings should be interpreted in the context of substantial competing mortality.

Keywords: Bioprosthetic valve failure, Edwards SAPIEN XT valve, long-term outcomes, structural valve deterioration, transcatheter aortic valve implantation

ORIGINAL INVESTIGATION

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INTRODUCTION

Transcatheter aortic valve implantation (TAVI), first performed in 2002, has now become an established treatment for severe aortic stenosis (AS) in patients with prohibitive, high, and intermediate surgical risk.[1-4]Recently, large studies comparing TAVI and surgical aortic valve replacement (SAVR) in low-risk patients have found that TAVI produces favorable clinical outcomes for short-term follow-up.[5,6] The fact that TAVI has been applied to lower-risk patients has increased the importance of long-term outcomes, including valve durability.

The Valve Academic Research Consortium (VARC) published the VARC-3 criteria in 2021. The VARC-3 criteria included some new definitions and changes. VARC-3 has been updated regarding clinical endpoints, procedural complications, and bioprosthetic valve dysfunction (BVD) and failure, and studies using these criteria are needed because limited data exist on long-term follow-up based on the updated VARC-3 criteria worldwide.[7]

In Türkiye, reimbursement policies restrict TAVI primarily to inoperable and high-surgical-risk patients, with selected intermediate-risk elderly individuals also

eligible. Consequently, long-term outcome data in Turkish TAVI populations remain particularly relevant.

The authors aimed to investigate the long-term outcomes of patients beyond 5 years who underwent TAVI with balloon-expandable SAPIEN XT valves in the center, according to the VARC-3 criteria.

METHODS

Study Design and Procedure

This was a single-center, registry-based observational study. Between January 2012 and March 2017, 270 consecutive patients who underwent TAVI with SAPIEN XT valves (Edwards Lifesciences, Irvine, CA, USA) at the hospital due to symptomatic severe AS, which were either inoperable or had a high surgical risk, were included in the study and follow-up data were collected until April 2024. In the center, the choice of severe AS treatment method is based on the decision of the heart team. The heart team consisted of cardiologists, cardiovascular surgeons, anesthesiologists, and pulmonologists. During the study period (2012-2017), treatment decisions were based on multidisciplinary assessment, incorporating clinical status, comorbidity burden, frailty, anatomical considerations, and life expectancy, in addition to conventional surgical risk scores, including the Society of Thoracic Surgeons (STS) score and EuroSCORE II (European System for Cardiac Operative Risk Evaluation II). All procedures were performed under general anesthesia. Procedural and follow-up data of the patients were obtained from the hospital database. After discharge, clinical and echocardiographic data of the patients were recorded at 1 month, 6 months, and annually. The follow-up information of the patients who were unable to come to the institution was collected by contacting the patients, their relatives, or their physicians. Vital status was available for all patients, with follow-up extending up to 7 years after TAVI. Follow-up echocardiographic assessments and changes in functional capacity from baseline were analyzed in patients who survived the corresponding follow-up time points and had available data. The authors analyzed the 7-year clinical outcomes of these patients according to the updated Valve Academic Research Consortium (VARC-3) criteria.[7]

HIGHLIGHTS

- Long-term (>5-year) durability data from Turkish transcatheter aortic valve implantation (TAVI) cohorts are scarce.
- Seven-year single-center cohort outcomes of early-generation SAPIEN XT valves are presented.
- In a high-mortality, elderly cohort, the observed cumulative incidence of SVD and BVF was low at 5 and 7 years using VARC-3 criteria and competing-risk analysis.
- Seven-year mortality reflected advanced age and comorbidity burden.
- Provides national long-term durability data from the early TAVI era.

Measurements

Demographic and clinical characteristics included age, gender, body mass index in kg/m^2, smoking habits (recorded as current, ever, never smoked), personal medical history of hypertension, type 2 diabetes mellitus, hyperlipidemia, chronic obstructive pulmonary disease, chronic kidney disease and renal replacement therapy, New York Heart Association (NYHA) functional capacity score, previous thoracic surgery, previous cardiac pacemaker, prior coronary artery disease (CAD) or any other manifestations of cardiovascular disease, and family history of CAD. Society of Thoracic Surgeons (STS) score, logistic European System for Cardiac Operative Risk Evaluation (logistic EuroSCORE), and the updated EuroSCORE II, which are approved risk assessment tools for open heart surgery, were calculated.[8,9] Functional status was assessed using the Katz index, which measures independence in activities of daily living.[10]

Imaging Tools

Two-dimensional transthoracic echocardiography (TTE) and transesophageal echocardiography were used to evaluate procedural outcomes. "Low flow" was defined as indexed stroke volume (SVi) of less than 35 mL/m^2. According to the 2012 ESC valvular heart disease guidelines, high-gradient AS was defined as mean gradient ≥40 mmHg, peak velocity ≥4.0 m/s, valve area ≤1 cm^2; classical low-flow low-gradient severe AS was defined as mean gradient <40 mmHg, valve area <1.0 cm^2, and poor left ventricular systolic function (LVEF<40%).[11] The diagnosis of classical low-flow, low-gradient severe AS was confirmed by excluding pseudo-severe AS with low-dose dobutamine stress echocardiography.[11] Paradoxical low-flow, low-gradient with preserved ejection fraction (mean gradient <40 mm Hg, valve area ≤1 cm^2, LVEF ≥50%, SVi <35 mL/m^2) was considered severe AS.[11] In patients with paradoxical low-flow, low-gradient severe AS, intervention decisions were individualized by the heart team, taking into account symptomatic status and anatomical severity. In selected symptomatic patients with borderline hemodynamic parameters, a valve area ≤0.8 cm^2 (or ≤0.6 cm^2/m^2 indexed) was considered supportive of severe AS in conjunction with clinical findings. Electrocardiogram-gated multislice computed tomography (CT) was performed to assess aortic root anatomy and vascular access. Valve sizing for the balloon-expandable prosthesis was based on CT-derived annular measurements. Porcelain aorta was defined as extensive calcification of the ascending aorta or aortic arch, which can be completely or near completely circumferential.

Structural valve deterioration (SVD) and bioprosthetic valve failure (BVF) were defined according to VARC-3 recommendations. Moderate hemodynamic valve deterioration (Stage 2 SVD) was considered when the mean transvalvular gradient increased by ≥10 and <20 mmHg, resulting in a final mean gradient ≥20 mm Hg, together with a reduction in effective orifice area (EOA) of ≥0.3 cm^2 or ≥25%, and/or a decrease in Doppler velocity index (DVI) of ≥0.1 or ≥20% compared with the echocardiographic assessment performed 1-3 months after the procedure. Alternatively, new onset or worsening (≥1 grade) intraprosthetic aortic regurgitation leading to

a moderate final grade was also classified as Stage 2 SVD. Severe hemodynamic valve deterioration (Stage 3 SVD) was defined as an increase in mean gradient ≥20 mm Hg leading to a final mean gradient ≥30 mm Hg, accompanied by a decrease in EOA ≥0.6 cm^2 or ≥50%, and/or a reduction in DVI ≥0.2 or ≥40% compared with the -3-month post-procedural study. New onset or worsening (≥2 grades) intraprosthetic regurgitation resulting in severe aortic regurgitation was also considered Stage 3 SVD. Bioprosthetic valve failure was defined as any bioprosthetic valve dysfunction associated with clinical consequences, irreversible Stage 3 SVD, valve reintervention, or valve-related death. This definition includes cases of infective endocarditis with clinical consequences, even in the absence of hemodynamic SVD criteria. Structural valve deterioration and bioprosthetic valve failure events were adjudicated according to VARC-3 definitions based on available echocardiographic data. All suspected valve-related events were reviewed by experienced cardiologists, and any discrepancies were resolved by consensus.

Primary and Secondary Outcomes

The primary endpoint was all-cause mortality during the 7-year follow-up. Deaths were categorized as cardiovascular or non-cardiovascular. In accordance with VARC-3 criteria, cardiovascular death included fatalities attributable to heart failure, cardiogenic shock, bioprosthetic valve dysfunction, myocardial infarction, stroke, thromboembolism, cardiac tamponade, vascular complications, arrhythmias or conduction disturbances, and cardiovascular infections such as mediastinitis or endocarditis. Intraprocedural death, sudden death, and deaths of unknown cause were also considered cardiovascular. Deaths clearly resulting from non-cardiovascular conditions were classified as non-cardiovascular mortality. The timing of death was categorized as periprocedural, early, or late according to VARC-3 definitions.[7] Composite endpoints, including technical success, device success, and early safety, were defined in accordance with VARC-3 recommendations.[7]

Secondary endpoints of this study were periprocedural complications, changes from baseline in NYHA functional capacity score, and echocardiographic endpoints at the 7-year follow-up. Periprocedural complications include paravalvular regurgitation (PVR), major cardiac structural complication, implantation of multiple (>1) valves during the index hospitalization, valve malposition, ischemic stroke, major vascular complications, bleeding (type 2-4), acute kidney injury (stage 2-4), conduction system disturbances resulting in a new permanent pacemaker implantation (PPI). The echocardiographic endpoints include mean aortic valve gradient, LVEF. Valve durability endpoints include SVD and BVF. All endpoints were defined according to VARC-3 criteria.[7]

Statistical Analysis

Statistical analyses were performed using SPSS version 27 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Continuous variables are presented as mean ± standard deviation or median (interquartile range), as appropriate, and categorical variables as counts and percentages. Group comparisons were performed using the chi-square test for categorical variables and the Student's *t*-test or Mann–Whitney *U*-test for continuous variables, depending on data distribution.

Time-to-event outcomes, including all-cause mortality and cardiovascular mortality, were analyzed using the Kaplan–Meier method and presented as survival curves.

To identify predictors of all-cause mortality during follow-up, Cox proportional hazards regression analysis was performed. Variables for the multivariable model were selected based on pre-specified clinical relevance (including age, STS score, functional status as assessed by the Katz index, and low-flow low-gradient AS) and variables with $P < .10$ in univariate analysis. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported.

Collinearity among candidate variables was assessed prior to model construction. EuroSCORE II and Logistic EuroSCORE were excluded from the multivariable model due to collinearity with STS score, and STS score was retained as the primary risk stratification variable.

The proportional hazards assumption was evaluated using Schoenfeld residuals. Variables violating this assumption were retained in the model but interpreted with caution. Model discrimination was assessed using the concordance index (C-index), and overall model fit was evaluated using the likelihood ratio test.

The cumulative incidence of SVD and BVF was estimated using cumulative incidence function (CIF) analysis, with death from any cause occurring prior to the valve-related event of interest treated as a competing event. Analyses were performed using the cmprsk package in R (version 4.3.3; R Foundation for Statistical Computing, Vienna, Austria). SVD was analyzed separately for Stage 2 and Stage 3, in addition to a combined Stage 2-3 endpoint.

A two-sided P value < .05 was considered statistically significant.

RESULTS

Baseline Characteristics

The baseline characteristics of the 270 patients are summarized in Table 1. The mean age was 82.5 ± 7.1 years, and 73.3% were female. Diabetes mellitus and hypertension were present in 27.4% and 89.2% of patients, respectively, and 13.3% were current smokers. The mean STS score was 7.6% ± 2.7%. According to STS categories, 168 (62.2%) patients were high risk (STS ≥8%) and 102 (37.8%) were intermediate risk (STS 4% to <8%). The mean EuroSCORE II was 9.1% ± 3.7%, and the mean Katz index was 4.6 ± 1.

Procedural Characteristics

Procedural characteristics are shown in Table 2. The transfemoral approach was used in 99.3% of patients. Valve sizes of 23 mm, 26 mm, and 29 mm were implanted, with 26 mm being the most frequently used size. Balloon predilatation was performed in 76.7% of cases and post-dilatation in 4.4%. Three patients underwent TAVI following

Table 1. Baseline Demographic and Clinical Characteristics of the 270 Patients

Characteristics	All Patients (n = 270)
Age (years)	82.5 ± 7.1
Female, n (%)	198 (73.3)
Body mass index (kg/m^2)	30.6 ± 6.3
Body surface area (m^2)	1.8 ± 0.2
Diabetes mellitus type II, n (%)	74 (27.4)
Arterial hypertension, n (%)	241 (89.2)
Dyslipidaemia, n (%)	82 (30.3)
Family history of coronary artery disease, n (%)	12 (4.4)
Current smoking, n (%)	36 (13.3)
Percutaneous coronary intervention, n (%)	51 (18.9)
Coronary artery bypass grafting, n (%)	45 (16.7)
Myocardial infarction, n (%)	40 (14.8)
Mitral valve replacement, n (%)	3 (1.1)
Hemodialysis, n (%)	2 (0.7)
Chronic obstructive pulmonary disease, n (%)	61 (22.6)
Ischemic stroke, n (%)	21 (7.8)
STS score %	7.6 ± 2.7
STS score categories	
High (STS score ≥ 8%), n (%)	168 (62.2)
Intermediate (4% ≤ STS score < 8%), n (%)	102 (37.8)
EuroSCORE II %	9.1 ± 3.7
Logistic EuroSCORE %	24.4 ± 10.1
Left ventricular ejection fraction %	53.1 ± 10.5
Aortic valve area (cm^2)	0.7 ± 0.2
Aortic valve area index (cm^2/ m^2)	0.4 ± 0.1
Aortic mean gradient (mm Hg)	46.5 ± 13.8
Serum glucose, mg/dL	138 ± 54.1
Creatinine mg/dL	1.1 ± 0.7
Glomerular filtration rate mL/min/1.73 m^2	60.9 ± 23.3
Hemoglobin g/dL	11.7 ± 1.8
Atrial fibrillation, n (%)	52 (19.3)
Pacemaker, n (%)	8 (3)
Left bundle branch block, n (%)	30 (11.1)
Right bundle branch block, n (%)	23 (8.5)
Porcelain aorta, n (%)	2 (0.7)
Dextrocardia, n (%)	1 (0.4)
Classification of aortic stenosis n (%)	
High-gradient	235 (87)
Low-flow, low-gradient with reduced ejection fraction	24 (8.9)
Paradoxical low-flow, low-gradient with preserved ejection fraction	11 (4.1)
Stages of heart failure, n (%)	
NYHA I	0 (0)
NYHA II	108 (40)
NYHA III	136 (50.4)
NYHA IV	26 (9.6)
Katz index	4.6 ± 1

Data are presented as mean ± SD, median (interquartile range (IQR)), or n (%), as appropriate.
NYHA, New York Heart Association; STS, Society of Thoracic Surgeons.

Table 2. Procedural Characteristics and Periprocedural Complications at 30-Day Follow-Up

Procedural Characteristics	n (%)
Access site, n (%)	
Transapical	2 (0.7)
Transfemoral	268 (99.3)
Valve size (mm), n (%)	
23	91 (33.7)
26	134 (49.6)
29	45 (16.7)
Pre-dilatation, n (%)	207 (76.7)
Post-dilatation, n (%)	12 (4.4)
Simultaneous TAVI and EVAR	3 (1.1)
Periprocedural (30-day) complications	
Major cardiac structural complication[a], n (%)	3 (1.1)
Implantation of multiple valves, n (%)	1 (0.4)
Valve migration/embolization, n (%)	4 (1.5)
Ischemic stroke, n (%)	5 (1.9)
Acute kidney injury (stage 2-4), n (%)	15 (5.6)
Major vascular complication, n (%)	17 (6.3)
New permanent pacemaker[b], n (%)	26 (9.9)
≥ Moderate paravalvular regurgitation, n (%)	9 (3.3)
Bleeding (type 2-4), n (%)	37 (13.7)

EVAR, endovascular aneurysm repair; TAVI, transcatheter aortic valve implantation.
[a]Annular rupture, cardiac tamponade, coronary obstruction (left main coronary artery).
[b]Eight patients with pacemakers at baseline were not included.

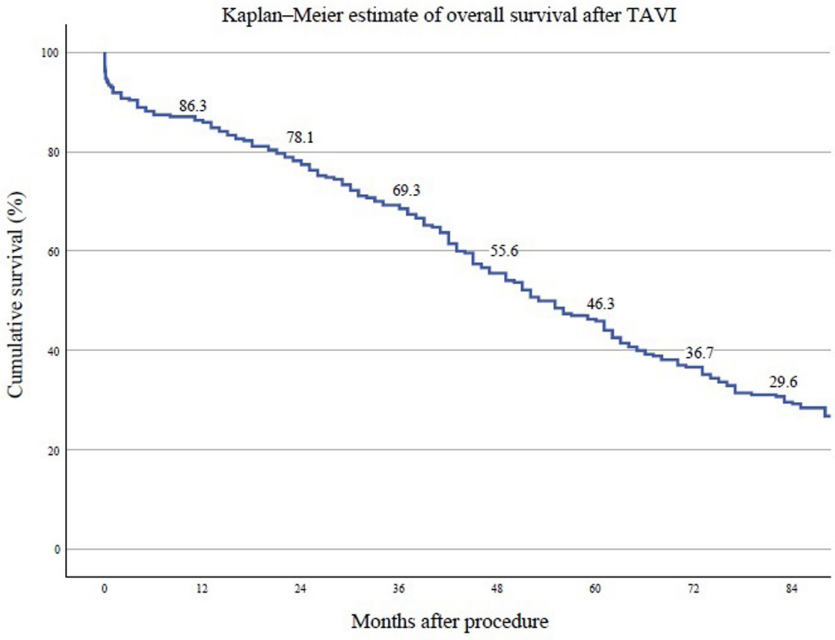
endovascular abdominal aortic aneurysm repair during the same procedure.

Primary Endpoints

The median follow-up duration was 54 months (interquartile range: 27-85), with a maximum follow-up of 147 months. Cumulative survival rates at 1, 2, 3, 4, 5, 6, and 7 years were 86.3%, 78.1%, 69.3%, 55.6%, 46.3%, 36.7%, and 29.6%, respectively (Figure 1). Freedom from cardiovascular death at 7 years was 64.8% (Figure 2).

Table 3 presents mortality data at 30-day, 1-year, 3-year, 5-year, and 7-year follow-ups. All-cause and cardiovascular mortality rates were 13.7% and 9.6% at 1 year, 30.7% and 18.9% at 3 years, 53.7% and 27.8% at 5 years, and 70.4% and 35.2% at 7 years, respectively. The distribution of causes of death is presented in Figure 3. Among cardiovascular causes, heart failure was the most frequent (19.5%), followed by acute myocardial infarction (6.8%) and stroke (5.8%). Among non-cardiovascular causes, pneumonia was the most frequent cause (13.2%).

Among the study population, 35 patients (12.9%) had low-flow, low-gradient (LFLG) AS, of whom 24 had classical (reduced LVEF) and 11 had paradoxical (preserved LVEF) LFLG AS. At 7-year follow-up, all-cause mortality was 80.0% in LFLG patients compared with 68.9% in non-LFLG patients ($P = .223$). This finding should be interpreted as exploratory given the limited sample size. Given the limited



Time (months)	0	12	24	36	48	60	72	84
No. at risk	270	233	211	187	150	125	99	80
No. of events	0	37	59	83	120	145	171	190

Figure 1. Kaplan–Meier estimate of overall survival after transcatheter aortic valve implantation. Overall survival is presented up to 7 years of follow-up. Numbers at risk and cumulative events at yearly intervals are shown in the graph.

number of patients in each subgroup, formal comparative analyses between classical and paradoxical LFLG AS were not performed.

Periprocedural mortality occurred in 19 patients (7.0%), predominantly from cardiovascular causes (78.9%). Early mortality occurred in 18 patients (6.7%), with 61.1% attributable

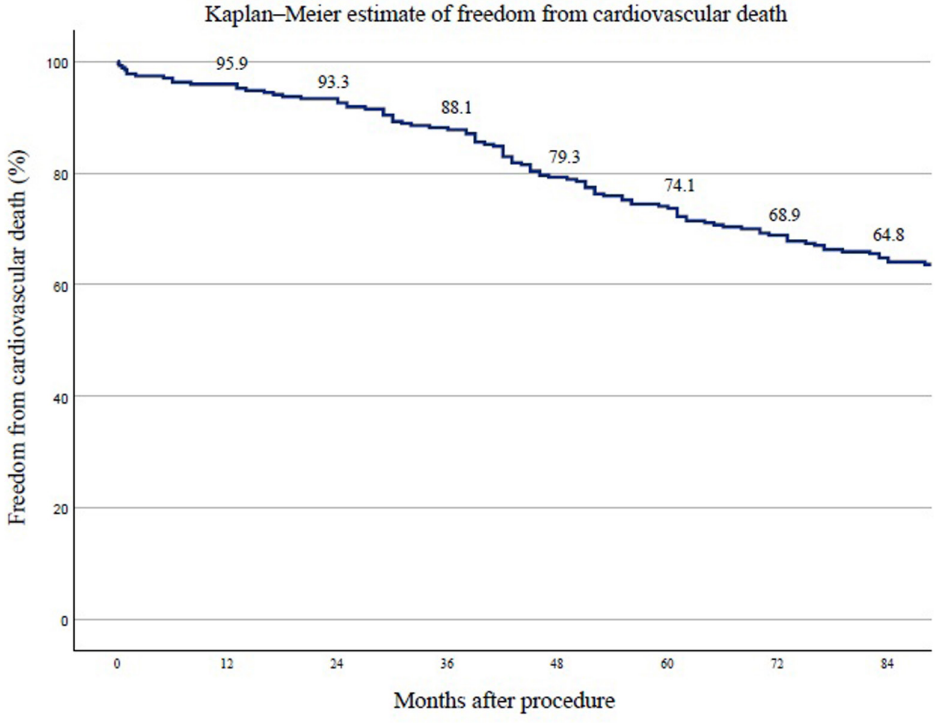


Figure 2. Kaplan–Meier estimate of freedom from cardiovascular death after transcatheter aortic valve implantation. Cardiovascular death was defined according to the Valve Academic Research Consortium-3 (VARC-3) criteria.

Table 3. Primary End Point(s) at 30-day, 1-year, 3-year, 5-year, and 7-year Follow-Up, Timing of Mortality and Composite Endpoints of the 270 Patients

Variables	30 days	1 year	3 years	5 years	7 years
All-cause mortality, yes (%)	19 (7)	37 (13.7)	83 (30.7)	145 (53.7)	190 (70.4)
Cardiovascular mortality, yes (%)	15 (5.6)	26 (9.6)	51 (18.9)	75 (27.8)	95 (35.2)
Non-cardiovascular mortality, yes (%)	4 (1.5)	11 (4.1)	32 (11.9)	70 (25.9)	95 (35.2)
Timing of mortality					
Periprocedural mortality, n (%)	19 (7)				
Early mortality, n (%)	18 (6.7)				
Late mortality, n (%)	153 (56.7)				
Composite endpoints (30-day)					
Technical success, n (%)	260 (96.3)				
Device success, n (%)	245 (90.7)				
Early safety, n (%)	195 (72.2)				

to cardiovascular causes. Late mortality occurred in 153 patients (56.7%), of whom 54.9% died from non-cardiovascular causes.

Univariate and multivariable Cox proportional hazards analyses were performed to identify factors associated with all-cause mortality during follow-up; results are presented in Supplementary Table 1. In multivariable analysis, Katz index (HR 0.698, 95% CI 0.594-0.821, $P < .001$) and higher body mass index (HR 0.959, 95% CI 0.933-0.986, $P = .003$) were inversely associated with all-cause mortality. An estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 was also associated with increased mortality risk (HR 1.737, 95% CI 1.1272.678, $P = .012$); however, this finding should be interpreted cautiously because the proportional hazards assumption was not fully satisfied for this variable. The model demonstrated moderate discriminative ability (C-index = 0.664) and was statistically significant overall (global $P < .001$).

Secondary Endpoints

Periprocedural complications are shown in Table 2. A new permanent pacemaker was implanted in 26 patients (9.9%) during the periprocedural period. The incidence of ≥ moderate PVR at 30 days was 3.3%. Ischemic stroke occurred in 5 patients (1.9%) within 30 days.

Left ventricular systolic function improved early after TAVI and partially declined over long-term follow-up (Supplementary Figure 1). New York Heart Association functional class improved significantly at 30 days after TAVI ($P <$ .001), with a reduction in the proportion of patients in NYHA

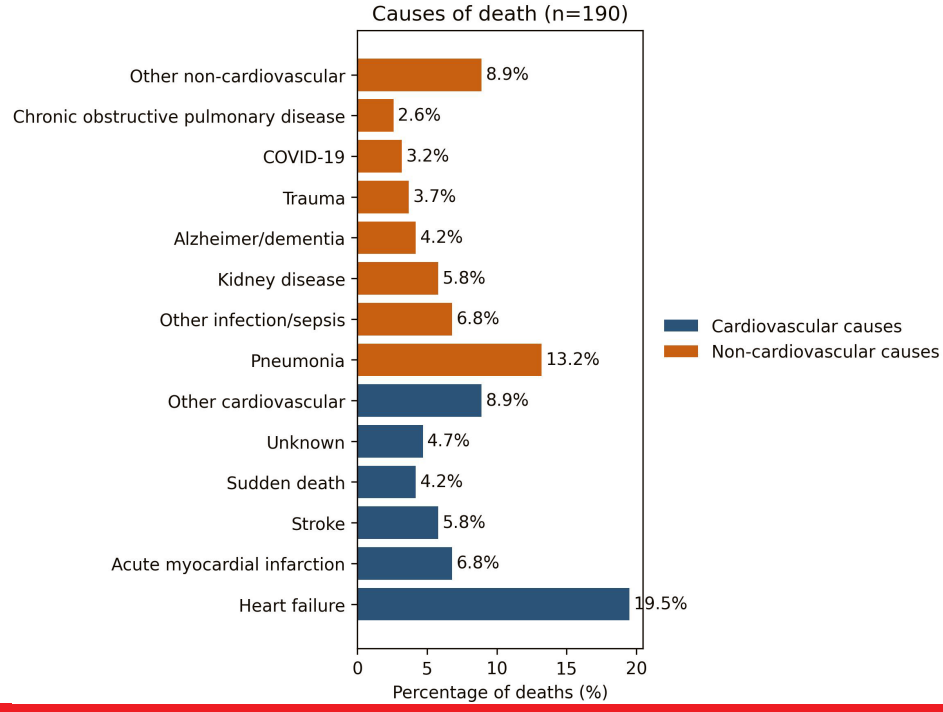


Figure 3. Causes of death during 7-year follow-up after transcatheter aortic valve implantation. Causes of death are shown as percentages of all deaths (n = 190) and grouped as cardiovascular and non-cardiovascular categories.

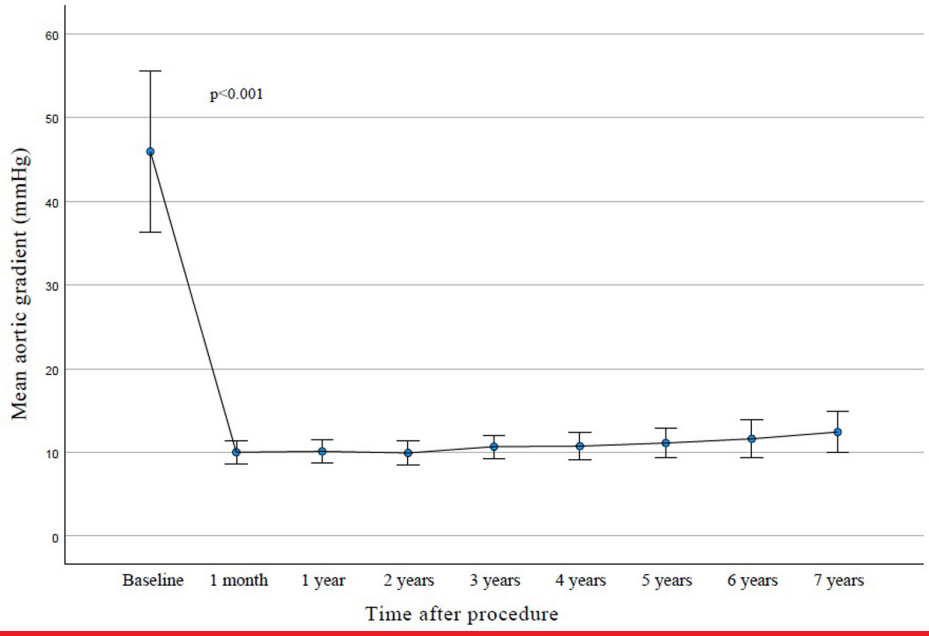


Figure 4. Change in mean aortic gradient over time after transcatheter aortic valve implantation. Values are presented as mean ± 95% confidence interval. The reduction from baseline to 1 month was statistically significant ($P < .001$).

class III-IV from 60.0% at baseline to 11.9% at 30 days. This early improvement remained stable over 7-year follow-up, with no significant change between 30 days and 7 years ($P = .641$) (Supplementary Figure 2). Pre-procedural mean aortic valve gradient decreased significantly at 30 days (46.3 vs. 10.0 mm Hg, $P < .001$). The mean gradient at 7-year follow-up remained similar to the 30-day value (12.4 vs. 10.0 mm Hg, $P = .062$), with no statistically significant change over time (Figure 4).

Echocardiographic follow-up at 7 years was available for 61 of 80 surviving patients (76.3%). During follow-up, Stage 2 SVD was observed in 6 patients and Stage 3 SVD in 4 patients (Table 4). Baseline characteristics were largely comparable between patients with and without late echocardiographic follow-up (Supplementary Table 2).

Cumulative incidence analysis, accounting for death from any cause as a competing event, demonstrated low observed cumulative incidence of SVD over long-term follow-up. The cumulative incidence of combined Stage 2-3 SVD was 0.74% at 5 years and 3.72% at 7 years (Figure 5). When analyzed separately, the 5- and 7-year cumulative incidences were 0% and 2.24% for Stage 2 SVD, and 0.74% and 1.49% for Stage 3 SVD, respectively (Figure 5). In a subset of patients, Stage 3 SVD events were observed before documented Stage 2 changes. This pattern likely reflects the small number of events and the heterogeneous mechanisms of valve deterioration, including cases without clearly documented intermediate Stage 2 progression.

Bioprosthetic valve failure occurred in 6 patients (Table 4), with cumulative incidence estimates of 1.11% at 5 years and 2.23% at 7 years. Confidence intervals widened at later time points, reflecting the diminishing number of patients remaining at risk because of high competing mortality (Figure 5).

DISCUSSION

The present study evaluated the 7-year clinical outcomes and performance of the balloon-expandable SAPIEN XT valve in patients with symptomatic severe AS in routine clinical practice using VARC-3 criteria. Long-term (>5-year) outcomes of early-generation balloon-expandable TAVI valves adjudicated according to VARC-3 definitions have been infrequently reported, particularly from Türkiye. In this context, the findings provide long-term clinical and durability data from a Turkish cohort treated during the early TAVI era. The SAPIEN XT valve demonstrated acceptable early procedural outcomes with respect to composite endpoints and periprocedural complications. In addition, an early improvement in LVEF was observed after TAVI, which partially declined over follow-up but remained higher than baseline at 7 years. Mean aortic valve gradient decreased significantly after TAVI and remained generally stable over time, while NYHA functional class improved and was maintained without significant deterioration during follow-up. The 7-year all-cause mortality reflected the advanced age, comorbidity burden, and high-risk clinical profile of the study population and was within the range reported in early-generation TAVI registries. Cardiovascular and non-cardiovascular deaths occurred at similar frequencies during follow-up. Heart failure, acute myocardial infarction, and stroke were the most common cardiovascular causes. The observed cumulative incidence of SVD and BVF was low at 7 years, as assessed using CIF analysis accounting for the competing risk of death, and was broadly consistent with previous reports of early-generation balloon-expandable valves. To the best of authors' knowledge, this study represents one of the few real-world, long-term follow-up analyses of early-generation balloon-expandable TAVI in Türkiye adjudicated according to VARC-3 criteria.

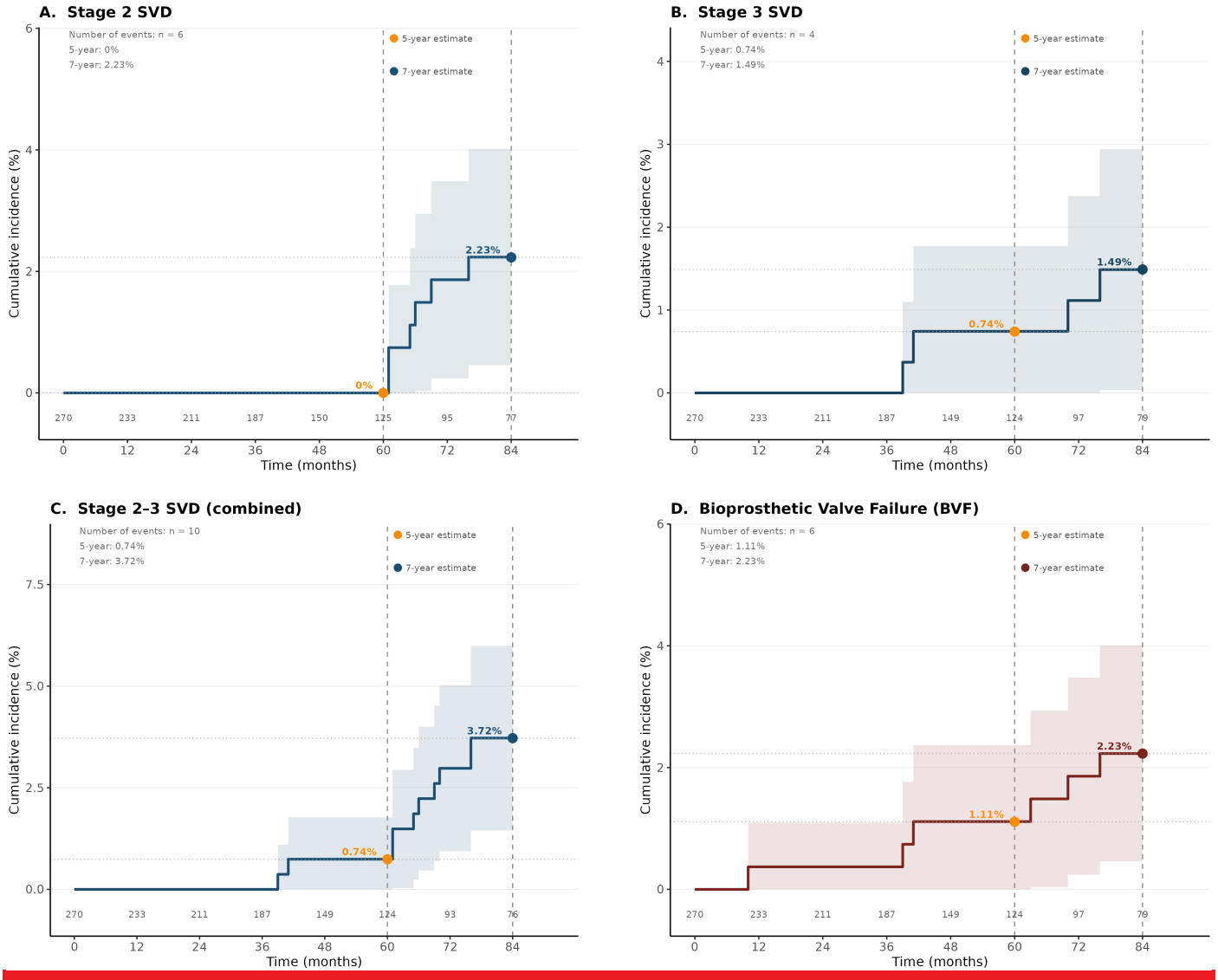


Figure 5. Cumulative incidence of structural valve deterioration (SVD) and bioprosthetic valve failure (BVF) after transcatheter aortic valve implantation using competing-risk analysis. Cumulative incidence functions (CIF) for (A) Stage 2 SVD, (B) Stage 3 SVD, (C) combined Stage 2-3 SVD, and (D) BVF over 7-year follow-up. Death from any cause occurring prior to the valve-related event of interest was treated as a competing event. Shaded areas represent 95% confidence intervals. Orange and blue markers denote the 5- and 7-year cumulative incidence estimates, respectively. Numbers at risk are displayed along the x-axis.

In this study, cumulative survival rates were 46.3% at 5 years and 29.6% at 7 years. Given the advanced age, high comorbidity burden, and surgical inoperability or high-risk profile of the study population, long-term survival was expected to be limited. Survival rates in the present cohort were broadly consistent with those reported by Şentürk et al[12] in a Turkish single-center TAVI registry using early-generation devices. In multicenter registries, Durand et al[13] reported a 7-year survival rate of 18.6%, while Deutsch et al[14] reported 5- and 7-year survival rates of 40.2% and 23.2%, respectively. Differences in survival across studies should be interpreted with caution, given variations in patient characteristics, risk profiles, and study design. Larger multicenter registries often include more heterogeneous populations and differing endpoint definitions. In contrast, the present study represents a relatively homogeneous early-generation balloon-expandable valve cohort with outcomes adjudicated according to VARC-3 criteria.

Although long-term comparative data between SAVR and TAVI from Türkiye remain limited, available Turkish surgical series in predominantly elderly and high-risk patients—including elective aortic valve replacement cohorts—report a substantial long-term mortality burden.[15] In parallel, large randomized and comparative analyses, particularly in high-risk patient populations, have demonstrated broadly similar survival outcomes between TAVI and SAVR.[16,17] These findings appear consistent with the outcomes observed in the TAVI cohort. However, given the differences in patient selection, procedural era, and study design, such comparisons should be interpreted cautiously.

Table 4. Details of Patients with Structural Valve Deterioration and Bioprosthetic Valve Failure at 7-Year Follow-Up

Patients	Age, years	Gender	Valve size, mm	SVD	BVF	Stages of SVD	Timing of SVD, years	Treatment	Death
#1	84	Male	26	Yes	Yes	Stage 3	3.4	Medication	Yes
#2	75	Female	26	Yes	No	Stage 2	5.5	Medication	Yes
#3	84	Female	23	Yes	Yes	Stage 3	5.8	Medication	Yes
#4	62	Female	23	Yes	No	Stage 2	6.3	Medication	No
#5	77	Female	23	Yes	Yes	Stage 3	3.3	ViV TAVI	Yes
#6	85	Male	29	Yes	No	Stage 2	5.4	Medication	Yes
#7	85	Male	26	Yes	Yes	Stage 2*	5.1	Medication	Yes
#8	92	Female	23	Yes	No	Stage 2	5.1	Medication	No
#9	85	Female	26	Yes	Yes	Stage 3	6.3	ViV TAVI	No
#10	78	Male	29	Yes	No	Stage 2	5.8	Medication	No
#11	78	Female	26	No	Yes	—[&]	—	Medication	Yes

BVF, bioprosthetic valve failure; SVD, structural valve deterioration; TAVI, transcatheter aortic valve implantation; ViV, valve-in-valve.
*Stage 2 SVD with valve-related death recorded as BVF.
[&]BVF due to infective endocarditis without hemodynamic SVD criteria (VARC-3: valve dysfunction with clinical consequences).

In the present study, periprocedural and early mortality were mostly due to cardiovascular causes, whereas late mortality was predominantly due to non-cardiovascular causes. The leading cause of cardiovascular death during the 7-year follow-up period was heart failure (19.5%). The shared risk profile between degenerative AS and atherosclerotic cardiovascular disease may partly explain why acute myocardial infarction (6.8%) and stroke (5.8%) were the second and third most common causes of death, respectively. In addition, the relatively high prevalence of atrial fibrillation (19.3%) may have contributed to stroke-related mortality. Among the 52 patients with atrial fibrillation, 50 (96.2%) patients were receiving oral anticoagulation therapy at baseline, including vitamin K antagonists (n=11) and direct oral anticoagulants (n=39). The rate of freedom from cardiovascular death at 5 and 7 years was 74.1% and 64.8%, respectively. In the PARTNER 1 study, 5-year freedom from cardiovascular death was 42.5% among inoperable patients and 46.9% among high-risk patients.[18] Despite differences in study design and patient characteristics, long-term cardiovascular mortality in the cohort was numerically comparable to that reported in early TAVI trials.

Beyond descriptive mortality patterns, the authors further explored factors associated with long-term outcomes using Cox proportional hazards analysis. In the present study, a higher Katz index, reflecting better functional status, was associated with lower mortality during follow-up. This finding is consistent with prior reports highlighting the prognostic importance of functional status in patients undergoing TAVI.[19,20] The Katz index may capture aspects of vulnerability that are not fully reflected by conventional risk scores such as STS score. However, given the observational design and limited sample size, these findings should be interpreted as associative rather than causal. Higher body mass index was inversely associated with mortality in the present cohort. This observation is consistent with the so-called "obesity paradox" described in elderly and high-risk cardiovascular populations. However, the underlying mechanisms remain uncertain and may reflect residual confounding, selection bias, or differences in nutritional and functional status. Therefore, this finding should be interpreted with caution rather than as evidence of a protective effect of increased body mass. Impaired renal function, as reflected by eGFR <30 mL/min/1.73 m^2, was also associated with increased mortality. However, this association should be interpreted cautiously, as the proportional hazards assumption was not fully satisfied for this variable, suggesting that its impact on mortality may vary over time. This limitation precludes definitive conclusions regarding the temporal stability of this relationship. Although STS score was associated with mortality in univariate analysis, it did not remain significant in the multivariable model. This may reflect the overlap between STS components and other variables included in the model, particularly functional status, as well as the modest number of events in the cohort. Overall, these findings underscore the multifactorial nature of long-term outcomes after TAVI, in which clinical vulnerability, comorbidity burden, and functional status appear to play a central role.

The study demonstrated technical success in 96.3% and device success in 90.7% of patients, with early safety achieved in 72.2% according to VARC-3 composite endpoints. Stroke, major vascular complications, cardiac structural complications, new permanent pacemaker implantation (PPI), VARC type 2-4 bleeding, ≥ moderate paravalvular regurgitation (PVR), and acute kidney injury grade 3 or 4 were systematically assessed. The rate of new PPI was 9.9% at 30 days. Previous studies have reported PPI rates ranging from 4% to 13% for the SAPIEN XT valve. One study reported a 12.6% PPI rate,[21] whereas another single-center Turkish study reported a rate of 6.3%.[22] The incidence of ≥ moderate PVR was 3.3%, and periprocedural stroke occurred in 1.9% of patients. These complication rates fall within the range reported in prior real-world studies of early-generation balloon-expandable TAVI.[23-28]

Structural bioprosthetic valve dysfunction (BVD), particularly structural valve deterioration (SVD), refers to permanent intrinsic changes in the prosthetic valve leading to

stenosis and/or regurgitation. Structural valve deterioration represents the principal mechanism limiting long-term durability of transcatheter bioprostheses. Historically, heterogeneity in definitions and staging of BVD has complicated interpretation of durability data. The VARC-3 criteria, introduced in 2021, provide a more standardized framework for assessing SVD and BVF. Earlier definitions, including the 2017 EAPCI/EACTS criteria, may have overestimated SVD by incorporating certain cases of prosthesis–patient mismatch or non-structural dysfunction.[29] Nevertheless, various forms of BVD—including SVD, non-structural dysfunction, thrombosis, and endocarditis—may ultimately lead to BVF and impact valve durability.

Long-term durability data for early-generation balloon-expandable valves beyond 5 years remain limited, particularly in real-world cohorts. In the study, mean transvalvular gradients remained stable between 30-day and 7-year follow-up, consistent with previously published reports.[30,31] The gradual upward trend observed in later years—particularly between years 6 and 7—warrants continued echocardiographic surveillance, as it may reflect early structural changes or the accumulation of subclinical valve deterioration in a subset of patients.

In the present study, the cumulative incidence of SVD and BVF remained low over 7 years of follow-up when analyzed using a competing-risk framework. These findings should be interpreted in the context of a high-risk, elderly population with substantial competing mortality, in whom the number of patients remaining at risk declined markedly over time. Accordingly, the observed low incidence does not necessarily reflect intrinsic valve durability but rather the combined effect of limited event occurrence and competing risk of death. In this context, the possibility that some patients died before developing SVD or BVF—thereby contributing to an underestimation of valve-related event incidence—cannot be excluded.

Stage-specific analyses demonstrated a low frequency of both Stage 2 and Stage 3 SVD, although in a subset of patients, Stage 3 events occurred without clearly documented antecedent Stage 2 changes. This observation likely reflects the heterogeneous nature of valve deterioration and the limited number of events, as well as the constraints of intermittent echocardiographic follow-up.

Cumulative incidence function analysis provides a more appropriate estimation of valve-related event rates in this setting compared with conventional Kaplan–Meier methods, which may overestimate incidence in the presence of competing risks. Overall, these findings suggest that, within the limitations of this cohort, clinically relevant valve-related events were infrequent during long-term follow-up; however, definitive conclusions regarding valve durability should be made with caution. These findings are broadly consistent with previously reported long-term outcomes of early-generation balloon-expandable transcatheter heart valves.[14,30,32] Consistent with a previous Turkish single-center study reporting low rates of SVD and BVF at long-term follow-up using early-generation devices,[12] the findings extend these observations to 7 years, using VARC-3 endpoint definitions and competing-risk analysis.

During follow-up, SVD was identified in 10 patients (6 with Stage 2 and 4 with Stage 3 hemodynamic deterioration). Among these, BVF developed in 6 patients: 4 due to irreversible Stage 3 SVD, 1 due to Stage 2 SVD accompanied by valve-related death, and 1 due to infective endocarditis without significant hemodynamic deterioration. Two patients underwent successful valve-in-valve (ViV) TAVI with post-procedural mean gradients <10 mmHg. These findings highlight that, although structural valve-related events may occur over time, reintervention with ViV TAVI was associated with favorable post-procedural hemodynamic profiles and may represent a viable management strategy for selected patients with BVF.

The present findings align with the overall pattern reported in major pivotal TAVI trials, including PARTNER 1, CoreValve/SURTAVI, and NOTION, in which valve-related events were relatively infrequent during long-term follow-up.[4,18,33] However, these observations should be interpreted with caution, given differences in patient risk profiles, valve generations, and analytical approaches, including the use of competing-risk methodology in the present study.

This study has several limitations. First, its single-center, observational design and the relatively small sample size limit generalizability and preclude causal inference. Second, the number of valve-related events was low, which restricts statistical power and necessitates cautious interpretation of stage-specific SVD analyses. Third, echocardiographic follow-up was incomplete at later time points, and SVD assessment relied on available imaging at discrete intervals; therefore, intermediate changes may have been missed and the timing of SVD onset may be imprecise. A formal comparison between patients with and without late echocardiographic follow-up did not reveal statistically significant differences; however, residual selection bias cannot be fully excluded given the limited number of patients without follow-up imaging. Fourth, although Cox proportional hazards modeling was used to explore factors associated with mortality, the proportional hazards assumption was not fully satisfied for some variables, indicating potential time-varying effects that could not be fully captured in this analysis. Finally, the high competing risk of death in this elderly, high-risk cohort reduces the number of patients remaining at risk over time and may influence the observed incidence of valve-related events, despite the use of competing-risk methodology. Furthermore, this cohort reflects early TAVI practice (2012-2017), during which procedures were performed under general anesthesia and predominantly via transfemoral access. The SAPIEN XT valve is no longer commercially available, and these procedural characteristics, together with the use of this early-generation platform, may limit the generalizability of the findings to contemporary TAVI practice, which has evolved substantially in terms of valve technology, procedural techniques, and patient selection.

Despite these limitations, the present study provides comprehensive long-term vital status follow-up and

VARC-3–based assessment of durability endpoints by experienced cardiologists in a homogeneous, early-generation, balloon-expandable valve cohort. The application of competing-risk methodology and uniform endpoint definitions strengthens the validity of durability assessment in this elderly population with substantial competing mortality risk.

CONCLUSIONS

In this TAVI cohort treated with early-generation balloon-expandable valves, early procedural outcomes were acceptable. Seven-year all-cause mortality largely reflected the advanced age, comorbidity burden, and high-risk clinical profile of the study population. Using a competing-risk framework, the observed cumulative incidence of SVD and BVF was low at 5 and 7 years; however, these findings should be interpreted in the context of substantial competing mortality. These findings contribute real-world 5- and 7-year outcome data from a Turkish TAVI cohort and may help contextualize outcomes observed with contemporary valve platforms.

Ethics Committee Approval: The study protocol was approved by the Scientific Research Ethics Committee of the University of Health Sciences, Trabzon Faculty of Medicine (approval date: 04 February 2025; approval number: 2025/160). The study was conducted in accordance with the Declaration of Helsinki.

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Supplementary Table 1. Univariate and Multivariable Cox Proportional Hazards Analyses for Predictors of 7-Year All-Cause Mortality

Variables	HR	95% CI	*P*
Part A. Univariate Cox Proportional Hazards Analysis			
Age, years	**1.027**	**1.001–1.053**	**0.045**
Female sex	0.885	0.623–1.258	0.497
Body mass index, kg/m^2	**0.968**	**0.942–0.994**	**0.017**
Diabetes mellitus	1.386	0.987–1.948	0.060
Arterial hypertension	0.891	0.572–1.388	0.608
Family history of coronary artery disease	0.773	0.362–1.650	0.506
Current smoking	0.872	0.539–1.409	0.575
Prior CABG	0.799	0.476–1.341	0.396
Prior ischemic stroke	1.246	0.740–2.097	0.408
Chronic obstructive pulmonary disease	0.984	0.699–1.385	0.927
Coronary artery disease	0.830	0.599–1.149	0.261
Atrial fibrillation	1.348	0.857–2.119	0.197
Preexisting left bundle branch block	1.272	0.624–2.594	0.508
Preexisting right bundle branch block	1.238	0.631–2.429	0.535
STS score, %	**1.095**	**1.034–1.158**	**0.002**
EuroSCORE II, %†	**1.047**	**1.003–1.093**	**0.036**
Logistic EuroSCORE, %†	**1.017**	**1.001–1.034**	**0.038**
Left ventricular ejection fraction, %	0.988	0.974–1.002	0.089
eGFR <30 mL/min/1.73 m^2	1.512	0.997–2.292	0.052
Katz index	**0.687**	**0.591–0.799**	**<0.001**
≥ Moderate paravalvular regurgitation	1.482	0.693–3.168	0.310
Permanent pacemaker implantation	0.910	0.515–1.606	0.744
Low-flow low-gradient aortic stenosis	1.359	0.885–2.087	0.092
Part B. Multivariable Cox Proportional Hazards Analysis			
Age, years	1.014	0.988–1.041	0.293
STS score, %	1.037	0.974–1.103	0.254
Katz index	**0.698**	**0.594–0.821**	**<0.001**
Low-flow low-gradient aortic stenosis	0.985	0.605–1.603	0.950
Body mass index, kg/m^2	**0.959**	**0.933–0.986**	**0.003**
Diabetes mellitus	1.190	0.829–1.710	0.346
Left ventricular ejection fraction, %	0.988	0.972–1.004	0.154
eGFR <30 mL/min/1.73 m^2‡	**1.737**	**1.127–2.678**	**0.012**

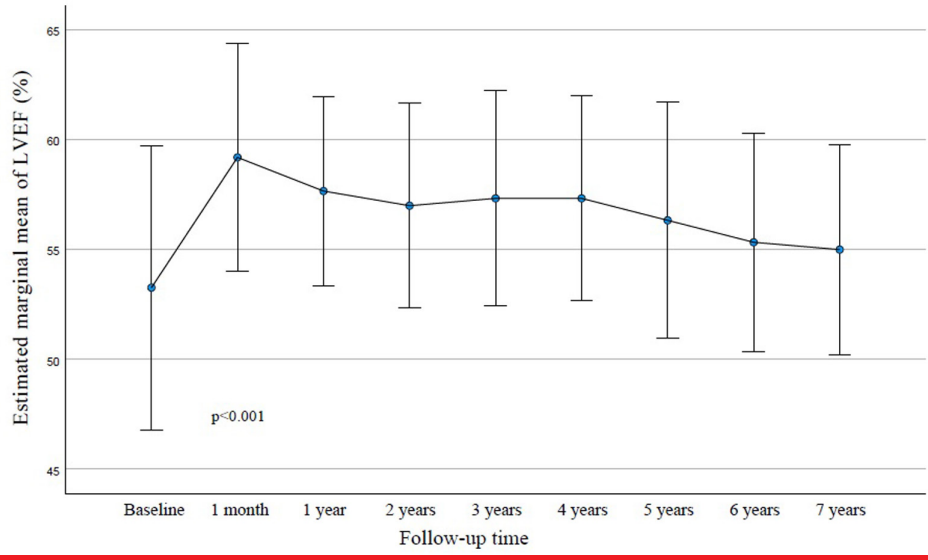
† EuroSCORE II and Logistic EuroSCORE are presented in the univariate analysis for completeness but were excluded from the multivariable model due to established collinearity with STS score; all three instruments measure operative risk from overlapping clinical variables. STS score was retained as the primary risk stratification tool. Bold red values: $p < 0.05$.

Variables entered into the multivariable model: pre-specified clinically relevant variables (age, STS score, Katz index, low-flow low-gradient AS) plus all variables with $p < 0.10$ in univariate analysis (BMI, diabetes mellitus, LVEF, eGFR <30 mL/min/1.73 m^2). EuroSCORE II and Logistic EuroSCORE were excluded due to collinearity with STS score. The model demonstrated moderate discrimination (C-index = 0.664) and was statistically significant overall ($p < 0.001$).

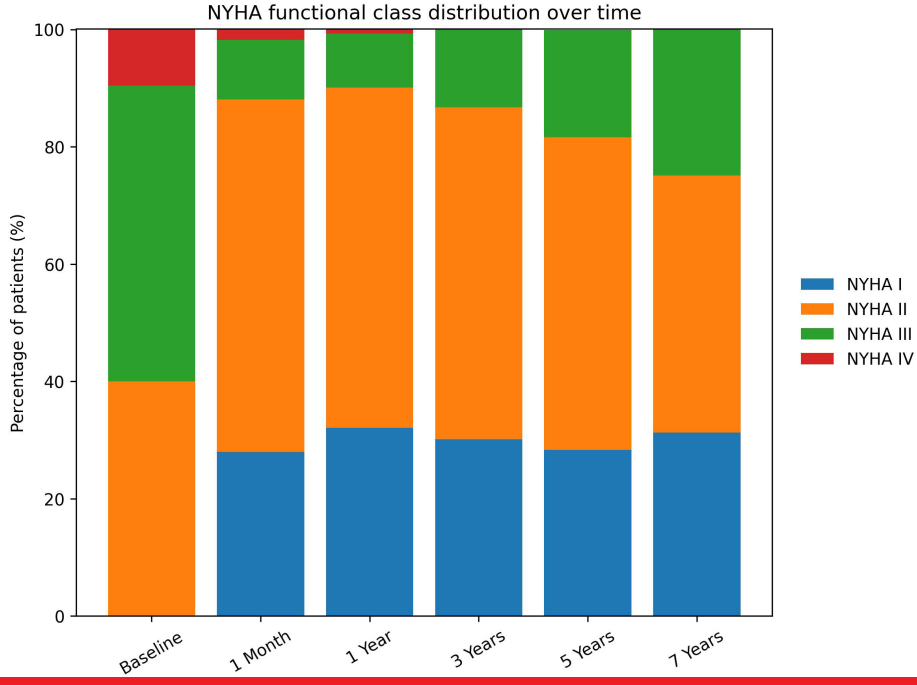
In multivariable Cox proportional hazards analysis, Katz index (HR 0.698, 95% CI 0.594–0.821, $p < 0.001$) and higher body mass index (HR 0.959, 95% CI 0.933–0.986, $p = 0.003$) were inversely associated with 7-year all-cause mortality. eGFR <30 mL/min/1.73 m^2 was also associated with increased mortality risk (HR 1.737, 95% CI 1.127–2.678, $p = 0.012$); however, this finding should be interpreted cautiously because the proportional hazards assumption was not fully satisfied for this variable‡.

‡ Proportional hazards assumption testing identified time-varying effects for diabetes mellitus and eGFR <30 mL/min/1.73 m^2, suggesting that their impact on mortality may vary over time.

AS, aortic stenosis; BMI, body mass index; CABG, coronary artery bypass grafting; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; STS, Society of Thoracic Surgeons.



Supplementary Figure 1. Change in estimated marginal mean left ventricular ejection fraction during follow-up after transcatheter aortic valve implantation.



Supplementary Figure 2. Distribution of New York Heart Association (NYHA) functional class at baseline and during follow-up.

Supplementary Table 2. Baseline Characteristics of 7-Year Survivors According to Availability of Late Echocardiographic Follow-Up

Variables	With echocardiographic follow-up (n = 61)	Without echocardiographic follow-up (n = 19)	*P*
Baseline demographics			
Age, years	79.8 ± 7.5	81.1 ± 7.3	0.555
Female sex, n (%)	47 (77.0%)	14 (73.7%)	0.751
Body mass index, kg/m^2	32.5 ± 8.0	30.2 ± 5.5	0.482
Risk stratification			
STS score, %	6.9 ± 2.5	6.5 ± 2.8	0.460
EuroSCORE II, %	8.7 ± 2.4	8.1 ± 3.7	0.197
Katz index	4.8 ± 1.0	5.2 ± 0.8	0.082
Comorbidities			
Diabetes mellitus, n (%)	3 (4.9%)	2 (10.5%)	0.421
Arterial hypertension, n (%)	49 (80.3%)	16 (84.2%)	0.678
COPD, n (%)	21 (34.4%)	4 (21.1%)	0.264
Atrial fibrillation, n (%)	7 (11.5%)	2 (10.5%)	0.913
Low-flow low-gradient AS, n (%)	3 (4.9%)	4 (21.1%)	0.141
Baseline echocardiographic parameters			
LVEF, %	51.8 ± 12.7	55.0 ± 9.6	0.410

Data are presented as mean ± standard deviation or n (%). Comparisons between groups were performed using the Mann-Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical variables. No statistically significant differences were observed between patients with and without late echocardiographic follow-up for any baseline characteristic examined.
AS, aortic stenosis; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; STS, Society of Thoracic Surgeons.