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FASTTRACK CLINICAL RESEARCH
TAVI

SOURCE 3: 1-year outcomes post-transcatheter aortic valve implantation using the latest generation of the balloon-expandable transcatheter heart valve

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Aims Transcatheter aortic valve implantation (TAVI) has developed from a procedure for patients with aortic stenosis inoperable or high risk for surgery, into a treatment option even for intermediate risk elderly patients. This development has been facilitated by the clinical learning curve and constant improvements of transcatheter heart valves used. We present total 1-year results of SOURCE 3, the European post-approval multicentre registry of the latest generation balloon expandable SAPIEN 3^{TM} (Edwards Lifesciences, Irvine, CA, USA).

Methods and results Participating centres have submitted their consecutive experience with the SAPIEN 3, dependent on patients consent. Data were prospectively collected and all end point-related outcomes adjudicated according to VARC-2 definitions by an independent committee. Between July 2014 and October 2015, in total 1946 patients (mean age 81.6 ± 6.7 years, 52% male) were enrolled in 80 centres from 10 European countries. At 1 year, all-cause mortality was 12.6%, cardiovascular mortality 8.0%, stroke 3.1%, disabling stroke 1.4%, and rate of new pacemakers 13.2%. Causes of death were 62.0% cardiovascular and 38.0% non-cardiovascular, with heart failure (13.4%) and pulmonary complications (12.7%) being the main reasons for fatal outcomes. Multivariable analysis identified New York Heart Association Class IV and renal insufficiency as predictors of mortality, while higher BMI's improved survival. Severe (zero) and moderate paravalvular leakage (2.6%) was rare at 1 year.

Conclusion In SOURCE 3, we observe a low complication rate and mortality at 1 year. Given the low incidence of higher degree paravalvular leakages, this variable did no longer affect outcome.
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Keywords Aortic stenosis • Transcatheter aortic valve implantation • Balloon expandable valve • SAPIEN 3 • Predictors of mortality • Causes of death

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Introduction

Over the last decade, transcatheter aortic valve implantation (TAVI) has progressed from being a procedure solely for inoperable and high-risk patients for surgical aortic valve replacement, to an alternative treatment option in elderly patients with even intermediate risk.[1] At its introduction, the key for success was to find technical solutions to perform the procedure safely. Nowadays, with the knowledge that specific post-operative events such as vascular complications and paravalvular leakage (PVL) affect short- and mid-term survival, the goal is also to reduce these events to make long-term outcomes predictable for individual patients.[1–3]

The most recent modifications to the 3rd-generation of the SAPIEN™ transcatheter heart valve (THV), the SAPIEN 3™ (both Edwards Lifesciences, Irvine, CA, USA), have been reported previously.[4] They have been developed to potentially improve implantation, facilitate transfemoral access, and reduce strokes, vascular complications and PVLs. Outcome in Europe using the SAPIEN 3 is currently assessed through the post-approval SOURCE 3 (SAPIEN 3 Aortic Bioprosthesis European Outcome) Registry, to observe safety and performance under 'real-world' conditions. While outcomes from registries usually have their own limitations and are seen to be inferior compared to randomized trials, they provide additional value in that they represent experience from what clinicians call the 'Real World'. Therefore, SOURCE 3 does not only provide information on how the 3rd-generation balloon-expandable valve performs but also makes it feasible to reflect on contemporary heart team decisions on TAVI strategies and their outcome in an all comers cohort of patients.

Thirty-day results of SOURCE 3 have recently been published and demonstrated high-procedural success with low risk of early complications and mortality.[5] Here we present the outcomes and predictors of the total 1-year results of the SOURCE 3 Registry.

Methods

Registry design and purpose of this report

SOURCE 3 is an European post-approval multicentre and observational registry, aimed to evaluate the safety and performance of the SAPIEN 3 THV in 'real-life' practice for 5 years, as previously described in detail.[5] It has been approved by the local ethics committees, and respective health authorities, if applicable of the participating countries, and all the patients who have provided written informed consent.

An independent clinical events committee (CEC) reviewed and adjudicated all key clinical events according to Valve Academic Research Consortium 2 (VARC-2) criteria (a list of CEC members is provided in Supplementary material online, *File S1*). Post-index procedure vascular complications, acute kidney injury, and bleeding were adjudicated up to 30 days. Other events, such as death, transient ischaemic attack, rehospitalization for valve-related symptoms or worsening congestive heart failure post-discharge, new conduction abnormalities and pacemakers, myocardial infarction, new onset of atrial fibrillation and other TAVI-related complications were adjudicated over 1 year.

Events of death were adjudicated by an independent CEC to determine if the cause was of cardiovascular or non-cardiovascular origin. All strokes were reviewed and characterized by an independent neurologist (see Supplementary material online, *File S1*) into disabling or non-disabling stroke.

Study population

Eighty centres in 10 European countries are registered in SOURCE 3 (centres listed in Supplementary material online, *File S2*). As per the indication for use and the ESC/EACTS guidelines,[6] patients for whom TAVI was deemed the best treatment option were selected on the basis of the clinical consensus of the 'Heart Team', a multidisciplinary team of cardiac surgeons, interventional cardiologists, anaesthetists, and imaging specialists. The appropriate size of SAPIEN 3 (23 mm, 26 mm, or 29 mm) was determined based on pre-procedural echocardiographic and/or computed tomographic findings. The devices were delivered via transfemoral (TF) or other alternative access approaches [non-transfemoral (Non-TF): i.e. transapical, transaortic, transsubclavian, or transcarotid], as described in detail previously.[5]

Intervention and purpose

Patients underwent echocardiographic measurements, electrocardiogram recordings and a global clinical status evaluation including New York Heart Association (NYHA) functional class assessment at baseline, discharge, 30-days and 1-year post-index procedure. Echocardiographic data presented were site reported. Electrocardiographic records were analysed by a cardiologist at each centre and conduction abnormalities assessed on the basis of VARC-2 definitions.

Transcatheter heart valve and delivery devices

All patients were treated using the SAPIEN 3 THV. Details of the device have been highlighted in previous publications.[4,5]

Data collection and statistical analysis

All data were entered in the electronic data capture system by the participating centres and monitored by the Sponsor.

The modality of TAVI treatment, TF, or Non-TF, was decided by the local heart teams, based on the patient's condition. Due to this selection bias, the two cohorts are very different in terms of their baseline characteristics as highlighted in *Table 1* (the *P*-values in this table serve descriptive purpose only to highlight the differences of baseline characteristics between the TF and Non-TF cohort). For that reason a direct comparison of the post-TAVI outcomes was not performed.

Continuous variables are presented as mean ± standard deviation or median [Q1, Q3] and were compared between groups using the two-sample *t*-tests or Mann–Whitney *U* test. Categorical variables are given as frequencies and percentages, and were compared using Fisher's exact tests. Kaplan–Meier (KM) analyses were performed using the log-rank test. A paired analysis was conducted on haemodynamic parameters (mean gradient, peak gradient, effective orifice area, left-ventricular ejection fraction).

Univariate Cox proportional hazard models were performed to obtain the hazard ratio estimates on all-cause mortality using patient baseline characteristics, procedural and post-procedural variables (listed in Supplementary material online, *File S3*). Univariate *P*-values <0.2 were further selected as the starting subset for multivariable stepwise Cox proportional hazards model for all-cause mortality. Proportional hazards were checked in the subset and highly correlated variables were further removed. Thereafter, a multivariable stepwise Cox proportional hazard model was computed for all-cause mortality.

All statistical analyses were performed using SAS, version 9.3 (SAS Institute Inc, Cary, NC, USA).

Table 1 Demographic and baseline characteristics of the transfemoral (TF: *n* = 1694) and non-transfemoral (Non-TF: *n* = 252) group

	TF Mean ± SD (*N*) or *n*/*N* (%)	Non-TF Mean ± SD (*N*) or *n*/*N* (%)	*P*-value*
Age (years)	81.7 ± 6.7 (*n* = 1694)	80.8 ± 6.4 (*n* = 251)	0.025
Age ≥80 years (%)	1163/1694 (68.7%)	157/252 (62.3%)	0.051
Female	834/1694 (49.2%)	100/252 (39.7%)	0.006
Hypertension	1381/1694 (81.5%)	210/252 (83.3%)	0.54
Dyslipidaemia	906/1694 (53.5%)	148/252 (58.7%)	0.12
History of smoking	467/1694 (27.6%)	118/251 (47.0%)	<0.0001
Diabetes	487/1694 (28.7%)	88/252 (34.9%)	0.054
Insulin dependent	172/1694 (10.2%)	38/252 (15.1%)	0.022
Coronary artery disease	827/1694 (48.8%)	175/252 (69.4%)	<0.0001
Myocardial infarction	180/1694 (10.6%)	48/252 (19.0%)	0.0003
Percutaneous coronary intervention	553/1693 (32.7%)	105/252 (41.7%)	0.005
Coronary bypass grafting	159/1693 (9.4%)	62/252 (24.6%)	<0.0001
Congestive heart failure	589/1694 (34.8%)	118/252 (46.8%)	0.0003
Left ventricular ejection fraction <30%	91/1435 (6.3%)	9/215 (4.2%)	0.28
New York Heart Association Class IV	152/1634 (9.3%)	17/245 (6.9%)	0.35
Mitral regurgitation (degree moderate to severe)	217/1545 (14.0%)	32/229 (14.0%)	1.00
Tricuspid regurgitation (degree moderate to severe)	153/1439 (10.6%)	27/211 (12.8%)	0.35
Atrial fibrillation	365/1632 (22.4%)	59/241 (24.5%)	0.46
Pacemaker	195/1693 (11.5%)	35/252 (13.9%)	0.29
Chronic obstructive pulmonary disease	256/1694 (15.1%)	57/252 (22.6%)	0.004
Renal Insufficiency	455/1694 (26.9%)	80/252 (31.7%)	0.11
Severe liver disease/cirrhosis	33/1694 (1.9%)	2/252 (0.8%)	0.31
Porcelain aorta	59/1694 (3.5%)	34/252 (13.5%)	<0.0001
Peripheral vascular disease	202/1694 (11.9%)	94/252 (37.5%)	<0.0001
Peripheral Stent (femoral, iliac)	25/1693 (1.5%)	25/252 (9.9%)	<0.0001
Stroke	132/1694 (7.8%)	32/252 (12.7%)	0.014
Transient ischaemic attack	65/1694 (3.8%)	12/252 (4.8%)	0.49
Carotid disease	235/1694 (13.9%)	64/252 (25.4%)	<0.0001
Carotid endarterectomy/stent	53/1693 (3.1%)	17/252 (6.7%)	0.01
Coagulopathy	20/1694 (1.2%)	3/252 (1.2%)	1.00
Logistic EuroSCORE I[a]	13.96 [8.97, 22.78] (1553)	17.83 [11.40, 29.25] (232)	<0.0001
EuroSCORE I < 10	475/1553 (30.6%)	43/235 (18.5%)	<0.0001
EuroSCORE I > 30	225/1553 (14.5%)	57/232 (24.6%)	0.0002

SD, standard deviation.
[a]Logistic EuroSCORE I presented as median and interquartile range.
**P*-value of Fisher exact test for categorical variables and Mann–Whitney *U* test for continuous variables.

Results

Patients and procedural characteristics

Patients with severe, symptomatic aortic stenosis, consecutively treated using the SAPIEN 3, were enrolled between July 2014 and October 2015. Compared to the previous cohort, investigated at 30 days (*n* = 1947), 1 withdrawal of consent occurred, resulting in a total number of 1946 patients for this 1-year analysis. Most patients (*n* = 1694, 87.1%) were treated using TF approach, while 12.9% of patients (*n* = 252) underwent TAVI through Non-TF access (transapical 72%, transaortic 21%, transsubclavian 2%, transcarotid 5%).

The mean age was 81.6 ± 6.7 years and major comorbidities were frequent, resulting in a mean logistic EuroSCORE I (logES) of 18.3 ± 13.2%. Patients were predominantly male (52%) and 73.3% of patients were in NYHA Class III/IV at enrolment. As detailed in *Table 1*, Non-TF patients presented with a higher risk profile compared to the TF cohort.

The majority of TF patients underwent the procedure under conscious sedation (1014/1694, 59.9%), while the remaining cohort was treated under general anaesthesia. Implantation success was 98.5% (1915/1946) in all patients. A pre-TAVI balloon dilatation was completed in 50.5% of all patients and post-TAVI dilatations in 10.7% (207/1943) of the total cohort (TF: 10.4%, Non-TF: 12.7%).

Table 2 One-year clinical outcomes

End points		Total N = 1946	TF N = 1694	Non-TF N = 252
All-cause mortality %	30 days	2.2 [1.6, 3.0]	1.9 [1.4, 2.7]	4.0 [2.2, 7.2]
	1 year	12.6 [11.2, 14.2]	11.8 [10.3, 13.4]	18.5 [14.2, 23.9]
Cardiovascular mortality %	30 days	1.6 [1.1, 2.3]	1.5 [1.0, 2.2]	2.4 [1.1, 5.3]
	1 year	8.0 [6.8, 9.3]	7.5 [6.3, 8.9]	11.3 [7.9, 16.0]
All stroke %	30 days	1.4 [1.0, 2.1]	1.2 [0.8, 1.9]	2.8 [1.3, 5.8]
	1 year	3.1 [2.4, 4.0]	2.7 [2.0, 3.6]	5.6 [3.3, 9.5]
Disabling stroke %	30 days	0.5 [0.3, 1.0]	0.5 [0.2, 0.9]	0.8 [0.2, 3.1]
	1 year	1.4 [0.9, 2.0]	1.1 [0.7, 1.7]	3.6 [1.8, 7.1]
Transient ischaemic attack %	30 days	0.6 [0.3, 1.1]	0.6 [0.3, 1.1]	0.8 [0.2, 3.2]
	1 year	1.2 [0.8, 1.8]	1.2 [0.7, 1.8]	1.3 [0.4, 3.9]
Myocardial infarction %	30 days	0.3 [0.1, 0.7]	0.2 [0.1, 0.6]	0.8 [0.2, 3.1]
	1 year	0.9 [0.6, 1.5]	0.8 [0.5, 1.4]	1.8 [0.7, 4.6]
New onset of atrial fibrillation %	30 days	6.3 [5.3, 7.5]	5.6 [4.6, 6.8]	11.6 [8.2, 16.2]
	1 year	7.9 [6.8, 9.2]	7.1 [5.9, 8.4]	13.3 [9.7, 18.2]
New permanent pacemaker %	30 days	12.1 [10.7, 13.6]	12.4 [10.9, 14.0]	10.4 [7.2, 14.8]
	1 year	13.2 [11.7, 14.8]	13.6 [12.0, 15.3]	10.4 [7.2, 14.8]
Endocarditis %	30 days	0.3 [0.1, 0.6]	0.2 [0.1, 0.6]	0.4 [0.1, 2.8]
	1 year	1.3 [0.9, 2.0]	1.3 [0.9, 2.0]	1.2 [0.4, 3.8]
Valve thrombosis %	30 days	0.1 [0.0, 0.4]	0.1 [0.0, 0.4]	0.4 [0.1, 2.8]
	1 year	0.4 [0.2, 0.8]	0.3 [0.1, 0.7]	0.8 [0.2, 3.2]
Rehospitalisation %[a]	30 days	1.0 [0.6, 1.5]	1.0 [0.6, 1.6]	0.8 [0.2, 3.2]
	1 year	8.1 [6.9, 9.5]	8.0 [6.8, 9.5]	8.7 [5.7, 13.2]

All events are CEC adjudicated; values are Kaplan–Meier estimates (%) [95% confidence interval].
TF, transfemoral.
[a]Rehospitalizations for valve-related symptoms or worsening congestive heart failure.

Procedural complications were previously reported, with unplanned valve-in-valve procedures in 0.7% (14/1946), conversion to open heart surgery in 0.6% (11/1946) and supportive use of cardiopulmonary bypass during the TAVI procedure in 0.3% (6/1945) (*Table 2*).[5]

One-year clinical outcomes

Follow-up for patients was 100% complete. The KM estimate for all-cause mortality at 1-year was 12.6% for the total cohort, 11.8% after TF, and 18.5% after Non-TF access (*Table 2*). Mortality was lower in patients with logES of <10 (10.3%) compared to those with logES >30 (19.6%; $P = 0.0002$, *Figure 1*). Cardiovascular mortality was 8.0% overall, 7.5% in TF patients and 11.3% in Non-TF patients. In patients who were converted to open-heart surgery ($n = 11$) or in whom cardiopulmonary bypass was used during TAVI ($n = 6$), 1-year mortality was high with 63.6% ($n = 6$) and 50% ($n = 3$), respectively.

The KM event rate for stroke was 3.1%, which were disabling in 1.4%. Other CEC adjudicated post-TAVI complications included new pacemaker implantations (13.2%), new onset of atrial fibrillation (7.9%), myocardial infarction (0.9%), endocarditis (1.3%), and valve thrombosis (0.4%). Rehospitalization for valve-related symptoms or worsening congestive heart failure was recorded in 8.1% of patients (*Table 2*).

Causes of deaths

A total of 245/1946 patients (12.6%) died during the 1st year from cardiovascular ($n = 152/245$, 62.0%) or non-cardiovascular events ($n = 93/245$, 38.0%). Most common causes for cardiovascular deaths were heart failure (21.7%), sudden cardiac death (10.5%), and endocarditis (7.9%). A new pacemaker implantation post-TAVI did not affect sudden cardiac death at 1 year. In patients, who suffered from post-TAVI endocarditis, the 1-year mortality was 50% ($n = 12$). Most common causes for non-cardiovascular deaths were of pulmonary (30.1%), cancer (22.6%) and sepsis (15.1%) origin (*Table 3*).

Predictors of all-cause 1-year mortality

Univariate analysis was performed to assess associations between patient's baseline characteristics, procedural and post-procedural complications, and 1-year mortality (a summary of all variables analysed are listed in Supplementary material online, *File S3*). The results of risk factors with $P < 0.2$ (continuous variable, and levels of categorical variables with $P < 0.2$), which were also later used for the multivariable analysis, are displayed in *Table 4*. Strongest patient's characteristics to predict 1-year mortality were logES, renal insufficiency moderate to severe tricuspid regurgitation, and atrial fibrillation. Female gender, higher mean aortic gradients, and body mass index were identified as indicators of improved survival. TF access and post-procedural characteristics such as acute kidney injury, length of stay in intensive care, and recovery time, were among the

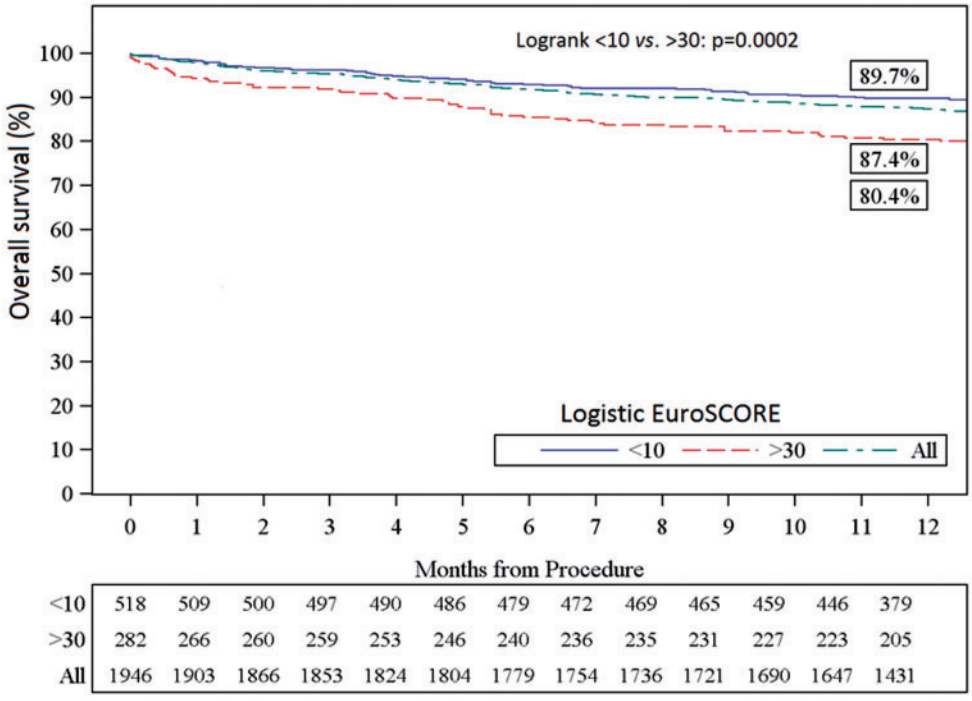

Figure 1 Overall survival, for the total cohort and for patients with a baseline. EuroSCORE I < 10 and >30.

Table 3 Main causes of mortality at 1 year

Cardiovascular deaths		**Non-cardiovascular deaths**	
Total	**152/245[a] (62.0%)**	**Total**	**93/245[a] (38.0%)**
Main causes of cardiovascular deaths		**Main causes of non-cardiovascular deaths**	
Heart failure	33/152 (21.7%)	Pulmonary	28/93 (30.1%)
Sudden cardiac death	16/152 (10.5%)	Cancer	21/93 (22.6%)
Endocarditis	12/152 (7.9%)	Sepsis	14/93 (15.1%)
Stroke	9/152 (6%)	Cachexia	9/93 (9.7%)
Haemorrhagic	3/152 (2.0%)	Multi-system organ failure	6/93 (6.5%)
Undetermined	1/152 (0.7%)	Bleeding	4/93 (4.3%)
Ischaemic	5/152 (3.3%)	Gastro-intestinal	3/93 (3.2%)
Vascular injury/access site-related complications	7/152 (4.6%)	Accidental/trauma	3/93 (3.2%)
Thromboembolism	4/152 (2.6%)	Renal failure	2/93 (2.2%)
Bleeding	3/152 (2.0%)	Other causes[c]	3/93 (3.2%)
Cardiac tamponade	3/152 (2.0%)		
Cardiogenic shock	3/152 (2.0%)		
Unknown cause[b]	39/152 (25.7%)		
Other causes[c]	23/152 (15.1%)		

[a]Number of deaths overall at 1 year.
[b]All deaths, including those of unknown cause were adjudicated.
[c]All procedural complications have been described previously[5]; this table presents causes of death occurring at a rate ≥2% in the two categories cardiovascular and non-cardiovascular, over 1 year. Causes of deaths <2% are summarized under 'other causes'.

strongest predictors of 1-year mortality after performing TAVI (*Table 4*).

Eighteen variables with $P < 0.2$ from the univariate analysis were selected to enter the stepwise Cox proportional hazards model. Final results of the multivariable analysis identified pre-procedural (NYHA Class IV and renal insufficiency), procedural (longer procedure time; skin-to-skin), and post-procedural indicators (acute kidney injury, length of stay in intensive care) as independent predictors for 1-year mortality. Higher body mass index remained a protective predictor of survival (*Table 4*).

Functional evaluation

While most patients were in NYHA Class III/IV at baseline (73.3%), the procedure significantly improved functional capabilities of patients as assessed 30 days after the procedure, with most patients (87.3%) in NYHA class I/II. This improvement was sustained at 1-year with most patients in NYHA class I/II (87.1%). The difference, previously observed at 30 days between the TF and Non-TF cohort, with slower functional recovery in patients who underwent TAVI through Non-TF access, has now disappeared (*Figure 2*).

Haemodynamics

Mean transaortic gradients significantly decreased and mean effective orifice areas significantly increased after the index procedure. Both parameters remained stable up to 1-year, as did the left-ventricular ejection fraction (*Table 5*). At 1-year, PVLs were classified of none/trace degree in 72.2% of patients and 25.2% were classified with mild PVLs, while moderate PVLs were rare (2.6%) and no patient experienced severe PVL (*Figure 3*).

Discussion

One-year outcomes of SOURCE 3, the largest registry on TAVI using the SAPIEN 3, demonstrate that the low 30-day mortality and high-procedural success rate previously reported,[5] translates to a low all-cause mortality at 1 year. Survival according to risk profile, measured using logES, is significantly higher at 1 year in patients with logES <10 compared to those with logES >30 (*Figure 1*).

Main causes of deaths were of cardiovascular origin (62%). Non-cardiovascular fatal complications were observed in 38% of the total cohort of these elderly high-risk patients. Independent predictors of 1-year mortality were found in baseline characteristics (NYHA Class IV and renal insufficiency), procedural characteristics (duration of the procedure), as well as post-procedural characteristics (acute kidney injury, length of stay in intensive care after the procedure). Interestingly, higher BMIs predicted improved 1-year survival, which given the advanced age of patients in SOURCE 3 was not surprising.

Comparison to SOURCE family of registries

In comparison to previous SOURCE registries using the SAPIEN and SAPIEN XT™ THV's (Edwards Lifesciences, Irvine, CA, USA), these SOURCE 3 results show that 1-year all-cause mortality has continuously dropped over recent years (SOURCE: 23.9%, SOURCE XT: 19.4%).[2,3] This is certainly a result of lower risk profiles of patients, particularly of the TF cohort, indicated by lower logESs, but also the high-initial procedural success and low-complication rate, as highlighted in our publication on 30-day outcomes.[5] However, it needs to be emphasized that outcomes after TAVI are also influenced by the learning curve of physicians in terms of patient selection, valve sizing and implantation techniques. Rehospitalization rates have also substantially reduced from 29.5% during the 1st year post TAVI in SOURCE XT, to now 8.1%. This will not only improve quality of patient's life but also positively affect the economic benefit of TAVI.

In previous SOURCE registries, a large number of cardiac and non-cardiac patient baseline characteristics predicted mortality at 1 year.[2,3] However, in SOURCE 3 only NYHA Class IV and renal insufficiency are independent predictors, similar to the recent findings reported elsewhere.[6,7] Procedural complications such as major vascular complications and PVL[2] were also previously observed as strong predictors of 1-year mortality. Due to the low rate of PVL at 1 year achieved using the SAPIEN 3, this variable did not affect 1-year mortality in SOURCE 3 any longer. Major vascular complications appear to be a predictor of 1-year mortality in the univariate analysis. However, when investigated using multivariable analysis, they violate proportional hazard assumptions, most likely as a result of their low occurrence reported previously and improved management in the few patients affected.[5]

Comparison to other transcatheter aortic valve implantation registries

Two registries have also reported on the 1-year outcomes for the latest generation self-expanding THV technology. However, the number of patients enrolled in the REPRISE II Study on the Lotus™ THV (Boston Scientific, Marlborough, MA, USA) ($n = 120$)[10] and the DISCOVER Study on the Direct Flow™ THV (Direct Flow Medical, Santa Rosa, CA, USA) ($n = 100$)[11] are small. All cause 1-year mortality was comparable to our findings (REPRISE 10.9%, DISCOVER 10%), while major stroke at 1-year was higher in DISCOVER (8%), major bleeding was higher in REPRISE II (21%). The rate of new pacemaker implantations at 1 year was 31.9% (REPRISE) and 21% (DISCOVER) and thus increased compared to SOURCE 3. Neither of the studies provided detailed analysis of predictors for 1-year outcomes or causes of death.

The ADVANCE Study with the CoreValve™ THV (Medtronic, Minneapolis, MN, USA) is larger, with a total of 1015 patients enrolled.[12] All-cause mortality was higher (17.9%), with similar rates of major stroke at 1 year (2.2%) compared to SOURCE 3. Independent predictors of 1-year mortality included mean baseline transaortic valve gradient, postoperative acute kidney injury, and aortic regurgitation at discharge, which has been discussed by the authors to reflect the higher rate of moderate and severe aortic regurgitation of 15.6% at discharge after the index procedure.

Comparison to other SAPIEN 3 registries

Interestingly, the 1-year mortality in SOURCE 3 is very similar compared to the North American experience (PARTNER II) with the SAPIEN 3 (all-cause mortality 14.4%, cardiovascular mortality 8.1% vs. SOURCE 3 12.6% and 8.0%). Differences of all-cause and cardiovascular mortality between TF and Non-TF access groups were higher in PARTNER II, when compared to SOURCE 3.[9] In PARTNER

Table 4 Predictors of mortality at 1 year

	Univariate model HR (95% CI)	*P*-value	Multivariable model HR (95% CI)	*P*-value
Baseline characteristics				
Gender female	0.77 (0.6, 0.99)	0.042		
Body mass index	0.97 (0.94, 1)	0.021	0.98 (0.96, 1.00)	0.027
Baseline NYHA IV	2.37 (0.83, 6.81)	0.109	2.53 (1.25, 5.12)	0.010
Baseline NYHA III	2.23 (0.83, 6.01)	0.12		
Left ventricular ejection fraction ≤35%	1.76 (1.24, 2.48)	0.001		
Left ventricular ejection fraction	0.99 (0.98, 1)	0.003		
Mean aortic valve gradient	0.98 (0.98, 0.99)	<0.0001		
Logistic EuroSCORE I	1.02 (1.01, 1.03)	<0.0001		
Logistic EuroSCORE I ≥ 20	1.73 (1.24, 2.42)	0.001		
Country Germany	1.73 (1, 2.99)	0.051		
Myocardial infarction	1.29 (0.9, 1.85)	0.16		
Renal insufficiency	2.04 (1.59, 2.63)	<0.0001	1.30 (1.06, 1.59)	0.010
Mitral regurgitation mod-severe	1.62 (1.1, 2.37)	0.014		
Tricuspid regurgitation mod-severe	2.19 (1.48, 3.23)	<0.0001		
Congestive heart failure	1.28 (0.99, 1.65)	0.059		
Coronary artery disease	1.49 (1.15, 1.93)	0.002		
Diabetes	1.2 (0.92, 1.56)	0.19		
Chronic obstructive pulmonary disease	1.39 (1.02, 1.89)	0.04		
Insulin dependent diabetes mellitus	1.35 (0.94, 1.94)	0.105		
Previous pacemaker implantation	1.31 (0.92, 1.87)	0.14		
Atrial fibrillation	1.77 (1.35, 2.33)	<0.0001		
Procedural characteristics				
Device size (29 mm)	1.49 (1.09, 2.04)	0.014		
Anaesthesia type conscious sedation to general anaesthesia	2.37 (0.88, 6.42)	0.09		
Volume of contrast media	0.998 (0.99, 1.00)	0.18		
Procedure time (skin to skin)	1.002 (0.99, 1.01)	0.15	1.005 (1.00, 1.01)	<0.0001
Transfemoral access	0.61 (0.44, 0.84)	0.003		
New pacemaker at procedure	0.09 (0.01, 0.67)	0.019		
Paravalvular leak at discharge mod-severe	0.09 (0.00, NA)	0.97		
Post-procedural characteristics				
Days from implant to discharge	1.04 (1.03, 1.05)	<0.0001		
Length of stay in intensive care unit	1.07 (1.05, 1.08)	<0.0001	1.05 (1.04, 1.06)	<0.0001
Major vascular complications (up to 30 days)	2.59 (1.69, 3.98)	<0.0001		
Acute kidney injury (up to 7 days)	3.13 (1.93, 5.05)	<0.0001	1.93 (1.32, 2.83)	0.0007

CI, confidence interval; HR, hazard ratio; NYHA, New York Heart Association.

II, Non-TF access, higher STS score, and disabling strokes were found to be independent predictors of 1-year mortality.

The similarities in the 30-day and 1-year outcomes of the North American and European experience are reassuring and may indicate that the present balloon-expandable THV technology has evolved towards more predictable implantation results, which are independent of operator variability.

Limitations

SOURCE 3 is a clinical registry and all outcomes, including those on PVL, are self-reported by the participating centres. Monitoring was conducted by Edwards Lifesciences and 100% of adverse events were monitored on-site.

The modality of TAVI treatment, TF or Non-TF, was decided by the local Heart Teams, based on patients' condition. Due to this selection bias, the two cohorts are very different in terms of their baseline characteristics as highlighted in *Table 1*. For that reason, their post-TAVI outcomes could not be compared to each other directly and do not allow conclusions on how the access route itself affects outcomes.

In SOURCE 3, the EuroSCORE I is used to describe the predicted risk of patients for surgical aortic valve replacement. While this makes the comparison with previous SOURCE registries easier, comparison with newer TAVI investigations, in which the STS score or EuroSCORE II are used, is more challenging.

In individuals who suffered from strokes a routine neurological assessment was not performed in all patients. Strokes are self-reported and no routine neurological assessment was performed in all patients.

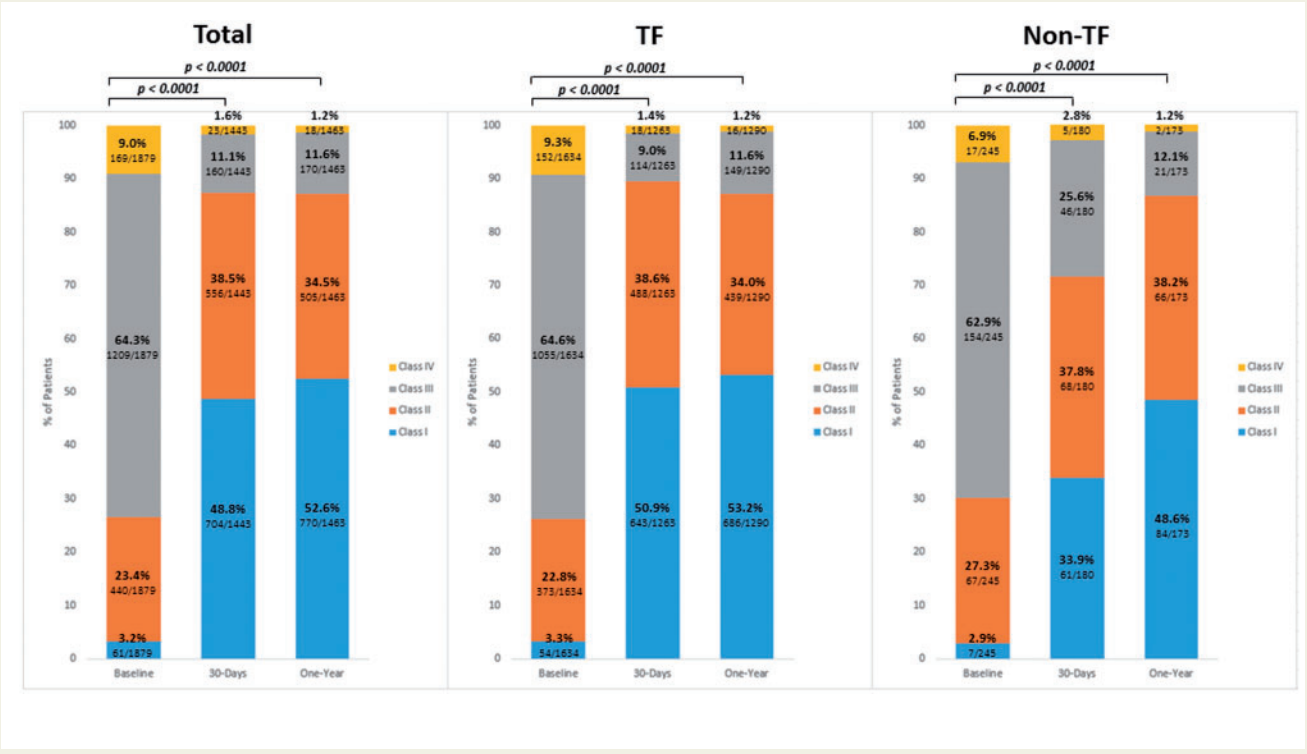

Figure 2 Categorization of patients by NYHA functional class.

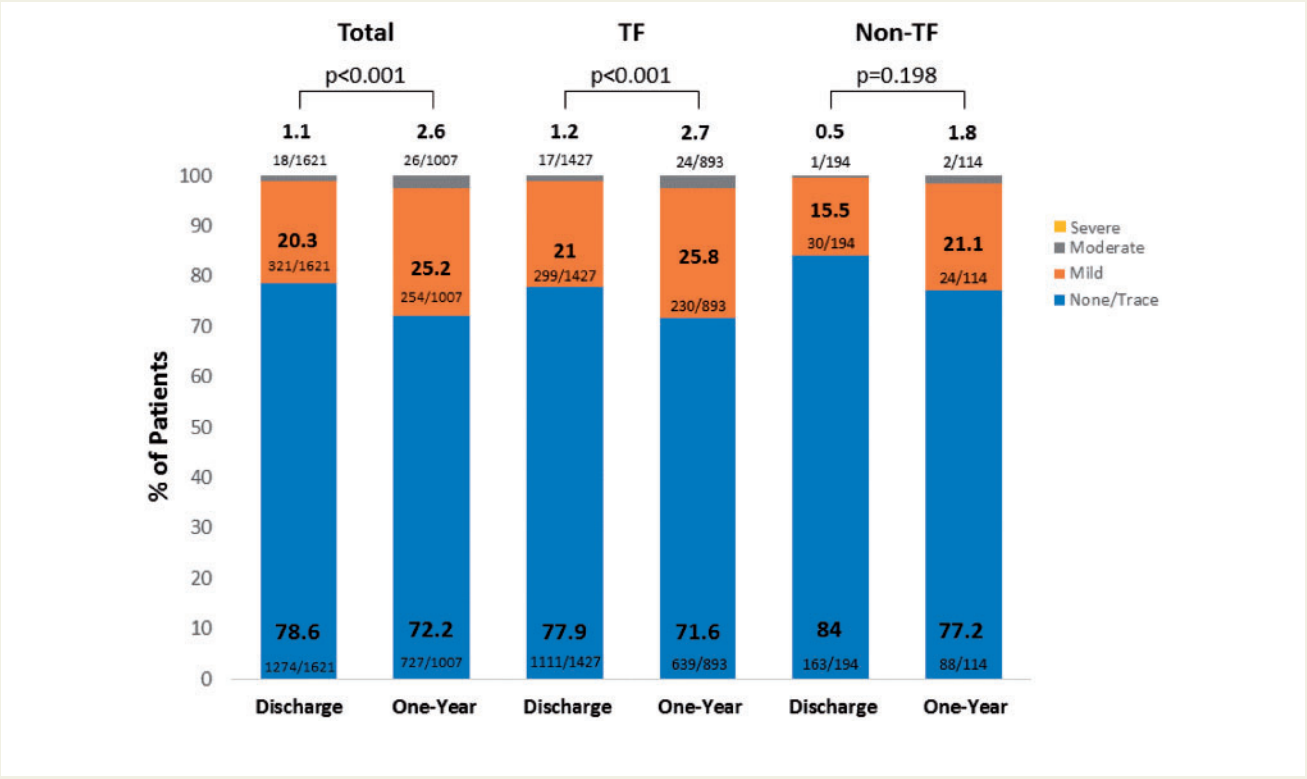

Figure 3 Categorization of patients by PVL grade.

Table 5 Haemodynamic outcomes at baseline, 30 days, and 1 year, with paired analysis on mean change from baseline to 1 year

Mean ± SD (*N*)	Baseline	30 days	1 year	Mean change from baseline to one year
Mean aortic gradient (mmHg)	44.1 ± 16.0 (858)	11.8 ± 5.1 (568)	12.3 ± 5.1 (858)	-31.9 ± 15.93 (858)
Peak aortic gradient (mmHg)	71.4 ± 23.8 (728)	21.3 ± 9.2 (465)	21.9 ± 9.0 (728)	-49.5 ± 23.75 (728)
Effective orifice area (cm^2)	0.73 ± 0.210 (434)	1.64 ± 0.46 (263)	1.70 ± 1.40 (434)	0.97 ± 1.41 (434)
Left ventricular ejection fraction (%)	55.5 ± 13.3 (830)	57.3 ± 11.6 (588)	57.9 ± 11.3 (830)	2.4 ± 11.20 (830)

However, strokes, as all clinical events, were subsequently CEC adjudicated (details are in Supplementary material online, *File S1*).

Conclusions

SOURCE 3 is a large, 'real-world' registry, which confirms the good performance and safety of the SAPIEN 3 at 1-year post-TAVI. The results will inform medical teams in their discussions to identify the optimal treatment option for their patients with aortic stenosis. It provides further evidence on the indication of TAVI and is important for the evaluation of this technique towards lower risk patients. However, longer follow-up is vital to get a better understanding about the durability of this new THV.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Author's contributions

O.W. and A.V. wrote the first draft of the manuscript, which was revised and approved by all co-authors.

This manuscript was prepared using a clinical extract of completed and adjudicated 1-year follow-up results from the SOURCE 3 Registry. The Registry is in active follow-up and interim analyses were completed for this report. The authors are aware of the data and leave full responsibility for data completeness and analysis accuracy with the Sponsor.

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