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European Experience With the Second-Generation Edwards SAPIEN XT Transcatheter Heart Valve in Patients With Severe Aortic Stenosis

1-Year Outcomes From the SOURCE XT Registry

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ABSTRACT

OBJECTIVES The SOURCE XT Registry (Edwards SAPIEN XT Aortic Bioprosthesis Multi-Region Outcome Registry) assessed the use and clinical outcomes with the SAPIEN XT (Edwards Lifesciences, Irvine, California) valve in the real-world setting.

BACKGROUND Transcatheter aortic valve replacement is an established treatment for high-risk/inoperable patients with severe aortic stenosis. The SAPIEN XT is a balloon-expandable valve with enhanced features allowing delivery via a lower profile sheath.

METHODS The SOURCE XT Registry is a prospective, multicenter, post-approval study. Data from 2,688 patients at 99 sites were analyzed. The main outcome measures were all-cause mortality, stroke, major vascular complications, bleeding, and pacemaker implantations at 30-days and 1 year post-procedure.

RESULTS The mean age was 81.4 ± 6.6 years, 42.3% were male, and the mean logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation) was 20.4 ± 12.4%. Patients had a high burden of coronary disease (44.2%), diabetes (29.4%), renal insufficiency (28.9%), atrial fibrillation (25.6%), and peripheral vascular disease (21.2%). Survival was 93.7% at 30 days and 80.6% at 1 year. At 30-day follow-up, the stroke rate was 3.6%, the rate of major vascular complications was 6.5%, the rate of life-threatening bleeding was 5.5%, the rate of new pacemakers was 9.5%, and the rate of moderate/severe paravalvular leak was 5.5%. Multivariable analysis identified nontransfemoral approach (hazard ratio [HR]: 1.84; $p < 0.0001$), renal insufficiency (HR: 1.53; $p < 0.0001$), liver disease (HR: 1.67; $p = 0.0453$), moderate/severe tricuspid regurgitation (HR: 1.47; $p = 0.0019$), porcelain aorta (HR: 1.47; $p = 0.0352$), and atrial fibrillation (HR: 1.41; $p = 0.0014$), with the highest HRs for 1-year mortality. Major vascular complications and major/life-threatening bleeding were the most frequently seen complications associated with a significant increase in 1-year mortality.

CONCLUSIONS The SOURCE XT Registry demonstrated appropriate use of the SAPIEN XT THV in the first year post-commercialization in Europe. The safety profile is sustained, and clinical benefits have been established in the real-world setting. (SOURCE XT Registry; NCT01238497) (J Am Coll Cardiol Intv 2015;8:657–69) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

EOA = effective orifice area

EuroSCORE = European System for Cardiac Operative Risk Evaluation

NYHA = New York Heart Association

PVL = paravalvular leak

TA = transapical

TAVR = transcatheter aortic valve replacement

TF = transfemoral

THV = transcatheter heart valve

Transcatheter aortic valve replacement (TAVR) has revolutionized the treatment of severe degenerative aortic stenosis in elderly patients and has become a routine procedure in more than 40 countries around the world (1,2). The first-generation balloon-expandable SAPIEN transcatheter heart valve (THV) (Edwards Lifesciences, Irvine, California) was fully approved for commercial use via the transfemoral (TF) or transapical (TA) approach in the European Union and United States in January 2008 and October 2012, respectively. The safety profile and clinical benefits of the SAPIEN valve were demonstrated in the SOURCE Registry (3,4). The second-generation SAPIEN XT valve incorporated technological developments, including a cobalt-chromium stent and a lower profile delivery system. Following CE mark approval of the SAPIEN XT valve, the SOURCE XT Registry (Edwards SAPIEN XT Aortic Bioprosthesis Multi-Region Outcome Registry) was initiated to study the pattern of use during the first years of commercialization, as TAVR moved beyond the clinical trial care and evolved to a routine treatment. The SOURCE XT Registry was designed to further assess safety and efficacy of the SAPIEN XT valve according to the newly developed Valve Academic Research Consortium definitions (5). This paper describes the baseline risk factors in the patient population undergoing TAVR with the balloon-expandable valve and the clinical outcomes at 30 days and 1 year after implantation of the SAPIEN XT valve in a real-world setting.

METHODS

REGISTRY. The SOURCE XT study is a multicenter, prospective, consecutively enrolled, observational registry (Online Appendix). Data for all patients consecutively treated with the commercially available SAPIEN XT valve at 99 sites in 17 countries were used for this analysis. Patients treated with other valves were not included. One site, which enrolled 6 patients, was excluded for noncompliance with regulatory requirements. Additionally, 9 patients from participating sites were excluded for not providing an informed consent form. From a total of 2,706 consented patients enrolled between July 2010 and November 2011, no procedure was attempted in 18 patients; therefore, 2,688 patients remained in the final cohort and were included in this analysis (**Figure 1**). Patient data were collected at discharge, 30 days, and 12 months post-implantation.

DEVICES AND PROCEDURE. The SAPIEN XT valve is composed of a nickel-cobalt chromium stent frame, a trileaflet bovine pericardial tissue valve, and a polyethylene-terephthalate fabric skirt. The valve was available in sizes of 23 and 26 mm for all delivery approaches. The 29-mm valve was available for the TA approach only. The NovaFlex delivery system (Edwards Lifesciences), which includes an integrated distal tip and a lower crossing profile, was used for the TF approach with 18-F (23-mm valve) or 19-F (26-mm valve) introducer sheaths. The Ascendra delivery system (Edwards Lifesciences) was used for the transapical access.

PATIENT SELECTION. High surgical risk patients with severe symptomatic aortic stenosis, were deemed eligible for the procedure. Logistic EuroSCORE I (European System for Cardiac Operative Risk Evaluation) was used as a general tool for a risk assessment; however, the final decision was made by the heart team, considering all underlying conditions. Examinations were on the basis of standards of care for TAVR at each participating site. Annulus diameter was measured by computed tomography scans or transthoracic and/or transesophageal echocardiography; however, only transthoracic echocardiographic data were required.

DATA COLLECTION. All data were entered in the electronic data capture system and monitored. All adverse events were adjudicated according to

The SOURCE XT Registry was funded by Edwards Lifesciences. Dr. Schymik is a proctor for and has received speaker honoraria from Edwards Lifesciences. Dr. Lefèvre is a proctor for Edwards Lifesciences; and has received minor fees from Symetis, Medtronic, and Direct Flow Medical. Dr. Vahanian has received speaker honoraria from Edwards Lifesciences and Abbott; and is on the advisory board of Valtech. Dr. Treede is a proctor and consultant for Edwards Lifesciences. Dr. Mandinov was a full-time employee of Edwards Lifesciences. Dr. Wendler is a proctor for and has received speaker fees from Edwards Lifesciences. Dr. Baumgartner is a consultant and proctor for Edwards Lifesciences; and has received speaker fees and travel support from Edwards Lifesciences, Abbott, Medtronic, St. Jude Medical, Gore, and Direct Flow Medical. Dr. Thomas is a consultant for Edwards Lifesciences. Dr. Urban has received honoraria from Edwards Lifesciences. Dr. Windecker has received institutional research grants from Biotronik and St. Jude Medical; and speaker fees from AstraZeneca, Eli Lilly, and Abbott. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Valve Academic Research Consortium criteria by an independent clinical events committee. All data used in the analysis are as of June 21, 2013.

ENDPOINT DEFINITIONS. All study endpoints were defined per the Valve Academic Research Consortium 1 (5). The principal outcome measures in the SOURCE XT Registry are all-cause death, cardiac death, and stroke. Secondary measures include major vascular complications, major and life-threatening bleeding, acute kidney injury, permanent pacemaker insertion, procedure- and device-related complications, functional status, and echocardiographic assessment of the valve and heart function. No echocardiography core laboratory was used; therefore, all echocardiographic data were site reported. Procedural success was defined as 1 valve implanted at the intended site by 1 attempted procedure and no procedure-related death within 48 h from implantation. Device success was further defined as a successfully delivered valve with gradient ≤20 mm Hg and no moderate or severe aortic regurgitation at discharge. A patient was considered frail if any of the following conditions were met: 1) 15-ft walk time ≥6 s; 2) grip strength <16 kg; 3) Katz index ≤4.

STATISTICAL ANALYSIS. Continuous variables were presented as mean ± SD and comparisons were performed with the 2-sample Student *t* test. Categorical data were presented as percents and comparisons between groups done by the Fisher exact or chi-square test. Paired comparisons of continuous and categorical variables were done by the paired Student *t* test and the McNemar test, respectively.

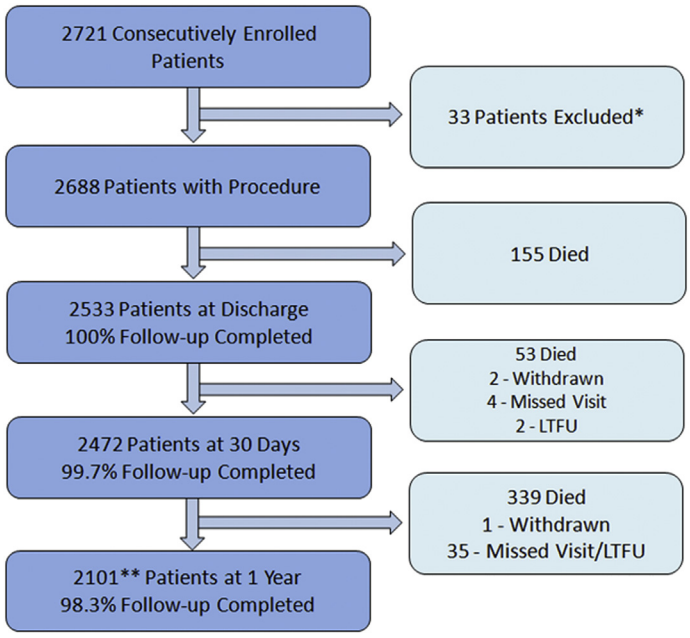
Survival analysis was performed by Kaplan-Meier method. Survival curves for time-to-event variables were constructed with the use of Kaplan-Meier estimates and were compared using the log-rank test.

Univariable Cox proportional hazard regression was performed to determine baseline and procedural predictors of 1-year mortality. All independent predictors with a p value <0.1 were entered in the multivariable model with stepwise procedure. The significance level for entry/exit was set at 0.10.

Differences were considered statistically significant when the p value was <0.05. All statistical analyses were performed with the use of SAS software, version 9.3 (SAS Institute, Cary, North Carolina).

The corresponding authors had full access to the reported data and takes responsibility for the integrity of the data presented. All authors have read and agreed to the paper as written.

FIGURE 1 Patient Disposition to 1-Year Follow-Up



Cascade diagram showing patient disposition from enrollment to procedure and at each follow-up interval to 1 year. *Reasons for exclusion: no informed consent, site noncompliance, and no procedure performed. **4 patients who missed 30-day visit were reached at 1-year follow-up. LTFU = lost to follow-up.

RESULTS

BASELINE CHARACTERISTICS AND RISK ASSESSMENT. The baseline characteristics are presented in Table 1. The mean age was 81.4 ± 6.6 years, more patients were female, and the majority of patients had severe functional limitations. Severe aortic stenosis was evident with a mean gradient of 47.6 ± 16.2 mm Hg and mean effective orifice area (EOA) of 0.7 ± 0.2 cm^2. Severe pulmonary hypertension was present in 25.5% of patients, moderate/severe tricuspid regurgitation in 14.1%, and moderate/severe mitral regurgitation in 19.8%. Patients had a high burden of coronary artery disease, atrial fibrillation, diabetes, peripheral vascular disease, and renal insufficiency. This resulted in a mean logistic EuroSCORE of 20.4 ± 12.4% (median, 17.6%; interquartile range, 11.4% to 27.0%), indicating significant surgical risk. Additional markers of increased risk of surgery were common: 83.5% of patients were frail, 6.5% had a porcelain aorta, 2.9% had severe liver disease, 1.6% had oxygen-dependent pulmonary disease, and 3.9% had a left ventricular ejection fraction of ≤30%. The vast majority of

TABLE 1 Baseline Patient Characteristics

	All Patients (N = 2,688)	Transfemoral (n = 1,685)	Transapical (n = 894)	p Value
Age, yrs	81.4 ± 6.6	82.0 ± 6.5	80.1 ± 6.4	<0.0001
Female	1,550/2,688 (57.7)	1,085/1,685 (64.4)	408/894 (45.6)	<0.0001
Logistic EuroSCORE, %	2,676, 20.4 ± 12.4	1,682, 19.8 ± 11.6	887, 21.9 ± 13.7	<0.0001
STS score, %	2,377, 7.9 ± 6.6	1436, 8.0 ± 6.8	841, 7.9 ± 6.3	0.8300
NYHA functional class				
I/II	619/2,676 (23.1)	377/1,676 (22.5)	211/891 (23.7)	0.5213
III/IV	2,057/2,676 (76.9)	1,299/1,676 (77.5)	680/891 (76.3)	
Angina CCS classes II–IV	588/2,663 (22.1)	389/1,668 (20.9)	226/887 (25.4)	0.0018
CAD	1,188/2,688 (44.2)	667/1,685 (39.6)	456/894 (51.0)	<0.0001
MI	406/2,688 (15.1)	205/1,685 (12.2)	187/894 (20.9)	<0.0001
Previous PCI	819/2,688 (30.5)	460/1,685 (27.3)	331/894 (37.0)	<0.0001
CABG	431/2,688 (16.0)	204/1,685 (12.1)	218/894 (24.4)	<0.0001
Hyperlipidemia	1,507/2,688 (56.1)	902/1,685 (53.5)	542/894 (60.6)	0.0006
Hypertension	2,175/2,688 (80.9)	1,332/1,685 (79.1)	767/894 (85.8)	<0.0001
Atrial fibrillation	685/2,676 (25.6)	395/1,678 (23.5)	271/889 (30.5)	0.0002
Pacemaker/ICD implantation	304/2,688 (11.3)	170/1,685 (10.1)	119/894 (13.3)	0.0152
Peripheral vascular disease	569/2,687 (21.2)	248/1,684 (14.7)	295/894 (33.0)	<0.0001
Previous peripheral intervention	65/2,687 (2.4)	20/1,684 (1.2)	43/894 (4.8)	<0.0001
Porcelain aorta	174/2,687 (6.5)	71/1,684 (4.2)	98/894 (11.0)	<0.0001
Pulmonary artery pressure ≥55 mm Hg	481/1,884 (25.5)	326/1,218 (26.8)	141/588 (24.0)	0.2078
COPD	546/2,687 (20.3)	327/1,684 (19.4)	202/894 (22.6)	0.0582
Pulmonary disease, oxygen dependent	43/2,687 (1.6)	31/1,684 (1.8)	9/894 (1.0)	0.1311
Diabetes	791/2,688 (29.4)	452/1,685 (26.8)	304/894 (34.0)	0.0002
Stroke	225/2,688 (8.4)	123/1,685 (7.3)	94/894 (10.5)	0.0058
TIA	120/2,687 (4.5)	76/1,684 (4.5)	40/894 (4.5)	>0.9999
Chest deformities	24/2,687 (0.9)	18/1,684 (1.1)	4/894 (0.4)	0.1186
Liver disease	79/2,688 (2.9)	52/1,685 (3.1)	25/894 (2.8)	0.7171
Renal insufficiency/failure or dialysis	777/2,687 (28.9)	432/1,684 (25.7)	327/894 (36.6)	<0.0001
Endocarditis	30/2,688 (1.1)	19/1,685 (1.1)	10/894 (1.1)	>0.9999
Cancer	480/2,688 (17.9)	300/1,685 (17.8)	153/894 (17.1)	0.7035
Frail conditions				
Katz Index ≤4	427/2,115 (20.2)	258/1,292 (20.0)	161/724 (22.2)	0.2301
Grip strength <16 kg	407/1,649 (24.7)	269/977 (27.5)	116/580 (20.0)	0.0008
15-ft walk time ≥6 s	1,008/1,351 (74.6)	613/802 (76.4)	340/ 474 (71.7)	0.0626
Frail	1,365/1,634 (83.5)	844/985 (85.7)	457/566 (80.7)	0.0120
Echocardiographic data				
Mean gradient, mm Hg	2,503, 47.6 ± 16.2	1,580, 49.2 ± 16.5	821, 45.0 ± 15.5	<0.0001
EOA, cm^2	2,253, 0.7 ± 0.2	1,402, 0.7 ± 0.2	751, 0.7 ± 0.2	<0.0001
Pulmonary artery pressure, mm Hg	1,884, 44.9 ± 14.9	1,218, 46.0 ± 14.8	588, 43.1 ± 15.3	0.0001
LVEF, %	2,536, 54.4 ± 12.5	1,594, 55.1 ± 12.5	837, 53.3 ± 12.3	0.0008
LVEF <30%	100/2,536 (3.9)	57/1,594 (3.6)	32/837 (3.8)	0.3080
Moderate/severe mitral regurgitation	519/2,615 (19.8)	345/1,633 (21.1)	161/880 (18.3)	0.0953
Moderate/severe tricuspid regurgitation	343/2,432 (14.1)	232/1,512 (15.3)	109/827 (13.2)	0.1593

Values are mean ± SD; n/N (%); or n, mean ± SD.

CABG = coronary artery bypass graft; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; COPD = chronic obstructive pulmonary disease; EOA = effective orifice area; EuroSCORE = European System for Cardiac Operative Risk Evaluation; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons; TIA = transient ischemic attack.

patients had at least 1 of these risk factors. There were significant differences in baseline characteristics between patients undergoing TAVR via the TF and TA approaches. Overall, the patients who had the TA were at higher risk (Table 1).

PROCEDURE AND INDEX HOSPITALIZATION. Procedural data are summarized in Table 2. The implantation approach was TF in 62.7% and TA in 33.3%. Only a small proportion of patients were treated with the TAo or subclavian approach. In 24.3% of TF

TABLE 2 Procedural Data, Procedural Complications, and Index Hospitalization

	All Patients (N = 2,688)	Transfemoral (n = 1,685)	Transapical (n = 894)	p Value
Procedural data				
Implantation approach				
Transapical	894/2,688 (33.3)	–	894/2,688 (33.3)	
Transfemoral	1,685/2,688 (62.7)	1,685/2,688 (62.7)	–	
Subclavian	8/2,688 (0.3)	–	–	
Transaortic	101/2,688 (3.8)	–	–	
Procedure room				<0.0001
Cath lab	1,426/2,686 (53.1)	1,093/1,684 (64.9)	278/893 (31.1)	
Hybrid room	1,030/2,686 (38.3)	548/1,684 (32.5)	430/893 (48.2)	
Surgical OR	230/2,686 (8.6)	43/1,684 (2.6)	185/893 (20.7)	
Type of anesthesia				<0.0001
General	1,801/2,501 (72.0)	848/1,536 (55.2)	850/861 (98.7)	
Conscious sedation/local/regional	700/2,501 (28.0)	688/1,536 (44.8)	11/861 (1.3)	
Pre-implantation BAV	2,599/2,685 (96.8)	1,659/1,685 (98.5)	832/891 (93.4)	<0.0001
No. of balloon inflations	1.2 ± 0.5	1619, 1.2 ± 0.6	801, 1.1 ± 0.4	<0.0001
None	23/2,528 (0.9)	12/1,619 (0.7)	10/801 (1.2)	
1	2,198/2,528 (86.9)	1,358/1,619 (83.9)	735/801 (91.8)	
≥2	307/2,528 (12.1)	249/1,619 (15.4)	56/801 (7.0)	
Valve size, mm				<0.0001
23	1135/2,675 (42.4)	801/1680 (47.7)	300/886 (33.9)	
26	1305/2,675 (48.8)	879/1680 (52.3)	374/886 (42.2)	
29	235/2,675 (8.8)	0/1,680 (0.0)	212/886 (23.9)	
Post-deployment balloon dilations				<0.0001
None	2114/2,674 (79.1)	1,400/1,675 (83.6)	650/890 (73.0)	
1	510/2,674 (19.1)	254/1,675 (15.2)	211/890 (23.7)	
≥2	50/2,674 (1.9)	21/1,675 (1.3)	29/890 (3.3)	
Total procedure time, min	2,652, 84.0 ± 54.9	1,655, 79.3 ± 51.9	888, 89.3 ± 56.9	<0.0001
Fluoroscopy time, min	2,613, 12.0 ± 20.2	1,640, 14.8 ± 20.7	865, 7.3 ± 19.3	<0.0001
Volume of contrast used, ml	2,642, 123.8 ± 98.2	1,659, 141.2 ± 103.5	875, 93.4 ± 81.3	<0.0001
Valve not implanted	22/2,687 (0.8)	10/1,685 (0.6)	12/893 (1.3)	0.0692
Procedural success	2,567/2,688 (95.5)	1,624/1,685 (96.4)	844/894 (94.4)	0.0244
Device success	1,862/2,105 (88.5)	1,241/1,443 (86.0)	544/644 (84.5)	0.3813
Procedural complications				
Procedure-related death	53/2,688 (2.0)	26/1,685 (1.5)	22/894 (2.5)	0.1248
Procedure-related stroke	54/2,688 (2.0)	38/1,685 (2.3)	15/894 (1.7)	0.3826
Annulus rupture or dissection	11/2,688 (0.4)	8/1,685 (0.5)	1/894 (0.1)	0.1757
Aortic dissection	14/2,688 (0.5)	8/1,685 (0.5)	1/894 (0.1)	0.1757
Cardiac tamponade	24/2,688 (0.9)	20/1,685 (1.2)	3/894 (0.3)	0.0280
Pericardial effusion	34/2,688 (1.3)	24/1,685 (1.4)	9/894 (1.0)	0.4627
Coronary occlusion	12/2,688 (0.4)	6/1,685 (0.4)	4/894 (0.4)	0.7456
Mitral valve injury	8/2,688 (0.3)	2/1,685 (0.1)	6/894 (0.7)	0.0239
Conversion to conventional surgery	11/2,688 (0.4)	5/1,684 (0.3)	5/893 (0.6)	0.3296
New permanent pacemaker	162/2,688 (6.0)	96/1,685 (5.7)	64/894 (7.2)	0.1456
New-onset atrial fibrillation (at discharge)	121/2,459 (4.9%)	51/1,618 (3.2%)	70/841 (8.3%)	<0.0001

Values are n/N (%); mean ± SD; n, mean ± SD; or n (%).
BAV = bicuspid aortic valve; OR = operating room.

patients, access was achieved by surgical cut-down, whereas in 75.7%, the access was percutaneous. In 47.9% of TF patients, the vessel diameter was ≤7 mm (mean, 7.6 ± 1.3 mm). Pre-implantation balloon aortic valvuloplasty, usually with 1 balloon inflation, was performed in the vast majority of patients. Only a small proportion of patients were implanted with the 29-mm valve, as it was initially available for the TA approach only. Balloon post-deployment dilation was performed in 20.9%. Valve position was correct at the intended site in 97.1%, and technical success was 95.5%.

The mean duration of hospitalization for the index procedure was 11.1 ± 9.2 days. The majority of time was spent in a general ward (8.4 ± 6.2 days), and fewer days were spent in an intensive care/intermediate care unit (5.3 ± 6.8 days). Compared with the TF approach, the TA approach was characterized by fewer bicuspid aortic valve and more post-dilations, a longer procedure time, a shorter fluoroscopy time, and less use of contrast (Table 2).

PROCEDURAL COMPLICATIONS. The most frequently seen serious procedural complications within 48 h after valve implantation were major/life-threatening bleeding and vascular access-related complications (Table 2). All other severe complications were rare. The procedure-related mortality rate was 2.0%. The procedure-related stroke rate was observed in 2.0% of patients. Annulus rupture and coronary occlusion occurred in 0.4% each and cardiac tamponade in 0.9%. Valve embolization occurred in 0.7% (n = 18); one-half of all embolization's traveled to the aorta and the other half to the left ventricle. Valve-in-valve implantation due to procedural complication was needed in 29 patients (1.1%). Conversion to conventional surgery was required only in a few patients (0.4%). In general, the procedural complications were similar for the TF and TA approaches; however, mitral valve injury and atrial fibrillation occurred more frequently with the TA approach (Table 2).

CLINICAL OUTCOMES. At 30-days post-implantation, the overall mortality rate was 6.3% (4.2% TF/10.0% TA) and 3.6% had a stroke (Table 3). Major/life-threatening bleeding had occurred in 14.9%, major vascular complications in 6.5%, and acute kidney injury in 17.8%. Permanent pacemakers were implanted in 9.5% of patients.

At 1-year follow-up, an additional 2.7% had had a stroke, an additional 1.5% had a new pacemaker implanted, and an additional 13.1% of patients had died. Clinical outcomes with the TF and TA approaches are presented in Table 3. The TA approach was associated with higher mortality and significantly more bleeding and acute kidney injury, whereas the TF approach had a significantly higher rate of vascular complications.

There were a total of 515 deaths, 124 of which occurred within the first 14 days, 44 within 15 to 30 days, and 347 within 1 month to 1 year after TAVR. Congestive heart failure, multiple organ failure, and cardiac arrest were the leading causes of death within the first 30 days (17.3%, 15.5%, and 9.5%, respectively) and thereafter at 1 year (13.8%, 12.2%, and 8.6%, respectively).

PREDICTORS OF 1-YEAR MORTALITY. The 1-year Kaplan-Meier survival curves for the entire patient cohort and by approach are shown in Figures 2A and 2B, respectively. The relationship between logistic EuroSCORE and 1-year survival after TAVR was examined (Figure 2C). In patients with a EuroSCORE ≥15, the 1-year survival rate was significantly lower than in patients with a logistic EuroSCORE

TABLE 3 Clinical Outcomes at 30 Days and 1 Year After TAVR

	Kaplan-Meier Event Rate at 30 Days				Kaplan-Meier Event Rate at 1 Year			
Complication	All Patients (N = 2,688)	Transfemoral (n = 1,685)	Transapical (n = 894)	p Value	All Patients (N = 2,688)	Transfemoral (n = 1,685)	Transapical (n = 894)	p Value
All-cause death	6.3	4.2	10.0	<0.0001	19.4	15.0	27.1	<0.0001
Cardiac death	3.0	1.7	5.7	<0.0001	9.5	6.7	14.7	<0.0001
Stroke	3.6	3.4	4.2	0.3290	6.3	5.6	7.9	0.0473
All vascular complications	15.8	21.2	5.7	<0.0001	17.1	22.0	8.2	<0.0001
Major	6.5	7.9	3.5	<0.0001	7.2	8.3	4.6	0.0003
All bleeding	19.7	15.1	27.0	<0.0001	22.9	18.2	30.3	<0.0001
Life-threatening	5.5	3.8	8.3	<0.0001	6.7	4.5	10.1	<0.0001
Major	10.2	7.7	13.9	<0.0001	12.0	9.2	16.2	<0.0001
Major/life-threatening	14.9	10.9	20.9	<0.0001	17.2	13.0	23.6	<0.0001
Myocardial infarction	0.6	0.4	1.1	0.0630	1.8	1.5	2.6	0.0510
Acute kidney injury	17.8	11.9	28.1	<0.0001	20.6	14.7	31.0	<0.0001
Rehospitalizations	6.4	4.9	8.9	<0.0001	29.5	25.5	36.8	<0.0001
Endocarditis	0.2	0.1	0.2	0.4910	1.1	1.0	1.4	0.4085
New permanent pacemaker	9.5	8.7	11.6	0.0212	11.0	10.0	13.4	0.0121
New-onset atrial fibrillation	5.3	3.3	8.9	<0.0001	7.9	5.6	12.5	<0.0001

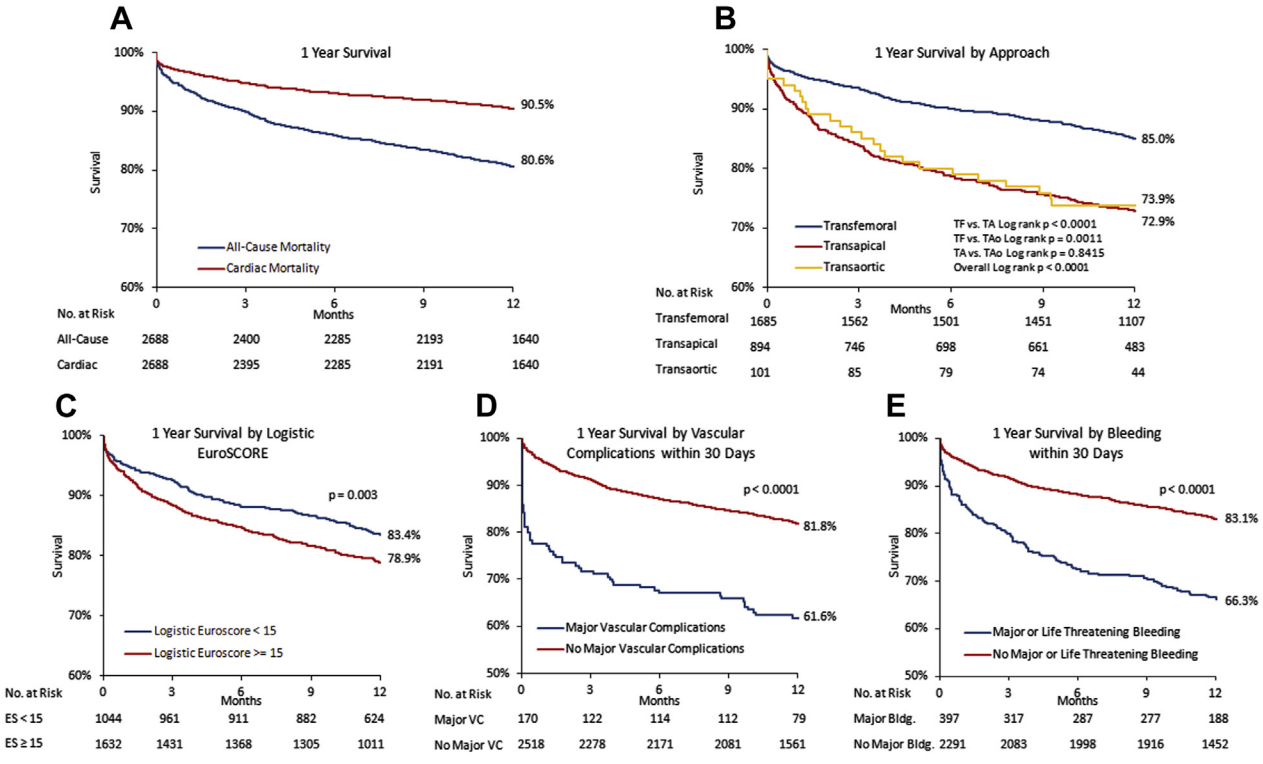
Values are % unless otherwise indicated.
TAVR = transcatheter aortic valve replacement.

<15 (78.9% vs. 83.4%; p = 0.003). The 1-year survival rate for the TF patients (85.0%) was significantly better than for the TA (72.9%; p < 0.0001) and transaortic (73.9%; p = 0.0011) patients. The most frequent TAVR complications (major vascular complications and major/life-threatening bleeding) were undesirably associated with the 1-year survival (Figures 2D and 2E). Although patients with no major vascular complications had an 81.8% survival rate at 1 year, those with major vascular complications had a significantly lower chance to survive (61.6%; p < 0.0001). Similarly, patients with major/life-threatening bleeding had significantly worse 1-year survival rates compared with those with no major/life-threatening bleeding (66.3% vs. 83.1%; p < 0.0001).

Univariate predictors of 1-year mortality are shown in Table 4, and the multivariate predictors are presented in Figure 3. Non-TF access was a significant predictor of mortality. Baseline liver disease and renal insufficiency/failure were associated with the highest risk (>50%) of mortality. Cardiovascular conditions such as moderate/severe tricuspid regurgitation, porcelain aorta, atrial fibrillation, coronary artery disease, and New York Heart Association (NYHA) functional class III/IV increased the risk of death to between 20% and 50%. Cancer and chronic obstructive pulmonary disease increased the risk of 1 year mortality by 33% and 31%, respectively. Age, logistic EuroSCORE, lower mean gradient, and body mass index were significant multivariate predictors of 1-year mortality. However, they individually only increased the risk by <5%.

FUNCTIONAL CLASS, SYMPTOMS, AND QUALITY OF LIFE. At baseline, the majority of patients were in NYHA functional class III or IV; however, at 30-day and 1-year follow-up, the majority of the patients showed significant improvement and were in NYHA functional class I or II (Figure 4A, all patients). Using paired comparisons, the proportion of patients with

FIGURE 2 Kaplan-Meier Survival Analyses at 1 Year



(A) Overall/cardiac survival for all SOURCE XT patients. **(B)** Overall survival: transfemoral (TF), transapical (TA), and transaortic (Tao) access. **(C)** Overall survival logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation [ES]) <15 and ≥15. **(D)** Overall survival: major vascular complications (VC) within 30 days. **(E)** Overall survival: major/life-threatening bleeding (Bldg.) within 30 days.

TABLE 4 Univariable Proportional Hazard Regression for 1-Year Mortality

Significant Predictors	N	HR (95% CI)	p Value
Baseline factors			
Logistic EuroSCORE, %	2,676	1.0228 (1.0166–1.0290)	<0.0001
Renal insufficiency/failure	2,687	1.6798 (1.4070–2.0056)	<0.0001
Worse Katz Index	2,115	1.1750 (1.1095–1.2444)	<0.0001
Atrial fibrillation	2,676	1.6541 (1.3793–1.9836)	<0.0001
Tricuspid regurgitation (moderate/severe)	2,432	1.7359 (1.3904–2.1672)	<0.0001
BMI	2,684	0.9581 (0.9399–0.9766)	<0.0001
Mean gradient	2,503	0.9873 (0.9815–0.9932)	<0.0001
Coronary artery disease	2,688	1.3919 (1.1710–1.6545)	0.0002
Pulmonary disease/COPD	2,687	1.4292 (1.1732–1.7410)	0.0004
NYHA functional class III/IV	2,676	1.5032 (1.1963–1.8889)	0.0005
LVEF, %	2,536	0.9881 (0.9813–0.9950)	0.0007
Previous myocardial infarction	2,688	1.4001 (1.1246–1.7431)	0.0026
Peripheral vascular disease	2,687	1.3201 (1.0826–1.6096)	0.0061
Female	2,688	0.7965 (0.6701–0.9469)	0.0099
Liver disease	2,688	1.6854 (1.1188–2.5389)	0.0125
Mitral regurgitation (moderate/severe)	2,615	1.2972 (1.0550–1.5950)	0.0136
Age, yrs	2,688	1.0162 (1.0021–1.0304)	0.0238
Pacemaker/ICD implanted	2,688	1.3171 (1.0267–1.6895)	0.0302
Pulmonary hypertension	2,687	1.2203 (1.0055–1.4812)	0.0439
Cancer	2,688	1.2168 (0.9835–1.5055)	0.0708
Porcelain aorta	2,687	1.3099 (0.9555–1.7958)	0.0935
Previous PCI	2,688	1.1342 (0.9436–1.3633)	0.1796
Previous stroke	2,688	1.2152 (0.9101–1.6226)	0.1864
Diabetes	2,688	1.1308 (0.9394–1.3611)	0.1938
Hypoalbuminemia	2,688	0.8529 (0.4693–1.5501)	0.6017
Hypertension	2,688	1.0537 (0.8433–1.3165)	0.6454
CABG	2,688	1.0323 (0.8171–1.3041)	0.7900
Syncope	2,686	1.0186 (0.7963–1.3029)	0.8835
Procedural factors			
Delivery approach (non-TF)	2,688	1.9790 (1.6648–2.3526)	<0.0001
Procedure time	2,652	1.0042 (1.0027–1.0056)	<0.0001
Anesthesia (general vs. nongeneral)	2,501	0.6361 (0.5099–0.7935)	<0.0001
Procedure location (cath lab vs. noncath lab)	2,686	0.8073 (0.6792–0.9596)	0.0152
Annulus size	2,296	1.0351 (0.9919–1.0801)	0.1129
Pre-implantation BAV	2,685	0.7267 (0.4697–1.1243)	0.1517
Post-deployment BAV	2,674	1.1485 (0.9356–1.4097)	0.1856
Effective valve area	2,253	1.1134 (0.7262–1.7070)	0.6223

BMI = body mass index; CI = confidence interval; non-TF = nontransfemoral; other abbreviations as in Tables 1 and 2.

NYHA functional class III/IV decreased significantly at both baseline to 30 days (76.1% vs. 9.9%; $p < 0.0001$), and baseline to 1 year (75.3% vs. 9.7%; $p < 0.0001$). Improvement in NYHA functional class occurred primarily during the first 30 days post-valve implantation and remained unchanged between 30 days and 1 year. Symptoms of angina improved after TAVR (Figure 4B, all patients). In a paired analysis, the proportion of patients with angina Canadian Cardiovascular Society class II or higher was significantly reduced from baseline to 30 days (22.1% vs. 4.0%; $p < 0.001$), and from baseline to 1 year (21.8% vs. 2.8%; $p < 0.001$). This improvement was sustained between 30 days and 1 year (3.5% vs. 2.8%; $p = 0.1698$).

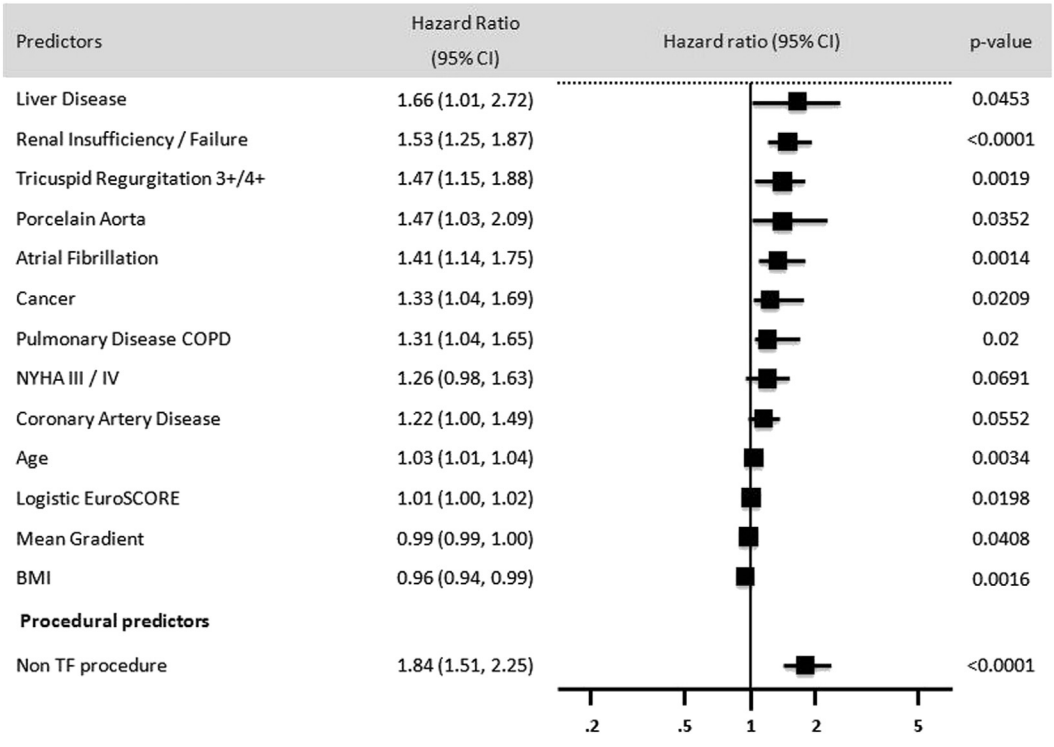
Quality of life improved continuously throughout the follow-up (Figure 4C, all patients). In a paired analysis, the improvement in the quality of life EQ-5D score was 12.4 ± 20.1 at discharge ($p < 0.0001$) and 17.8 ± 23.9 ($p < 0.0001$) at 30-day follow-up. The mean quality of life EQ-5D score increased 40% ($p < 0.0001$) at 1-year follow-up.

ECHOCARDIOGRAPHIC DATA. After SAPIEN XT valve implantation, there was immediate improvement in both mean gradient and EOA that was sustained throughout the follow-up (Figures 5A and 5B). The incidence of paravalvular leak (PVL) and total aortic regurgitation were very low throughout the entire follow-up (Figures 5C and 5D). PVL was assessed as none/trace in the majority of patients at discharge and throughout the follow up. Mild PVL occurred in one-fourth of patients. Only a small portion of patients (between 4.4% and 6.2%) had moderate or severe PVL throughout the follow-up, and only 0.2% of patients had severe PVL.

DISCUSSION

One of the major objectives of the SOURCE XT Registry was to evaluate the risk profile of patients undergoing SAPIEN XT implantation in a real-world setting, as TAVR matured from a study procedure in a limited number of well-selected study patients to a routine treatment available for a broader population. TAVR is emerging as a multidisciplinary field, and the heart team is essential to select the best treatment for patients with severe degenerative aortic stenosis (6). The logistic EuroSCORE and/or Society of Thoracic Surgeons score are still used for an initial risk assessment. However, both scoring systems were established as a mortality risk assessment for open cardiac surgery and were shown to be not well suited for TAVR (7–9). Despite these limitations, a logistic EuroSCORE >15% is still used as an indication for the SAPIEN XT valve, and the majority of the SOURCE XT patients met this criterion. Although this is a product-specific indication in the European Union, the European guidelines for TAVR do not require the use of the EuroSCORE in isolation, but emphasize the critical importance of the heart team evaluation for patient selection (6). Several important risk factors such as frailty, severe liver disease, porcelain aorta, and hostile chest, which are not considered in any risk score algorithm (10,11), were present in 95.8% of patients and were

FIGURE 3 Multivariate Predictors of 1-Year Mortality



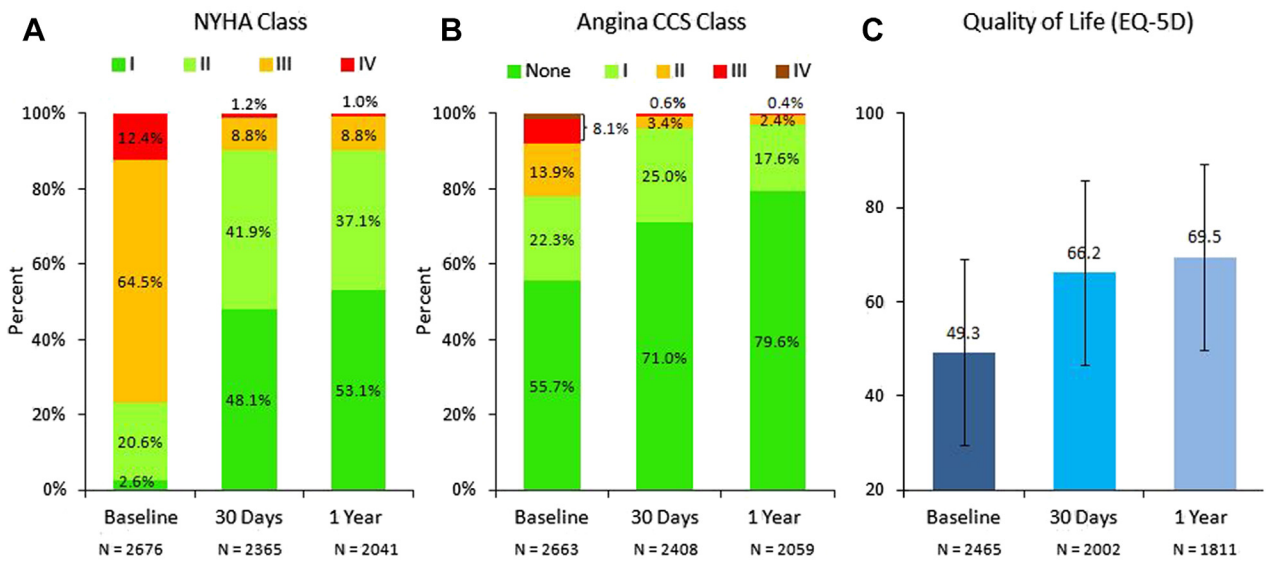
The forest plot shows the multivariable predictors of 1-year mortality with corresponding hazard ratios and p values. BMI = body mass index; CI = confidence interval; COPD = chronic obstruction pulmonary disease; NYHA = New York Heart Association; TF = transfemoral.

thoroughly examined by the heart teams during the patient selection process. This underscores the importance of incorporating the heart team concept, as described in the European Society of Cardiology/European Association for Cardiothoracic Surgery guidelines, especially when a TAVR-specific risk-assessment tool is not available (6). The SOURCE XT Registry was able to confirm the high-risk profile of patients treated with the SAPIEN XT valve (3). As noted previously, the TA patients were at higher surgical risk and presented with more risk factors and comorbidities.

TAVR was performed transfemorally in 62.7% and transapically in 33.3% of patients. Only a small proportion of patients were treated with TAo or subclavian approaches, which are considered emerging approaches for the balloon-expandable valves. The majority of patients received either the 23-mm or 26-mm valve, and <10% of patients were treated with the 29-mm valve. This imbalance in valve sizes was driven by 29-mm valve availability for TA use only later during the course of the SOURCE XT Registry. Balloon post-dilation was done in 20.9% of patients and this was significantly lower than the 41% published by Daneault et al. (12) for the SAPIEN valve in a single-center PARTNER (Placement of Aortic Transcatheter Valves Trial) experience. The rates of balloon post-dilation reported in the published data are between 5% and 41% (13,14), and it is commonly performed to better expand the stent of the THV and reduce the degree of PVL. However, post-dilation has been identified as an independent predictor of cerebrovascular events (15) and may be also associated with complications such as conduction disturbances, annulus rupture, and coronary occlusion (13,16). These risks may outweigh the benefits achieved by reduction in PVL, suggesting that PVL should be addressed by the improvement in valve design rather than through post-dilation. From this point of view, it was reassuring to see that in the SOURCE XT Registry, the rate of post-dilation was showing a downward trend.

TAVR was carried out successfully in the majority of patients, with a technical success rate

FIGURE 4 Clinical Symptom Improvement Throughout 1-Year Follow-up

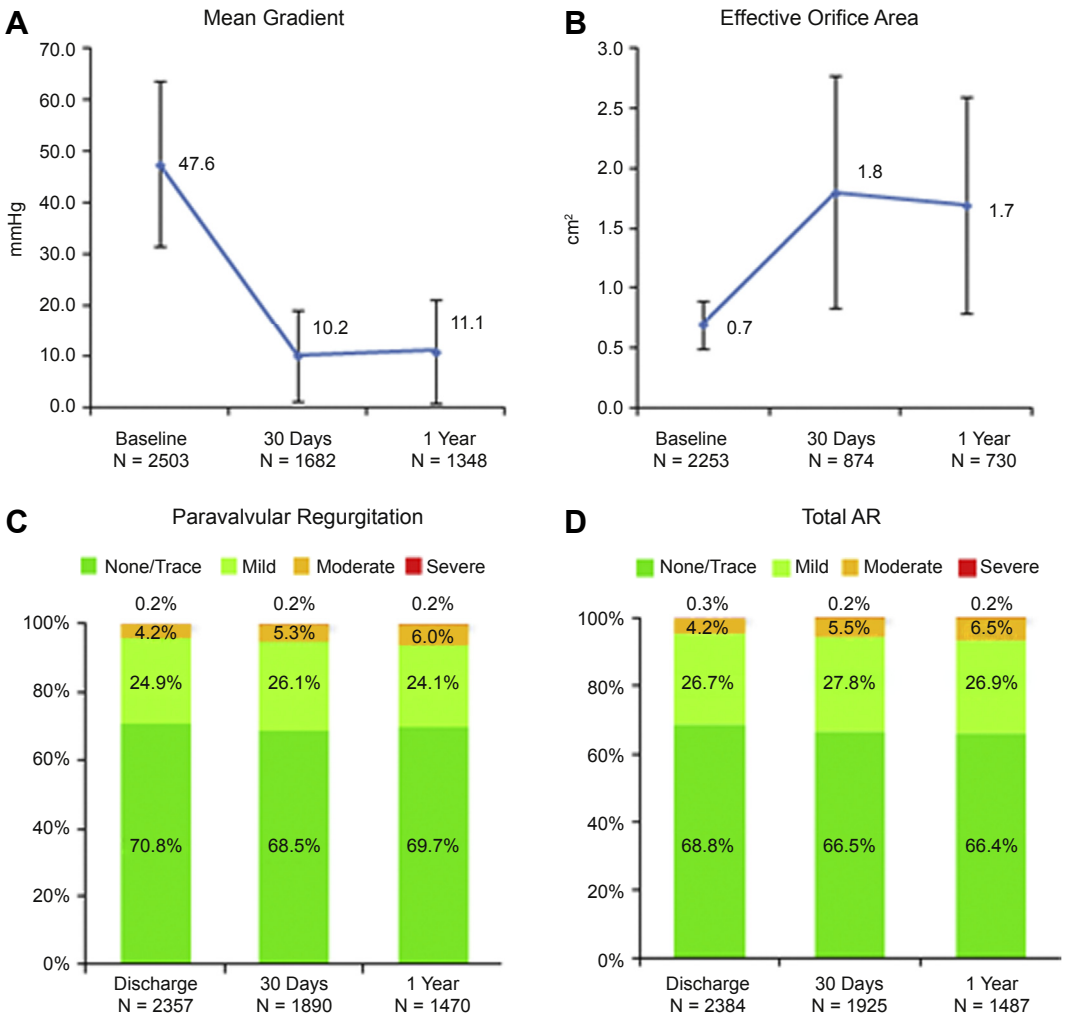


All SOURCE XT patients. Observations at baseline, 30 days, and 1 year. **(A)** New York Heart Association (NYHA) functional class. **(B)** Angina Canadian Cardiovascular Society (CCS) class. **(C)** Quality of life (EQ-5D) score.

of 95.5%. Conversion-to-conventional surgery and valve-in-valve implantation due to complications was needed in only a few patients. The need for emergent cardiac surgery in the SOURCE XT Registry was comparable to the 1.1% incidence reported by Eggebrecht et al. (17) in a meta-analysis on 9,251 patients. The 30-day all-cause mortality rate was 6.3% in the SOURCE XT Registry and 8.5% in the SOURCE Registry (3). The reduction in the mortality observed in the SOURCE XT registry may be associated with optimized patient selection, fewer baseline comorbidities, improved valve design, and increased learning experience of the operators. Similar trends were shown in other national registries (18-20). The FRANCE 2 Registry, which enrolled 3,195 patients between January 2010 and October 2011, reported a 30-day mortality rate of 9.7%, which was almost 50% higher than that in the SOURCE XT (18). The U.K. Transcatheter Aortic Valve Implantation Registry enrolled 870 patients between January 2007 and December 2009 and reported a 30-day mortality rate of 7.1% (19). The German Aortic Valve Registry enrolled 3,875 patients (2,694 TF patients, 1,181 TA patients) in 2011 and reported a 5.1% in-hospital mortality rate for the TF approach (20), which was slightly higher than the 4.2% 30-day mortality for the TF access in the SOURCE XT Registry.

The 1-year mortality rate of TF patients in the SOURCE XT Registry was 15% and is one of the lowest observed for any THV study in the real-world setting (4,18,19,21). As expected, the 1-year mortality rate for the TA approach was higher at 27.6% and can most likely be attributed to the higher baseline risk typically seen in this patient population (3). As also shown by the multivariate prediction model, liver disease and renal insufficiency/failure were the baseline characteristics with the highest increase in the risk of mortality, followed by moderate/severe tricuspid regurgitation, porcelain aorta, atrial fibrillation, coronary artery disease, and severe congestive heart failure symptoms (NYHA functional class III/IV). On the one hand, these results demonstrated the strong correlation between existing comorbidities and 1-year mortality after TAVR. On the other hand, this also emphasized the urgent need for the development of a reliable TAVR-specific risk-assessment algorithm that incorporates all the important baseline risk factors. Mortality after TAVR is not solely driven by the risk profile of the patients. As shown previously, the more frequently seen TAVR complications such as major vascular complications and major or life-threatening bleeding were associated with a higher mortality rate (4,22,23). These complications need to become a clear target for further improvement by better patient management and, more importantly, through an

FIGURE 5 Echocardiographic Data



All SOURCE XT patients: observations at baseline, 30 days, and 1 year. **(A)** Mean pressure gradient. **(B)** Effective orifice area. **(C)** Paravalvular leak. **(D)** Total aortic regurgitation (AR).

improved device design with smaller profile delivery systems.

The hemodynamic performance of the SAPIEN XT THV, measured by echocardiography at follow-up, demonstrated a significant and sustained decrease in the mean gradient and increase in the EOA. As in previous reports (24), there was no evidence of any structural valve deterioration with the SAPIEN XT THV, although longer follow-up is required to understand the valve durability. The occurrence of PVL represents a significant limitation of TAVR, particularly when expanding this treatment for intermediate-risk patients is contemplated (25). In the SOURCE XT Registry, PVL at 1 year was none/trace in the majority of patients (69.7%), mild in 24.1%, and moderate or severe in 6.2%. The PVL assessment in the SOURCE XT Registry was conducted by echocardiographers on-site rather than an echocardiography core laboratory. Given the lack of standardized methods to assess PVL even across echocardiography core laboratories, SOURCE XT offered a real-life assessment of this concerning issue with transcatheter valves. This registry confirmed the low rates of significant PVL with the SAPIEN XT valve and clearly demonstrated that it remained stable throughout follow-up. Although moderate/severe PVL affected only a small portion of the treated patients, its association with mortality warrants further

improvements through better patient selection, optimized implantation technique, and enhanced device design (25).

The SOURCE XT Registry has demonstrated a large treatment effect with use of the SAPIEN XT THV in patients with severe aortic stenosis. At 30 days post-implantation, NYHA functional class improved, angina symptoms decreased, and the quality of life EQ-5D score increased significantly. These changes remained sustained throughout the entire follow-up period.

STUDY LIMITATIONS. This study was an observational registry, and patients were selected to receive a SAPIEN XT valve by an approach on the basis of technical and clinical features. The primary reasons for the heart team to offer TAVR and not surgery and to select 1 delivery approach versus another remained unknown. Also, capturing health and functional status was limited and did not include all potentially important comorbidities, laboratory, and functional parameters. Although the transthoracic echocardiography-derived annulus diameter was reported, the actual imaging tool and the respective measures of the annulus diameter that were used for valve size selection were not reported. Finally, the echocardiographic data were site reported, and no echocardiography core laboratory was used.

CONCLUSIONS

The SOURCE XT Registry demonstrated appropriate use of the SAPIEN XT THV in the first year post-commercialization in Europe, where a comprehensive and collaborative program tailored to TAVR had been successfully established. The safety profile of the newer generation valve and the clinical benefits have been established in a real-world setting.

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PERSPECTIVES

WHAT IS KNOWN: In multiple randomized trials, TAVR has been proved to be a safe and effective treatment for high-risk and inoperable patients with severe degenerative aortic stenosis.

WHAT IS NEW: The SOURCE XT Registry is the largest multicenter all-comers TAVR registry with a second-generation balloon expandable transcatheter valve. Early and late clinical outcomes and survival showed that TAVR matured from a study procedure in a limited number of well-selected study patients to a routine treatment, available for a broader population of patients with aortic stenosis. The safety profile is sustained, and the clinical benefits of the second-generation balloon-expandable valve is established in a real-world setting. This study clearly demonstrated that design improvements along with the gained operator's experience can overcome some early safety concerns with the first-generation balloon expandable valve.

WHAT IS NEXT: Additional improvement in clinical outcomes related to vascular complications and paravalvular regurgitation may be achieved with further device iterations and can make TAVR a viable treatment option for a broader subset of patients with aortic stenosis and intermediate surgical risk.

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KEY WORDS aortic valve stenosis, minimally invasive, transapical, transcatheter, transfemoral

APPENDIX For a list of SOURCE XT participating centers and investigators, please see the online version of this article.