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Original Article

A prospective, non-randomized comparison of SAPIEN XT and CoreValve implantation in two sequential cohorts of patients with severe aortic stenosis

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Abstract: Objectives: Few data is available comparing Edwards SAPIEN XT - SXT (*Edwards Lifesciences, Irvine, California*) with Medtronic CoreValve - CoV (*Medtronic Inc., Minneapolis, Minnesota*) in patients with severe aortic stenosis undergoing transcatheter aortic valve replacement (TAVR). Methods: We selected consecutive patients undergoing transfemoral TAVR with SXT or CoV at our Institution. Main outcomes were Valve Academic Research Consortium (VARC)-combined safety endpoints. Results: A total of 100 patients (SXT, n=50 versus CoV, n=50) were analyzed. Both SXT and CoV showed good device success rates (98% versus 90%, p=0.20). SXT versus CoV reduced the occurrence of paravalvular regurgitation after TAVR (26% versus 90%, p<0.0001) though not affecting the rate of moderate/severe regurgitation (p=0.20). SXT versus CoV required less frequently a permanent pacemaker after TAVR (8% versus 38%, p<0.0001). In-hospital major vascular complications (8% versus 4%, p>0.99), life-threatening bleedings (2% versus 4%, p>0.99), stroke (4% versus 6%, p>0.99) and death (6% versus 2%, p>0.99) did not differ between SXT and CoV. However, safety endpoints favored SXT (17% versus 34.6%, p=0.01), due to a numerically higher incidence of ischemic stroke and Acute Kidney Injury Stage 3 after CoV. At multivariate analysis, TAVR with SXT (odds ratio=0.21, 95% confidence intervals [0.05-0.84], p=0.03) was predictive of fewer adverse events. Conclusions: Transcatheter valve implantation with Edwards SAPIEN XT was associated with lower VARC-combined safety endpoints as compared with Medtronic CoreValve. More extensive cohorts are needed to confirm these results.

Keywords: Aortic valve stenosis, TAVR, SAPIEN XT, CoreValve

Introduction

Transcatheter aortic valve replacement (TAVR) represents a breakthrough in technology for the treatment of symptomatic, severe aortic stenosis (AS) [1-3]. The PARTNER (Placement of Aortic Transcatheter Valve) Trial showed a survival benefit of TAVR as compared with medical therapy alone in patients unfit for surgery [4]. Moreover, TAVR was found non-inferior to surgery in high-risk population for which both strategies were equally feasible [5]. These results have recently been confirmed up to 2-year follow-up [6, 7].

However, the cerebral and vascular complications associated with the balloon-expandable Edwards SAPIEN valve (ES - *Edwards Lifesciences, Irvine, California*) tempered initial enthusiasm. The less flexible and large-caliber delivery systems required for ES implantation have been supposed to be responsible for these outcomes [4, 5]. In contrast, the self-expandable Medtronic CoreValve (CoV - *Medtronic Inc., Minneapolis, Minnesota*) uses a lower-profile sheath (18F) and more flexible materials. In line with these arguments, previous observations suggested higher risk of complications with ES versus CoV [8].

Recent technological improvements led to Edwards SAPIEN XT valve (SXT - *Edwards Lifesciences, Irvine, California*) to possibly exceed the limits associated with ES prosthesis [9]. To date, data on SXT versus CoV, assessing the VARC (Valve Academic Research Consor-

tium)-combined endpoints occurrence [10], is still scanty [11].

Here we report the incidence and predictors of VARC-combined safety endpoints among two sequential cohorts of high-risk consecutive patients undergoing TAVR with SXT versus CoV.

Methods

Screening rules

Patients with severe, symptomatic AS, referred to the *Klinik für Kardiologie und Intensivmedizin, Klinikum Bogenhausen* (München, Germany) entered a multidisciplinary selection process. This approach involved interventional cardiologists, cardiac surgeons, anesthesiologists and other specialists. An internal audit ensured that all patients with symptomatic, severe AS had been evaluated for TAVR, if clinically indicated and technically feasible.

Indication for TAVR comprised of: symptomatic, severe AS (aortic valve area - AVA <1 cm^2 and/or transvalvular mean pressure gradient - MPG >40 mmHg) with high-risk surgical features according to logistic European System for Cardiac Operative Risk Evaluation (logistic-EuroSCORE ≥20%) and Society of Thoracic Surgeons Predicted Risk of Mortality (STS PROM ≥10%), or other comorbidities excluded from these scores (i.e. coronary artery bypass surgery with non-occluded grafts, previous chest irradiation, porcelain aorta and frailty [12]). We excluded bicuspid aortic valves and patients with poor life expectancy (the so-called "futility" category of high-risk patients). All patients suitable for TAVR underwent: transesophageal echocardiography (TEE), transthoracic echocardiography (TTE), gated computed tomography (CT) scans and heart catheterization (coronary, aortic, peripheral vascular angiography). The measurement of the AV annulus was based on TEE and CT as elsewhere described [13].

For this study, the CoV and the SXT systems were used. We began with the CoV in December 2007, and then switched to SXT in April 2010. Based on the enrolment period, CoV prostheses 26 or 29 mm were selected for annulus diameter ranging 20 to 24 mm and from 24 to 27 mm, whilst SXT prostheses 23 or 26 mm were selected for annulus diameter ranging from 18 to 22 mm and from 21 to 25 mm. The vascular access suitability was based on the iliac-femoral artery diameters from multi-slice CT scan. Access site calcification was graded as previously published [14]. Additionally, the outer sheath diameter/minimum lumen diameter (MLD) ratio was calculated [15]. The transfemoral route was the preferred vascular approach during the entire enrolment period. Patients who were deemed to be anatomically unsuitable for vascular accesses were treated via transapical route or with conventional surgery, if feasible.

TAVR procedure

All the procedures were carried out in a "hybrid" catheterization laboratory, almost all under local anesthesia and with conscious sedation, without any mechanical respiratory assistance. The technical aspects of the procedure have been described elsewhere [16]. In short, the best access site was decided in accordance with pre-procedural imaging. Two ProGlide percutaneous closure devices (*Abbott Vascular, Santa Clara, California*) were prepared on the selected access site, aiming for final hemostasis by means of "parallel sutures technique", a modified "preclose technique" [17], with sutures deployed parallel to the vessel axis instead of crosswise. Introducer sheaths, dependent on prosthesis measure and type, were inserted over an extra-stiff (SXT) or a super-stiff (CoV) guidewire and put in place in the descending aorta.

Conventional balloon aortic valvuloplasty was performed under rapid pacing (180-200 beats per minute). During valvuloplasty, simultaneous contrast injection confirmed aortic annulus size and coronary artery patency in order to exclude the presence of bulky leaflets possibly crushing against the coronary ostia during prosthesis deployment.

The prostheses and delivery systems peculiarities have been previously detailed [9, 18]. After the exact position at cusps level was achieved [19], the SXT was balloon expanded under rapid pacing whilst the self-expanding CoV was released through progressive pullback of the delivery system without rapid pacing. A final aortography at root level ruled out relevant insufficiencies or other complications. The angiography of pelvic axes was mandatory to

disclose any vascular injury, with percutaneous or surgical management immediately performed in case of traumatic lesions and/or active bleeding. Finally, in the SXT group the prophylactic pacemaker lead was removed - the exceptions being those cases with conduction abnormalities at any stage of the procedure. In the CoV group pacemaker lead was left in place for at least 48h, unless otherwise indicated.

Therapy

Perioperative drug administration consisted of pre-procedural aspirin (500 mg, iv.), antibiotics (cephalosporin) given just before TAVR and continued up to 24h, unless a longer time was required. Periprocedural heparin (80-100 U/kg, iv.) was given to achieve a 250 sec activated clotting time during the procedure. After TAVR, the heparin effect was reverted with protamin administration and the patients were transferred to the Intensive Care Unit for close monitoring of vital signs and fluids. Blood samples were taken upon admission, as well as during the hospital stay, looking for markers of organ failure, as well as Brain Natriuretic Peptide (BNP) levels. Cardiac markers (i.e. Troponin I and Creatine Kinase-myocardial band) were collected after TAVR up until discharge. A TTE was performed 6h after the procedure and prior to discharge to assess prosthesis performance and left ventricular ejection fraction (LVEF). After discharge, patients undergoing CoV implantation were treated with clopidogrel (75 mg/die, 6 months) and aspirin (100 mg/day, indefinitely). For SXT patients only aspirin (100 mg/day, indefinitely) was prescribed, unless other compelling indications for dual antiplatelet therapy were present (i.e. recent percutaneous revascularization). For those patients with indication of oral anticoagulant therapy (i.e. in case of atrial fibrillation), antiplatelets were discontinued after a period of 1 month.

Objectives and definitions

VARC outcome definitions were endorsed [10]. We considered: death, stroke, myocardial infarction (MI), vascular complication at therapeutic site, bleeding, acute kidney injury (AKI) with modified RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) classification [20], device success, prosthetic valve performance and the combined safety endpoint at 30-day follow-up (the primary endpoint).

Chronic obstructive pulmonary disease (COPD) was defined as the reduction of a forced expiratory volume in 1-second ≥20% than predicted or forced expiratory flow at 25% to 75% of vital capacity ≥20% than predicted with or without the requirement for home-oxygen therapy. Carotid artery disease was defined as the presence at echographic-duplex assessment of a ≥50% stenosis; coronary artery disease (CAD) was defined as the presence of a ≥50% lesion in major coronary arteries or their major branches; cerebral-vascular disease (CVD) was defined as the presence of a prior history of cerebrovascular accident; peripheral artery disease (PAD) was defined as the presence at echographic-duplex or at angiography of a ≥50% lesion in major arteries or their major branches. All patients underwent coronary angiography before TAVR. When clinically indicated, revascularization was performed before TAVR. Chronic kidney disease (CKD) stages were defined in accordance with National Kidney Foundation Disease Outcomes Quality Initiative (NKF-KDOQI) [21]. Prostheses performance was evaluated during hospital stay as well as at 1-month follow-up by measuring AVA, MPG, and by quantitative (mild, moderate, severe) and qualitative (paravalvular, transvalvular) evaluation of degree of aortic regurgitation (AR).

Data collection and analysis

All patients undergoing TAVR with SXT or CoV were prospectively enrolled after duly signing their consent allowing scheduled follow-up and data collection storage for scientific purposes. Data regarding clinical status, emergent and concurrent therapies, preoperative TEE, TTE and CT scan values and findings, procedural features, as well as data pertaining to procedural performances of SXT and CoV were carefully collected upon admission, as well as during and after hospital stay by completion of an electronic Case Report Form; this data was input in a database and prospectively analyzed. Clinical and instrumental (TTE) follow-up was obtained from routine clinical visits to our Institution 30 days after TAVR. In case of repeat intervention (either percutaneous or surgical) or new hospitalization, care was taken to record inherent data. In case of an adverse event at another center, medical records or discharge letters from the other institutions were systematically reviewed. General practitioners and referring physicians were contacted for addi-

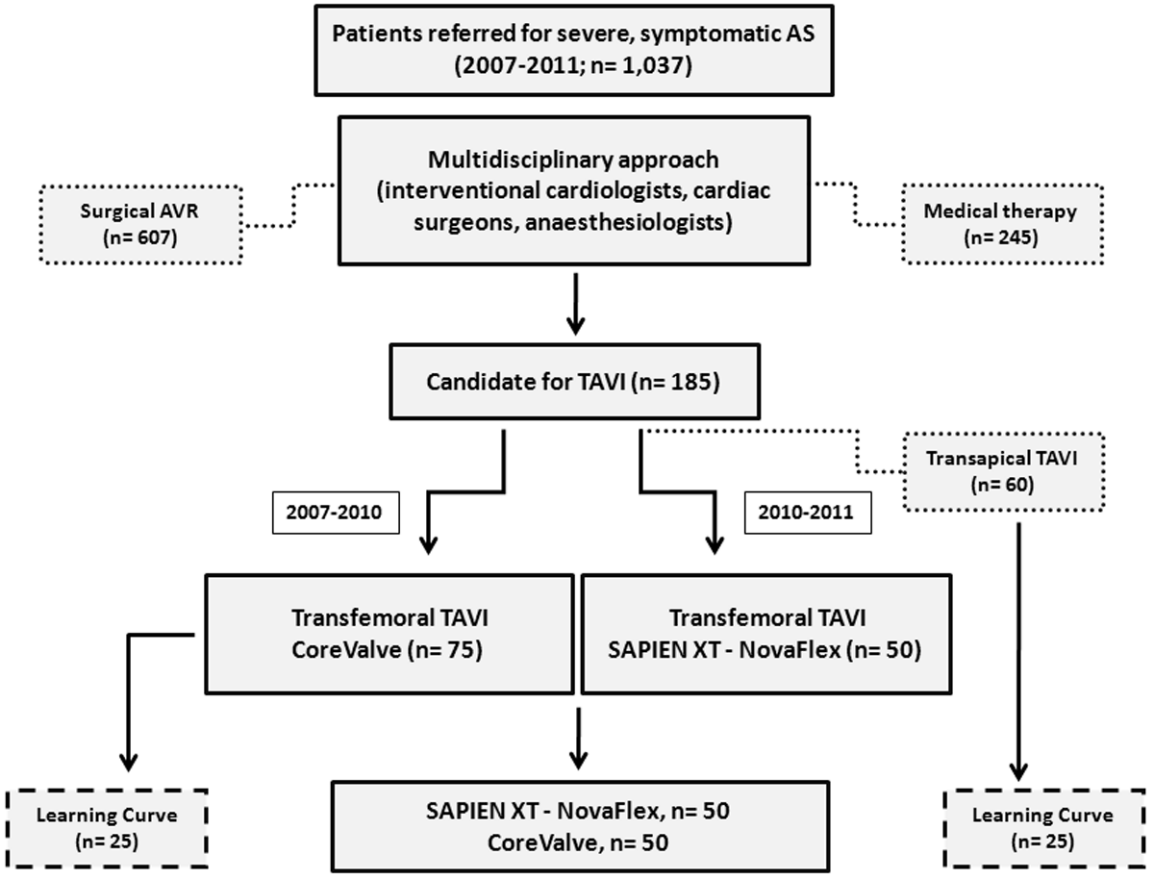

Figure 1. Flow-diagram resuming algorithm of treatments allocation during the enrolment period. AS: Aortic stenosis; AVR: Aortic valve replacement; TAVI: Transcatheter aortic valve implantation.

tional information, if necessary. The study was approved from local ethics committee and complied with the principles of the Declaration of Helsinki.

Continuous variables are presented as mean ± standard deviation, whereas categorical variables as numbers and percentages. The normality of distribution of continuous variables was evaluated by the Kolmogorov-Smirnov goodness-of-fit test, and therefore compared with independent sample Student t or Mann-Whitney U test. Categorical variables were compared with χ^2 statistic or Fisher-exact test when appropriate. In case of significance, the number needed to treat (NNT) with relative 95% confidence interval [95% CI]. Multivariable binary logistic regression analysis was performed to ascertain the independent predictors of VARC-combined safety endpoints after adjustment for potential covariates and baseline differences. Variables associated at the univariate analysis with primary outcome occurrence ($p<0.1$) were eligible for inclusion in the multivariable model. The single components of combined safety endpoints definition were not included in the multivariate model. Goodness-of-fit of the logistic regression model was assessed with the Hosmer-Lemeshow statistic. Data were processed using the Stata 11.0 statistical software (*STATA Corp, College Station, Texas, USA*) and were presented according to type of prosthesis groups. The Authors vouch for the accuracy and completeness of the data.

Results

From December 2007 to August 2011, a number of 1,037 patients with severe symptomatic AS were referred to our Institution. Algorithm of treatments allocation is showed in the **Figure 1**. Among those (n=185) who were candidate for TAVR, a total of 60 patients underwent ES (n=35) or SXT (n=25) implantation with the same operators. The first consecutive 25 cases treated with CoV as well as the first consecutive

Table 1. Baseline clinical characteristics

	SXT	*CoV*	*p*
Patients	50	50	-
Age (y)	81.54±5.24	79.82±6.61	0.15
Male (n)	18% (9)	48% (24)	0.001
BMI (kg/m^2)	27.56±4.76	26.55±4.42	0.27
Hypertension (n)	74% (37)	64% (32)	0.28
Dyslipidemia (n)	22% (11)	54% (27)	0.001
Diabetes mellitus (n)	38% (19)	38% (19)	>0.99
Insulin treated (n)	12% (6)	6% (3)	0.48
COPD (n)	24% (12)	16% (8)	0.31
Carotid artery disease (n)	40% (20)	26% (13)	0.13
CAD (n)	44% (22)	58% (29)	0.10
Combined CAD/CVD (n)	8% (4)	6% (3)	>0.99
Previous MI (n)	10% (5)	14% (7)	0.53
Previous cardiovascular surgery (n)	10% (5)	32% (16)	0.007
History of malignancy (n)	30% (15)	26% (13)	0.65
Previous chest irradiation	18% (9)	2% (1)	0.01
Porcelain aorta (n)	12% (6)	6% (3)	0.48
Syncope (n)	4% (2)	12% (6)	0.269
NYHA Functional Class (n)			
III	82% (41)	60.2% (34)	0.31
IV	14% (7)	20% (10)	
CCS Angina Class (n)			
>II	24% (12)	10% (5)	0.18
CKD Stages (n, ml/min/1.73 m^2)			
III	52% (26)	42% (21)	0.08
≥IV	48% (24)	54% (27)	
STS PROM	9.25±8.33	10.02±6.50	0.60
STS morbidity and mortality	28.74±9.40	34.31±12.17	0.02
LogEuroSCORE	23.23±15.42	20.73±13.67	0.39
BNP (ng/L)	684.04±877.29	846.38±881.21	0.43
Hb (g/dl)	12.21±2.60	12.42±1.98	0.68
Rhythm and impulse conduction (n)			
Normal	56% (28)	40% (20)	0.001
Bundle branch block	6% (3)	30% (15)	
Atrial fibrillation	18% (9)	8% (4)	
Pacemaker	16% (8)	6% (3)	

SXT: SAPIEN XT; CoV: CoreValve; BMI: Body-mass index; COPD: Chronic obstructive pulmonary disease; CAD: Coronary artery disease; CVD: Cerebro-vascular disease; MI: Myocardial infarction; PAD: Peripheral artery disease; NYHA: New York Heart Association; CCS: Canadian Cardiovascular Society; CKD: Chronic kidney disease; STS PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; logEuroSCORE: logistic European System for Cardiac Operative Risk Evaluation; BNP: Brain natriuretic peptide.

25 cases receiving SXT (all transapical) were excluded from the present analysis in order to discard influences on device-related outcomes due to the learning curve [22, 23]. A total of 100 patients (SXT, n=50 and CoV, n=50) were available for further analysis.

Table 1 resumes baseline clinical features. Patients belonging to the SXT group had more frequently undergone chest irradiation (p= 0.01). In the CoV group there were higher proportions of males (p=0.001), dyslipidemia (p=0.001), history of previous cardiovascular

Table 2. Baseline imaging findings

	SXT	*CoV*	*p*
Patients, n	50	50	-
Echocardiography			
TEE AV Annulus (mm)	21.32±1.55	22.48±2.09	0.005
LVEF (%)	54±9.99	53.57±10.21	0.83
LV Septum (mm)	13.34±1.64	14.23±1.80	0.009
AV Mean PG (mmHg)	40.86±15.90	44.40±12.76	0.22
AVA (cm^2)	0.68±0.15	0.62±0.15	0.06
AR (n, moderate/severe)	26% (13)	32% (16)	0.60
PASP (mmHg)	43.55±12.97	44.18±14.28	0.30
Computed Tomography Scan			
MLD of access site vessel on therapeutic side (mm)	7.37±1.13	7.62±1.08	0.20
AV Annulus Effective Diam (mm)	22.50±1.24	23.65±1.93	0.003

SXT: SAPIEN XT; CoV: CoreValve; TEE: Transesophageal echocardiography; LVEF: Left ventricular ejection fraction; LV: Left ventricular; AV: Aortic Valve; PG: Pressure gradient; AVA: Aortic valve area; AR: Aortic rigurgitation; PASP: Pulmonary arterial systolic pressure; MLD: Minimum lumen diameter.

surgery (p=0.007), a higher STS morbidity and mortality Score (p=0.02) and more pre-existing bundle branch block at baseline ECG (p=0.001).

Table 2 resumes baseline imaging findings. At both TEE and CT scan (**Table 2**) aortic annulus diameter was significantly smaller for SXT versus CoV group. This is consistent with the available prostheses diameters and unravels gender disproportion among groups. Similarly, in the SXT versus CoV groups there was a smaller thickness of left ventricular septum at echocardiography (13.34±1.64 versus 14.23±1.80 mm, p=0.009). Moderate/severe AR was present in 26% versus 21.9% of patients (p=0.60; SXT and CoV, respectively).

Table 3 reports procedural outcomes. All cases underwent transfemoral valve implantation (outer sheath diameter/MLD ratio 1.02±0.14 versus 1.05±0.11, p=0.20; SXT versus CoV, respectively). A similar, good success rate was achieved with both devices (98% versus 90%, p=0.20; SXT versus CoV, respectively). However, the valve/patient ratio favored SXT versus CoV (1 versus 1.08±0.27, p=0.04). In this regard, in the CoV group one patient underwent second CoV implantation due to first valve embolization into the ascending aorta; two patients with severe residual AR (transvalvular, n=1; paravalvular, n=1) required the implantation of a second CoV prosthesis ("valve-in-valve").

Overall, two patients underwent conventional AVR due to TAVR failure: in the SXT group a patient had valve embolization into left ventricular outflow tract; in the CoV group urgent surgery was performed due to severe valve underexpansion.

After TAVR, TTE documented the mean transvalvular gradient reduction and a relevant AVA improvement with both prostheses. The pulmonary systolic pressure was significantly lower in the SXT versus CoV group (37.84±10.66 versus 46.09±13.12 mmHg, p=0.005). Paravalvular AR occurred predominantly after CoV implantation (26% versus 90%, p<0.0001; SXT versus CoV, respectively) without differences in moderate/severe regurgitation between groups.

Table 4 details in-hospital outcomes. Numerically fewer cases of AKI-RIFLE Stages 2 and 3 were reported in the SXT versus CoV group, likely due to less contrast amount used to deploy SXT as compared with CoV (211.64± 74.20 versus 295.06±122.91 ml, p=0.0001).

In the SXT group, 4 patients had pericardial effusion during hospital stay: 3 patients (cardiac decompensation) received pharmacological treatment, while 1 patient required pericardiocentesis. In this case, right ventricle injury caused by transvenous pacemaker led to subsequent pericardial effusion and cardiac tamponade. In the CoV group, 1 patient experienced pericardial effusion, which was medically managed.

No difference in major vascular complications was found between SXT and CoV (8% versus 4%, p>0.99), and all of these were successfully

Table 3. Procedural outcomes

	SXT	*CoV*	*p*
Patients (n)	50	50	-
Prosthesis measure (n)			
23 mm	46% (23)	-	-
26 mm	54% (27)	64% (32)	
29 mm	-	36% (18)	
Outer sheath diameter/MLD ratio[*]	1.02±0.14	1.05±0.11	0.20
Contrast medium[†] *amount (ml)*	211.64±74.20	295.06±122.91	0.0001
Fluoroscopy time (min)	17.30±13.70	16.78±8.10	0.81
CK-MB (ng/ml)[‡]	20.07±80.28	21.50±70.88	0.93
Troponin I (ng/ml)[‡]	10.20±57.43	2.38±5.13	0.40
LVEF (%)	52.80±7.91	53.4±7.69	0.71
AV Mean PG (mmHg)	8.58±7.27	8.04±3.44	0.64
AVA (cm^2)	1.84±0.42	2.11±0.68	0.15
AR (n, moderate/severe)	6% (3)	16% (8)	0.20
AR qualitative (n)			
Paravalvular	26% (13)	90% (45)	<0.0001
Transvalvular	2% (1)	2% (1)	
Para/Transvalvular	4% (2)	-	
PASP (mmHg)	37.84±10.66	46.09±13.12	0.005
ICU time (days)	5.04±12.44	6.72±6.68	0.40
Device success (n)	98% (49)	90% (45)	0.20
Coronary obstruction (n)	-	-	-
Valve/patient (n)	1	1.08±0.27	0.04
Valve embolization/migration (n)	2% (1)	2% (1)	>0.99
Switch to conventional AVR surgery (n)	2% (1)	2% (1)	>0.99

SXT: SAPIEN XT; CoV: CoreValve; ICU: Intensive care unit; CK-MB: Creatine kinase-MB isoform; BNP: Brain natriuretic peptide; LVEF: Left ventricular ejection fraction; AV: Aortic Valve; PG: Pressure gradient; AVA: Aortic valve area; AR: Aortic rigurgitation; PASP: Pulmonary arterial systolic pressure; AVR: Aortic valve replacement. [*]The ratio between the outer diameter of the sheath size (SXT, 18F: 7.2 mm and 19F: 7.5 mm; CoV, 18F: 7.3 mm) and MLD of the vessel at the access site. [†]Low osmolarity contrast medium (iomeprol 61.24 g/100 ml, *Iomeron, Bracco, UK*). [‡]72-hour after procedure.

treated (Supplementary Table 1). Life-threatening bleedings occurred in 2% versus 4% (p>0.99) of patients among SXT and CoV groups.

No periprocedural MI was reported. The use of SXT versus CoV was associated with less need for a permanent pacemaker (8% versus 38%, p<0.0001). The main cause for a permanent PM was the development of a third degree atrioventricular block soon after TAVR.

There was no significance with respect to in-hospital stroke among SXT and CoV (4% versus 6%, p>0.99): main causes were vascular (atherosclerotic debris) or cardiac (arrhythmias).

The use of SXT versus CoV had no impact on death occurrence (6% versus 2%, p>0.99). Causes of death in the SXT group were intraprocedural aortic root rupture, n=1; periprocedural stroke sequelae, n=1; post-operative multi organ failure after AVR due to valve embolization, n=1. In the CoV group there was one death due to intraprocedural left ventricular failure after valvuloplasty.

Table 5 summarizes one-month outcomes. A total of 47 patients (94%) treated with SXT and 49 patients (98%) treated with CoV were available for TTE. A good hemodynamic performance of both prostheses was observed. Relevant symptom relief was recorded in almost all cases with both prostheses, as suggested from the NYHA Class improvement. One patient in the CoV group developed severe paravalvular insufficiency that was successfully managed with additional valve dilation. One

Table 4. In-hospital outcomes

	SXT	*CoV*	*p*
Patients (n)	50	50	-
Pericardial effusion (n)			
<10 mm	6% (3)	2% (1)	0.23
>10 mm	2% (1)*	-	
Tamponade	2% (1)*	-	
New procedure requirement (n)	-	2% (1)	>0.99
Major vascular complication (n)			
Vessel rupture	2% (1)	2% (1)	>0.99
Pseudoaneurysm	2% (1)	-	
Residual stenosis requiring intervention	4% (2)	2% (1)	
Bleeding (n)			
Life-threatening or disabling	2% (1)	4% (2)	0.90
Major	2% (1)	2% (1)	
Minor	2% (1)	2% (1)	
Periprocedural MI (n)	-	-	-
AKI (modified RIFLE Classification) (n)			
Stage 1	14% (7)	8% (4)	0.16
Stage 2	14% (7)	24% (12)	
Stage 3	-	6% (3)	
Cerebrovascular accident (n)			
TIA	-	2% (1)	>0.99
Stroke	4% (2)	6% (3)	
PPM implantation (n)	8% (4)	38% (19)	<0.0001
Death (n)	6% (3)	2% (1)	>0.99

SXT: SAPIEN XT; CoV: CoreValve; MI: Myocardial infarction; AKI: Acute kidney injury; RIFLE: Risk, Injury, Failure, Loss, and End-stage kidney disease; TIA: Transient ischemic attack; PPM: permanent pacemaker. *In one patient transvenous PM lead caused right ventricle injury with subsequent pericardial effusion and cardiac tamponade requiring pericardiocentesis.

endocarditis (Duke Criteria) [10] and one ischemic cerebrovascular accident occurred after discharge, with no cardiac death in the SXT group. In the CoV group, one MI (medical management), one peripheral thrombosis (surgical thrombus removal), one massive esophageal bleeding due to liver cirrhosis (surgical hemostasis) and two further cerebral ischemic accidents were registered without cardiac deaths.

Overall, VARC-combined safety endpoints incidence favored SXT versus CoV (17% versus 34.6%, p=0.01; NNT=6 [2.9-71.6]).

To rule-out any possible impact of a learning curve with respect to the main outcome among patients enrolled, SXT and CoV groups were divided in quintiles based on sequence number. Thereafter, the primary endpoint occurrence for each quintile was evaluated for both SXT and CoV, finally looking for differences between quintiles. No significance was reported (Supplementary Figure 1).

Multivariate analysis

Results of multivariable logistic regression analysis are reported in **Table 6** (univariate analysis in Supplementary Table 2). Interestingly, TAVR with SXT (odds ratio=0.21, [0.05-0.84], p=0.03) was found protective against VARC-combined safety endpoints occurrence. The Hosmer-Lemeshow statistic was not significant (p=0.42), confirming the goodness-of-fit of the logistic regression model.

Discussion

The main results of this study are: i) in patients suffering from symptomatic, severe AS, TAVR with either SXT or CoV is feasible, with acceptable complications rate up to 30-day follow-up; ii) the use of SXT versus CoV allows TAVR through transfemoral route without increasing the incidence of access site and cerebrovascular complications; iii) the use of SXT is associated with fewer occurrence of VARC-combined safety endpoints as compared with CoV.

Percutaneous aortic valve implantation significantly expanded the treatment options for symptomatic patients with severe AS at high-risk for AVR. However, the PARTNER study suggested more than a word of caution due to higher rates of vascular [4, 5] and cerebral [24, 25] complications with ES implantation, whilst large observational studies have reported very few complications associated with CoV [26].

To date, no randomized trial investigated ES versus CoV. Data gathering from mixed populations receiving either ES or CoV confirmed the use of ES associated with higher complication rate as compared to CoV [8, 27]. For these reasons, the wide use of balloon-expandable valve

Table 5. One-month outcomes

	SXT	*CoV*	*p*
Patients (n)	47	49	-
LVEF (%)	56.33±6.65	54.25±13.34	0.84
LV Septum (mm)	12.90±1.42	13.45±1.50	0.14
AV Mean PG (mmHg)	10.30±3.32	9.34±3.43	0.10
AVA (cm^2)	1.73±0.31	1.97±0.50	0.19
AR (n, moderate/severe)	8.5% (4)	25.7% (9)	0.35
PASP (mmHg)	41.80±16.77	40.90±11.50	0.83
NYHA Class (n)*			
I	59.5% (28)	55.1% (27)	0.16
II	27.6% (13)	38.7% (19)	
III	8.5% (4)	4% (2)	
IV	2.1% (1)	2% (1)	
Endocarditis (n)	-	2% (1)	>0.99
PPM implantation (n)	2% (1)	2% (1)	>0.99
Any vascular complication (n)	-	-	-
Major	-	2% (1)	>0.99
Any Bleeding (n)	-	2% (1)	>0.99
Major	-	2% (1)	>0.99
MI (n)	-	2% (1)	>0.99
AKI-Modified RIFLE Stage 3 (n)	-	-	-
TIA/Stroke (n)	2% (1)	4% (2)	>0.99
Death (n)			
Non cardiac	-	-	-
Cardiac	-	-	-
Combined safety end-points (n)	17% (8)	34.6% (17)	0.01

SXT: SAPIEN XT; CoV: CoreValve; LVEF: Left ventricular ejection fraction; LV: Left ventricular; AV: Aortic Valve; PG: Pressure gradient; AVA: Aortic valve area; AR: Aortic regurgitation; PASP: Pulmonary arterial systolic pressure; NYHA: New York Heart Association; PPM: permanent pacemaker; MI: Myocardial infarction; AKI: Acute kidney injury; RIFLE: Risk, Injury, Failure, Loss, and End-stage kidney disease; TIA: Transient ischemic attack. *SXT Group data were available for 46 out of 47 patients (97.8%) undergoing 1-month follow-up. In one case NYHA Class cannot be assessed due to disabling stroke sequelae (aphasia, hemiparesis).

was quite limited, and surgical preparation of the access site came as a frequent option to reduce the complications faced with a complete percutaneous approach [4, 28].

The SXT has been developed to possibly overcome the intrinsic limitations of the ES prosthesis. First Webb and co-workers [9], than Eltchaninoff and colleagues [29], have suggested a potential "broader application" of SXT versus ES in virtue of less cumbersome vascular access management and improved implant procedure. In this respect, two consecutive series of patients treated with either transfemoral ES or SXT found this latter associated with less vascular events [30], as well as fewer conversion to general anesthesia [28].

Given the relative novelty of SXT prosthesis, its performance as compared with CoV has not completely been established. The Transcatheter Valve Treatment Sentinel Pilot Registry has recently assessed predictors of in-hospital outcome and complications of contemporary TAVR practice: in this registry SXT and CoV reported similar outcomes, though more than one fourth of patients included received transapical SXT implantation [31]. More recently, the Pooled-Rotterdam-Milano-Toulouse In Collaboration (PRAGMATIC Plus) Initiative published a propensity matched cohort of patients undergoing ES/SXT versus CoV implantation. At 30-day as well as at 1-year follow-up, the adjusted analysis found no differences between these devices in terms of VARC endpoints, with higher incidence of permanent PM requirements after CoV [11].

In the present study, we compared transfemoral TAVR with SXT versus CoV in two sequential cohorts of consecutive patients suffering from severe AS and prospectively enrolled at a single Institution. The use of SXT was associated with a reduced occurrence of VARC-combined safety endpoints as compared to CoV up to 1-month follow-up.

The different VARC-combined safety endpoints incidence among groups was primarily driven by numerically higher incidence of ischemic stroke (10%) and AKI Stage 3 (6%) after CoV.

These results merit careful discussion. Firstly, the dislodgement of embolic debris during implantation is a common finding in patients undergoing TAVR, with no differences between available prostheses [32]. However, the present study cannot assess whether the continu-

Table 6. Multivariate logistic binary regression analysis for combined safety endpoints occurrence

Variables	*OR*	*95% CI*	*p*
SXT valve implantation	0.21	0.05-0.84	0.03
BNP (ng/L) at admission	1.00	0.99-1.02	0.51
STS morbidity and mortality	1.02	0.97-1.07	0.49
COPD at admission	2.80	0.77-10.12	0.11
Combined CAD/CVD	11.52	0.68-19.68	0.09

See Text for methodological details. OR: Odds ratio; CI: Confidence interval; SXT: SAPIEN XT; STS: Society of Thoracic Surgeons; BNP: Brain natriuretic peptide; COPD: Chronic obstructive pulmonary disease; CAD: Coronary artery disease; CVD: Cerebro-vascular disease.

ous expansion after deployment of the nitinol-frame based CoV may induce late events. Secondly, although overall contrast medium amount used in this series matched previous publications [8], the different implantation-techniques belonging to SXT and CoV is supposed to have influenced the frequency of AKI Stage 3.

Despite the rate of successful implantation of SXT versus CoV was not statistically different a higher valve/patient ratio was observed in the CoV group. This aspect mirrors previous data [27] and might be related to the inability of the operators to accurately predict final CoV position, until the valve/delivery-system is completely disconnected.

Not surprisingly, [33] in the current study it was observed a higher need of permanent PM after CoV implantation. However, the significant differences in bundle-branch block and septum thickness between SXT and CoV groups might have biased the real incidence of this complication.

The use of SXT versus CoV was associated with a significantly lower incidence of paravalvular regurgitation though no difference in terms of moderate/severe AR was observed between groups. The presence of paravalvular or hemodynamically relevant AR has been associated with a worse prognosis in patients undergoing TAVR [33]. In the present study, the possible influence of paravalvular AR on prognosis cannot be excluded.

Very few bleedings occurred in the overall population. As reported, in the first phase of our experience 6-month dual antiplatelet therapy after TAVR with CoV were prescribed. In comparison, patients undergoing SXT implantation were treated with aspirin only in nearly all cases. Although the evidences on this topic are quite empiric or absent [34, 35], the small sample-size of this series, as well as the strict association between antiplatelet therapy and valve type, precluded to discard interactions between drug regimens and adverse events (i.e. stroke, bleedings, vascular complications).

Strengths and limitations of the study

We aimed to evaluate a population of high-risk patients treated with transfemoral TAVR with either SXT or CoV. The prospective design pointed to overcome the limitation of a retrospective patient selection. The exclusion of patients enrolled during the learning-curve was in line with previous publication on this topic [22, 23] suggesting possible plateau proficiency after 25-30 TAVR procedures. The exclusion of a starting-up phase is believed to be of paramount importance in providing a more objective evaluation of new devices, without interference from less experienced operators [23, 36]. However, the possible influence of the extension of the learning-curve on the outcomes observed cannot be definitively discarded. The small sample size precludes sufficient power for definitive conclusions. This aspect may be due to the selection process [23]: indeed, TAVR is still reserved for a very high-selected population, in order not to overestimate the benefits of a procedure for which the very long-term results are still unknown. The study does not have a randomized design. On the one hand, prospective registries can provide strong external validity by including more heterogeneous populations. On the other hand, the lack of randomization led to several baseline differences among groups. The present study is based on a single-center experience, with skilled operators at high-volume TAVR practice. No independent event committee adjudicated the occurrence of the endpoints: we recognize the relevance of blind-to-treatment committees, although the adoption of VARC criteria aimed to warrant a high reproducibility level. The patients enrolled in this registry were discharged with different antiplatelet indications after TAVR. The interaction of different antiplatelet regimens with the patient outcome needs specifically designed

trials. Only thirty-day follow-up was reported: although procedure-specific outcomes are best revealed in early results, a longer follow-up would be preferable, to appropriately evaluate late events.

Conclusions

In two sequential cohorts of consecutive high-risk patients with symptomatic, severe AS, transfemoral TAVR with SAPIEN XT as compared with CoreValve was associated with lower VARC-combined safety endpoints occurrence. Properly-designed randomized trials are needed to confirm these results.

Disclosure of conflict of interest

Dr. A. Markus Kasel is a proctor for Edwards Lifesciences and Medtronic. Other Authors report no potential conflict of interest.

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References

[1] Cribier A, Eltchaninoff H, Tron C, Bauer F, Agatiello C, Nercolini D, Tapiero S, Litzler PY, Bessou JP and Babaliaros V. Treatment of calcific aortic stenosis with the percutaneous heart valve: mid-term follow-up from the initial feasibility studies: the French experience. J Am Coll Cardiol 2006; 47: 1214-1223.

[2] Webb JG, Pasupati S, Humphries K, Thompson C, Altwegg L, Moss R, Sinhal A, Carere RG, Munt B, Ricci D, Ye J, Cheung A and Lichtenstein SV. Percutaneous transarterial aortic valve replacement in selected high-risk patients with aortic stenosis. Circulation 2007; 116: 755-763.

[3] Grube E, Buellesfeld L, Mueller R, Sauren B, Zickmann B, Nair D, Beucher H, Felderhoff T, Iversen S and Gerckens U. Progress and current status of percutaneous aortic valve replacement: results of three device generations of the CoreValve Revalving system. Circ Cardiovasc Interv 2008; 1: 167-175.

[4] Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010; 363: 1597-1607.

[5] Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011; 364: 2187-2198.

[6] Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, Fontana GP, Dewey TM, Thourani VH, Pichard AD, Fischbein M, Szeto WY, Lim S, Greason KL, Teirstein PS, Malaisrie SC, Douglas PS, Hahn RT, Whisenant B, Zajarias A, Wang D, Akin JJ, Anderson WN, Leon MB; PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012; 366: 1686-1695.

[7] Makkar RR, Fontana GP, Jilaihawi H, Kapadia S, Pichard AD, Douglas PS, Thourani VH, Babaliaros VC, Webb JG, Herrmann HC, Bavaria JE, Kodali S, Brown DL, Bowers B, Dewey TM, Svensson LG, Tuzcu M, Moses JW, Williams MR, Siegel RJ, Akin JJ, Anderson WN, Pocock S, Smith CR, Leon MB; PARTNER Trial Investigators. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. N Engl J Med 2012; 366: 1696-1704.

[8] Wenaweser P, Pilgrim T, Roth N, Kadner A, Stortecky S, Kalesan B, Meuli F, Büllesfeld L, Khattab AA, Huber C, Eberle B, Erdös G, Meier B, Jüni P, Carrel T, Windecker S. Clinical outcome and predictors for adverse events after transcatheter aortic valve implantation with the use of different devices and access routes. Am Heart J 2011; 161: 1114-1124.

[9] Nietlispach F, Wijesinghe N, Wood D, Carere RG and Webb JG. Current balloon-expandable transcatheter heart valve and delivery systems. Catheter Cardiovasc Interv 2010; 75: 295-300.

[10] Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, Krucoff MW, Mack M, Mehran R, Miller C, Morel MA, Petersen J, Popma JJ, Takkenberg JJ, Vahanian A, van Es GA, Vranckx P, Webb JG, Windecker S, Serruys PW. Standardized endpoint definitions for Transcatheter Aortic Valve Implantation clinical trials: a consensus report from the Valve Academic Research Consortium. J Am Coll Cardiol 2011; 57: 253-269.

[11] Chieffo A, Buchanan GL, Van Mieghem NM, Tchetche D, Dumonteil N, Latib A, van der Boon RM, Vahdat O, Marcheix B, Farah B, Ser-

ruys PW, Fajadet J, Carrié D, de Jaegere PP, Colombo A. Transcatheter aortic valve implantation with the Edwards SAPIEN versus the Medtronic CoreValve Revalving system devices: a multicenter collaborative study: the PRAGMATIC Plus Initiative (Pooled-RotterdAm-Milano-Toulouse In Collaboration). J Am Coll Cardiol 2013; 61: 830-836.

[12] Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I and Mitnitski A. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005; 173: 489-495.

[13] Kasel AM, Cassese S, Bleiziffer S, Amaki M, Hahn RT, Kastrati A and Sengupta PP. Standardized imaging for aortic annular sizing: implications for transcatheter valve selection. JACC Cardiovasc Imaging 2013; 6: 249-262.

[14] Eltchaninoff H, Kerkeni M, Zajarias A, Tron C, Godin M, Sanchez Giron C, Baala B and Cribier A. Aorto-iliac angiography as a screening tool in selecting patients for transfemoral aortic valve implantation with the Edwards SAPIEN bioprosthesis. EuroIntervention 2009; 5: 438-442.

[15] Hayashida K, Lefevre T, Chevalier B, Hovasse T, Romano M, Garot P, Mylotte D, Uribe J, Farge A, Donzeau-Gouge P, Bouvier E, Cormier B and Morice MC. Transfemoral aortic valve implantation new criteria to predict vascular complications. JACC Cardiovasc Interv 2011; 4: 851-858.

[16] Webb JG, Chandavimol M, Thompson CR, Ricci DR, Carere RG, Munt BI, Buller CE, Pasupati S and Lichtenstein S. Percutaneous aortic valve implantation retrograde from the femoral artery. Circulation 2006; 113: 842-850.

[17] Lee WA, Brown MP, Nelson PR, Huber TS and Seeger JM. Midterm outcomes of femoral arteries after percutaneous endovascular aortic repair using the Preclose technique. J Vasc Surg 2008; 47: 919-923.

[18] Grube E, Schuler G, Buellesfeld L, Gerckens U, Linke A, Wenaweser P, Sauren B, Mohr FW, Walther T, Zickmann B, Iversen S, Felderhoff T, Cartier R, Bonan R. Percutaneous aortic valve replacement for severe aortic stenosis in high-risk patients using the second- and current third-generation self-expanding CoreValve prosthesis: device success and 30-day clinical outcome. J Am Coll Cardiol 2007; 50: 69-76.

[19] Kasel AM, Cassese S, Leber AW, von Scheidt W and Kastrati A. Fluoroscopy-guided aortic root imaging for TAVR: "follow the right cusp" rule. JACC Cardiovasc Imaging 2013; 6: 274-275.

[20] Bellomo R, Kellum JA and Ronco C. Defining and classifying acute renal failure: from advocacy to consensus and validation of the RIFLE criteria. Intensive Care Med 2007; 33: 409-413.

[21] Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, De Zeeuw D, Hostetter TH, Lameire N and Eknoyan G. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2005; 67: 2089-2100.

[22] Hernández-Antolín RA, García E, Sandoval S, Almería C, Cuadrado A, Serrano J, de Obeso E, Del Valle R, Bañuelos C, Alfonso F, Guerrero F, Heredia J, Benítez JC, García-Rubira JC, Rodríguez E, Macaya C. Findings of a mixed transfemoral aortic valve implantation program using Edwards and CoreValve devices. Rev Esp Cardiol 2011; 64: 35-42.

[23] Alli OO, Booker JD, Lennon RJ, Greason KL, Rihal CS and Holmes DR Jr. Transcatheter aortic valve implantation: assessing the learning curve. JACC Cardiovasc Interv 2012; 5: 72-79.

[24] Kahlert P, Knipp SC, Schlamann M, Thielmann M, Al-Rashid F, Weber M, Johansson U, Wendt D, Jakob HG, Forsting M, Sack S, Erbel R and Eggebrecht H. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. Circulation 2010; 121: 870-878.

[25] Rodés-Cabau J, Dumont E, Boone RH, Larose E, Bagur R, Gurvitch R, Bédard F, Doyle D, De Larochellière R, Jayasuria C, Villeneuve J, Marrero A, Côté M, Pibarot P, Webb JG. Cerebral embolism following transcatheter aortic valve implantation: comparison of transfemoral and transapical approaches. J Am Coll Cardiol 2011; 57: 18-28.

[26] Ussia GP, Barbanti M, Petronio AS, Tarantini G, Ettori F, Colombo A, Violini R, Ramondo A, Santoro G, Klugmann S, Bedogni F, Maisano F, Marzocchi A, Poli A, De Carlo M, Napodano M, Fiorina C, De Marco F, Antoniucci D, de Cillis E, Capodanno D, Tamburino C; CoreValve Italian Registry Investigators. Transcatheter aortic valve implantation: 3-year outcomes of self-expanding CoreValve prosthesis. Eur Heart J 2012; 33: 969-976.

[27] Godino C, Maisano F, Montorfano M, Latib A, Chieffo A, Michev I, Al-Lamee R, Bande M, Mussardo M, Arioli F, Ielasi A, Cioni M, Taramasso M, Arendar I, Grimaldi A, Spagnolo P, Zangrillo A, La Canna G, Alfieri O, Colombo A. Outcomes after transcatheter aortic valve implantation with both Edwards-SAPIEN and CoreValve devices in a single center: the Milan experience. JACC Cardiovasc Interv 2010; 3: 1110-1121.

[28] Durand E, Borz B, Godin M, Tron C, Litzler PY, Bessou JP, Bejar K, Fraccaro C, Sanchez-Giron C, Dacher JN, Bauer F, Cribier A and Eltchaninoff H. Transfemoral Aortic Valve Replacement

With the Edwards SAPIEN and Edwards SAPIEN XT Prosthesis Using Exclusively Local Anesthesia and Fluoroscopic Guidance: Feasibility and 30-Day Outcomes. JACC Cardiovasc Interv 2012 May; 5: 461-7.

[29] Eltchaninoff H, Durand E, Borz B, Godin M, Tron C, Litzler PY, Bessou JP, Bejar K, Fraccaro C, Sanchez-Giron C, Dacher JN, Bauer F and Cribier A. Prospective analysis of 30-day safety and performance of transfemoral transcatheter aortic valve implantation with Edwards SAPIEN XT versus SAPIEN prostheses. Arch Cardiovasc Dis 2012; 105: 132-140.

[30] Mussardo M, Latib A, Chieffo A, Godino C, Ielasi A, Cioni M, Takagi K, Davidavicius G, Montorfano M, Maisano F, Carlino M, Franco A, Covello RD, Spagnolo P, Grimaldi A, Alfieri O, Colombo A. Periprocedural and short-term outcomes of transfemoral transcatheter aortic valve implantation with the Sapien XT as compared with the Edwards Sapien valve. JACC Cardiovasc Interv 2011; 4: 743-750.

[31] Di Mario C, Eltchaninoff H, Moat N, Goicolea J, Ussia GP, Kala P, Wenaweser P, Zembala M, Nickenig G, Alegria Barrero E, Snow T, Iung B, Zamorano P, Schuler G, Corti R, Alfieri O, Prendergast B, Ludman P, Windecker S, Sabate M, Gilard M, Witowski A, Danenberg H, Schroeder E, Romeo F, Macaya C, Derumeaux G, Maggioni A, Tavazzi L; Transcatheter Valve Treatment Sentinel Registry (TCVT) Investigators of the EURObservational Research Programme (EORP) of the European Society of Cardiology. The 2011-12 pilot European Sentinel Registry of Transcatheter Aortic Valve Implantation: in-hospital results in 4,571 patients. EuroIntervention 2013 Apr 22; 8: 1362-71.

[32] Kahlert P, Al-Rashid F, Döttger P, Mori K, Plicht B, Wendt D, Bergmann L, Kottenberg E, Schlamann M, Mummel P, Holle D, Thielmann M, Jakob HG, Konorza T, Heusch G, Erbel R, Eggebrecht H. Cerebral embolization during transcatheter aortic valve implantation: a transcranial Doppler study. Circulation 2012; 126: 1245-1255.

[33] Gilard M, Eltchaninoff H, Iung B, Donzeau-Gouge P, Chevreul K, Fajadet J, Leprince P, Leguerrier A, Lievre M, Prat A, Teiger E, Lefevre T, Himbert D, Tchetche D, Carrié D, Albat B, Cribier A, Rioufol G, Sudre A, Blanchard D, Collet F, Dos Santos P, Meneveau N, Tirouvanziam A, Caussin C, Guyon P, Boschat J, Le Breton H, Collart F, Houel R, Delpine S, Souteyrand G, Favereau X, Ohlmann P, Doisy V, Grollier G, Gommeaux A, Claudel JP, Bourlon F, Bertrand B, Van Belle E, Laskar M; FRANCE 2 Investigators. Registry of transcatheter aortic-valve implantation in high-risk patients. N Engl J Med 2012; 366: 1705-1715.

[34] Ussia GP, Scarabelli M, Mule M, Barbanti M, Sarkar K, Cammalleri V, Imme S, Aruta P, Pistritto AM, Gulino S, Deste W, Capodanno D and Tamburino C. Dual Antiplatelet Therapy Versus Aspirin Alone in Patients Undergoing Transcatheter Aortic Valve Implantation. Am J Cardiol 2011 Dec 15; 108: 1772-6.

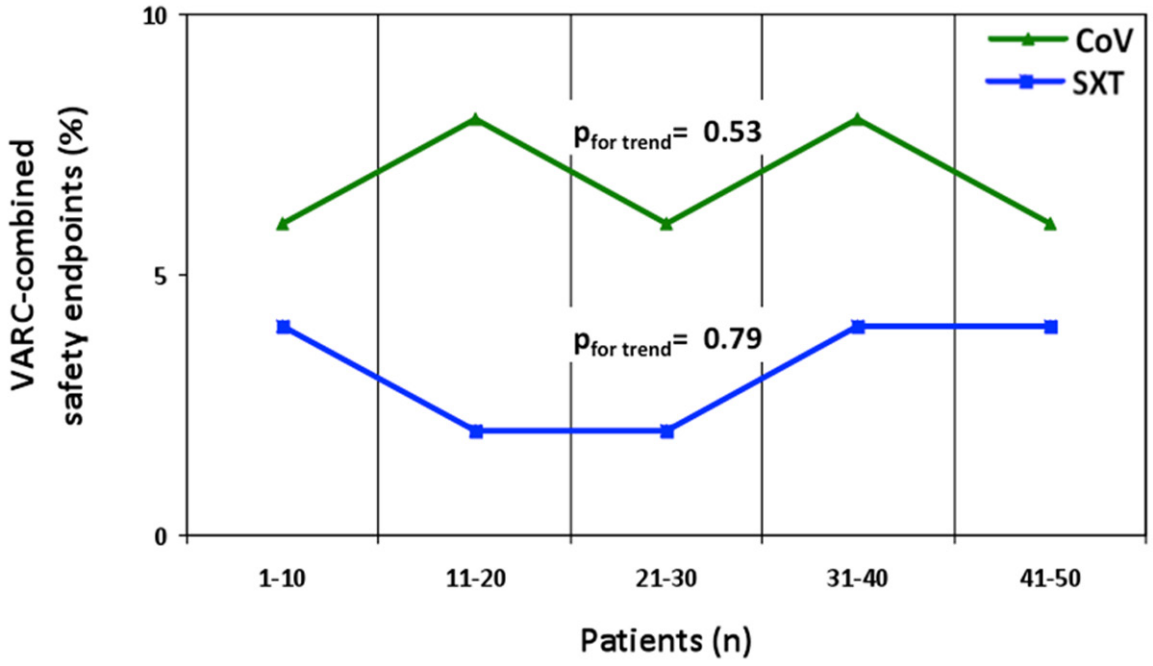
[35] Stabile E, Pucciarelli A, Cota L, Sorropago G, Tesorio T, Salemme L, Popusoi G, Ambrosini V, Cioppa A, Agrusta M, Catapano D, Moscariello C, Trimarco B, Esposito G, Rubino P. SAT-TAVI (single antiplatelet therapy for TAVI) study: A pilot randomized study comparing double to single antiplatelet therapy for transcatheter aortic valve implantation. Int J Cardiol 2014; 174: 624-7.

[36] Gurvitch R, Tay EL, Wijesinghe N, Ye J, Nietlispach F, Wood DA, Lichtenstein S, Cheung A and Webb JG. Transcatheter aortic valve implantation: lessons from the learning curve of the first 270 high-risk patients. Catheter Cardiovasc Interv 2011; 78: 977-984.

Supplementary Table 1. Type, time and treatment of major vascular complications

Patient number	*Valve type*	*Complication type*	*Time*	*Treatment*	*Outcome*
1	SXT	Right common femoral artery injury at puncture site	Procedure	Surgery	Resolved
2	SXT	Suture-driven right common femoral artery stenosis	Procedure	PTA (Conventional balloon)	Resolved
3	SXT	Suture-driven left common femoral artery stenosis	Procedure	PTA (Conventional balloon)	Resolved
4	SXT	Left common femoral artery pseudoaneurysm	Day 1 after procedure	Surgery + Blood transfusion	Resolved
5	CoV	Suture-driven left common femoral artery stenosis	Procedure	PTA (Conventional balloon)	Resolved
6	CoV	Left common iliac artery rupture	Procedure	Surgery	Resolved
7	CoV	Right common femoral artery thrombosis with embolization	Day 10 after procedure	Surgery	Resolved

SXT: SAPIEN XT; CoV: CoreValve; PTA: Percutaneous transluminal angioplasty.



Supplementary Figure 1. VARC-combined safety endpoints incidence in SXT and CoV groups divided in quintiles based on sequence number. Imbalance with respect to endpoints occurrence between quintiles was investigated with the Cochran-Armitage test for trend. A *p* value <0.05 is significant. VARC: Valve Academic Research Consortium; SXT: SAPIEN XT; CoV: CoreValve.

Supplementary Table 2. Baseline and procedural variables according to VARC combined endpoints occurrence

	VARC combined safety endpoint		*p*
	Yes (n=25)	*No (n=75)*	
Clinical variables			
Age (y)	81.44±6.13	80.42±5.97	0.46
Male (n)	40% (10)	30.6% (23)	0.39
BMI (kg/m²)	26.51±4.29	27.24±4.71	0.49
Hypertension (n)	72% (18)	68% (51)	0.80
Dyslipidemia (n)	36% (9)	38.6% (29)	0.81
Diabetes mellitus (n)	40% (10)	37.3% (28)	0.81
Insulin treated (n)	8% (2)	9.3% (7)	>0.99
COPD (n)	32% (8)	16% (12)	*0.09*
Carotid artery disease (n)	32% (8)	33.3% (25)	0.90
CAD (n)	60% (15)	48% (36)	0.39
Combined CAD/CVD (n)	16% (4)	4% (3)	*0.06*
Previous MI (n)	20% (5)	9.3% (7)	0.15
Previous cardiovascular surgery (n)	28% (7)	18.6% (14)	0.32
History of malignancy (n)	36% (9)	25.3% (19)	0.30
Previous chest irradiation	12% (3)	9.3% (7)	0.57
Porcelain aorta (n)	12% (3)	8% (6)	0.68
Syncope (n)	16% (4)	5.3% (4)	0.10
NYHA Functional Class (n)			
III	76% (19)	80% (60)	0.64
IV	24% (6)	20% (15)	
CCS Angina Class (n)			
>II	16% (4)	17.3% (13)	0.65
CKD Stages (n, ml/min/1.73 m²)			
III	36% (9)	50.6% (38)	0.21
≥IV	64% (16)	46.6% (35)	
STS PROM	11.72±9.04	8.94±6.76	0.10
STS morbidity and mortality	36.01±12.80	30.03±10.24	*0.03*
LogEuroSCORE	23.43±17.50	21.50±13.52	0.56
BNP (ng/L)	1086.81±592.79	623.24±413.47	*0.04*
Hb (g/dl)	11.78±3.03	12.46±2.08	0.24
Rhythm and impulse conduction (n)			
Normal	56% (14)	58% (44)	0.93
Bundle branch block	20% (5)	17.3% (13)	
Atrial fibrillation	16% (4)	12% (9)	
Pacemaker	8% (2)	12% (9)	
Imaging variables			
TEE AV Annulus (mm)	21.77±1.77	22.28±2.33	0.26
LVEF (%)	54.22±10.49	52.48±8.69	0.45
LV Septum (mm)	13.50±1.25	13.88±1.90	0.35
AV Mean PG (mmHg)	41.12±14.56	43.12±14.50	0.55
AVA (cm²)	0.62±0.15	0.66±0.15	0.34
AR (n, moderate/severe)	32% (8)	28% (21)	0.19
PASP (mmHg)	50.78±13.20	48.26±15.09	0.48
AV Annulus Effective Diam (mm)	23.28±1.69	22.99±1.72	0.47

MLD vascular access site (mm)	7.65±0.89	7.73±1.24	0.76
Procedural variables			
Prosthesis type			
SXT	32% (8)	56% (42)	*0.03*
CoV	68% (17)	44% (33)	
Prosthesis measure (n)			
23 mm	16% (4)	25.3% (19)	0.29
26 mm	56% (14)	60% (45)	
29 mm	28% (7)	14.6% (11)	
Outer sheath diameter/MLD ratio[*]	0.99±0.16	1.08±0.30	0.19
Contrast medium[†] *amount (ml)*	282.72±147.49	242.86±91.81	0.11
Fluoroscopy time (min)	18.94±10.95	16.43±11.36	0.34
LVEF (%)	51.14±7.16	53.68±7.89	0.18
AV Mean PG (mmHg)	9.68±9.51	7.88±3.73	0.55
AVA (cm^2)	2.05±0.78	1.90±0.45	0.50
AR (n, moderate/severe)	8% (2)	12% (9)	0.17
AR qualitative (n)			
Paravalvular	26% (18)	90% (40)	0.27
Transvalvular	-	2% (2)	
Para/Transvalvular	4% (2)	-	
PASP (mmHg)	43.55±11.74	42.12±13.09	0.19
Device success (n)	88% (22)	96% (72)	0.16
Switch to conventional AVR surgery (n)	8% (2)	-	>0.99
New procedure requirement (n)	-	1.3% (1)	0.25
Pericardial effusion (n)[‡]			
<10 mm	-	5.3% (4)	0.19
>10 mm	4% (1)	-	
PPM implantation (n)[§]	24% (6)	22.6% (17)	0.94

See Text for methodological details. In *Italic typewrite* variables that were selected for final multivariate model (p<0.1 as a reference for selection). VARC: Valve academic research consortium; BMI: Body-mass index; COPD: Chronic obstructive pulmonary disease; CAD: Coronary artery disease; CVD: Cerebro-vascular disease; MI: Myocardial infarction; PAD: Peripheral artery disease; NYHA: New York Heart Association; CCS: Canadian Cardiovascular Society; CKD: Chronic kidney disease; STS PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; LogEuroSCORE: logistic European System for Cardiac Operative Risk Evaluation; BNP: Brain Natriuretic peptide. TEE: Transesophageal echocardiography; LVEF: Left ventricular ejection fraction; LV: Left ventricular; AV: Aortic Valve; PG: Pressure gradient; AVA: Aortic valve area; AR: Aortic regurgitation; PASP: Pulmonary arterial systolic pressure; MLD: Minimum lumen diameter; SXT: SAPIEN XT; CoV: CoreValve; AVR: Aortic valve replacement; PPM: permanent pacemaker. [*]The ratio between the outer diameter of the sheath size (SXT, 18F: 7.2 mm and 19F: 7.5 mm; CoV, 18F: 7.3 mm) and MLD of the vessel at the therapeutic site. [†]Low osmolarity contrast medium (iomeprol 61.24 g/100 ml, *Iomeron, Bracco, UK*). [‡]Cardiac tamponade not included. [§]During hospitalization.