One-year outcomes after transcatheter aortic valve implantation with the latest-generation SAPIEN balloon-expandable valve: the S3U registry

Stefano Cannata[1], MD; Caterina Gandolfo[1]*, MD; Flavio Ribichini[2], MD; Nicolas Van Mieghem[3], MD; Sergio Buccheri[4], MD; Marco Barbanti[5], MD; Sergio Berti[6], MD; Rui Campante Teles[7], MD; Antonio L. Bartorelli[8], MD; Giuseppe Musumeci[9], MD; Tommaso Piva[10], MD; Luis Nombela-Franco[11], MD; Ketty La Spina[1], MD; Tullio Palmerini[12], MD; Rik Adrichem[3], MD; Augusto Esposito[6], MD; Pedro Lopes[7], MD; Paolo Olivares[8], MD; Gianmarco Annibali[9], MD; Elisa Nicolini[10], MD; Luis Marroquin[11], MD; Corrado Tamburino[6], MD; Giuseppe Tarantini[13], MD; Francesco Saia[12], MD

The authors' affiliations can be found in the Appendix paragraph.

GUEST EDITOR: Franz-Josef Neumann, MD; *Department of Cardiology and Angiology II, University Heart Center Freiburg – Bad Krozingen, Bad Krozingen, Germany.*

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Abstract

Background: Initial data about the performance of the new-generation SAPIEN 3 Ultra (S3U) valve are highly promising. However, evidence about the longer-term performance and safety of the S3U is scarce.

Aims: We aimed to investigate the 1-year clinical and echocardiographic outcomes of transcatheter aortic valve implantation (TAVI) using the S3U compared with its predecessor, the SAPIEN 3 valve (S3).

Methods: The SAPIEN 3 Ultra registry included consecutive patients who underwent transfemoral TAVI at 12 European centres with the S3U or S3 between October 2016 and December 2020. One-to-one propensity score (PS) matching was performed to account for differences in baseline characteristics. The primary outcomes of interest were all-cause death and the composite of all-cause death, disabling stroke and hospitalisation for heart failure at 1 year.

Results: The overall study cohort encompassed 1,692 patients treated with either the S3U (n=519) or S3 (n=1,173). The PS-matched population had a total of 992 patients (496 per group). At 1 year, the rate of death from any cause was 4.9% in the S3U group and 6.3% in the S3 group (p=0.743). Similarly, there were no significant differences in the rates of the primary composite outcome (9.5% in the S3 group and 6.6% in the S3U group; p=0.162). The S3U was associated with lower rates of mild paravalvular leak (PVL) compared with the S3 (odds ratio 0.63, 95% confidence interval: 0.44 to 0.88; p<0.01). No significant differences in transprosthetic gradients were observed between the two groups.

Conclusions: Compared with the S3, the S3U transcatheter heart valve was associated with similar 1-year clinical outcomes but reduced rates of mild PVL.

*Corresponding author: IRCCS-ISMETT, UPMC, Via E. Tricomi, 5, 90127 Palermo, Italy.
E-mail: cgandolfo@ismett.edu*

Abbreviations

AS	aortic stenosis
PPI	permanent pacemaker implantation
PVL	paravalvular leak
S3	SAPIEN 3 THV
S3U	SAPIEN 3 Ultra THV
TAVI	transcatheter aortic valve implantation
THV	transcatheter heart valve

Introduction

Transcatheter aortic valve implantation (TAVI) is an established treatment for patients with severe symptomatic aortic stenosis (AS) who are at increased surgical risk[1-3]. Recently, TAVI has been expanded to treat low-risk patients[3-5]. However, there are still concerns regarding the rate of permanent pacemaker implantation (PPI), valve durability and the incidence of paravalvular leak (PVL). The latter remains a main concern because it is well known that moderate to severe PVL is associated with an increased risk of mortality[6]. It remains unknown whether mild PVL affects outcomes[7], although recent evidence suggests an association with increased mortality[8,9]. As we are moving to treat low-risk and younger patients, it is essential to further improve TAVI performances in terms of residual PVL (any grade), with the aim of approaching those rates seen with surgical bioprostheses[4,5].

Over the past several years, the technological advancement of new-generation TAVI devices has been focused on the minimisation of PVL[10,11]. In fact, the latest-generation balloon-expandable transcatheter heart valve (THV), the SAPIEN 3 Ultra (S3U; Edwards Lifesciences) incorporates an outer skirt made from a textured polyethylene terephthalate (PET) which is 40% higher than that of the SAPIEN 3 (S3) to achieve better sealing. Initial data about the early post-implantation performance of S3U are promising, especially in terms of a reduced PVL rate[12-14]. However, there are limited data about the longer-term clinical outcomes and haemodynamic performance of the S3U[15]. Therefore, the principal aim of this study was to assess the clinical and echocardiographic outcomes at 1 year with the S3U compared to its predecessor, the S3 THV.

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Methods

STUDY POPULATION

The SAPIEN 3 Ultra registry[12] is an international, multicentre, observational, physician-led study that included consecutive patients with symptomatic severe AS who underwent transfemoral TAVI using a SAPIEN 3 Ultra balloon-expandable valve at 12 centres across 4 countries between October 2018 and December 2020 **(Supplementary Appendix 1)**. For comparison, we used an historical cohort of patients who underwent TAVI with the SAPIEN 3 THV from October 2016 to December 2020. We excluded patients who had undergone TAVI with the 29 mm S3, any patients who had undergone TAVI using alternative approaches other than the transfemoral access (non-TF TAVI), and those who had undergone TAVI for failed surgical aortic valve replacement (valve-in-valve). For the

purposes of the present analysis, patients with bicuspid aortic stenosis were also excluded. The study was approved by the local ethics committee of the coordinating institution; it was performed in accordance with the Declaration of Helsinki and under the auspices of the Italian Society of Interventional Cardiology (GISE).

The manufacturer of the SAPIEN 3 Ultra and SAPIEN 3 THV, Edwards Lifesciences, had no role in data collection, analysis, or manuscript drafting and did not provide any financial support for the study.

DEVICE DESCRIPTION

The SAPIEN 3 Ultra THV has the same cobalt-chromium alloy frame and bovine tissue leaflet design as the S3. The key difference between the two THV is the textured polyethylene terephthalate outer skirt of the SAPIEN 3 Ultra, which is approximately 40% higher compared to that of the S3 and was designed to improve annular sealing and to reduce PVL **(Figure 1)**. The S3U THV is available in 20 mm, 23 mm, and 26 mm sizes, whereas the S3 THV is also available in a 29 mm size. When initially released, the S3U THV was implanted using a novel delivery catheter system (SAPIEN 3 Ultra Delivery System; Edwards Lifesciences) with on-balloon valve crimping and the Axela sheath (Edwards Lifesciences). However, the SAPIEN 3 Ultra Delivery System was issued with a class I recall by the U.S. Food and Drug Administration (FDA)[16]. Following the recall, the S3U THV was implanted with the same delivery system used for the S3 THV (Commander Delivery System and eSheath; Edwards Lifesciences).

STUDY OUTCOMES

The primary outcomes of this analysis were death from any cause and the composite of death from any cause, disabling stroke and repeat hospitalisation for heart failure at 1 year.

Secondary outcomes of interest were cardiac death, new pacemaker implantation, repeat procedure and all components of the primary composite endpoint at 1 year. The incidence of selected procedural complications and clinical outcomes at 30 days were also considered. All clinical outcomes and procedural complications were assessed according to Valve Academic Research Consortium (VARC)-2 criteria[17]. Echocardiographic outcomes were evaluated before discharge and at 1 year. Paravalvular aortic leak severity was assessed according to VARC-2 criteria and classified as follows: none, trace, mild, moderate, or severe[17].

STATISTICAL ANALYSIS

All continuous variables are expressed as the mean±standard deviation (SD) and are compared using the unpaired Student's t-test. All categorical variables are compared using the chi-square test or Fisher's exact test. Missing baselines covariates were estimated using the multiple imputation chain method (n=5)[18]. The propensity score was used to adjust for differences in baseline characteristics and potential confounders that may lead to biased estimates of treatment outcomes. A 1-to-1 nearest-neighbour matching algorithm without replacement (calliper=0.2) was performed to identify PS-matched

Figure 1. *SAPIEN 3 Ultra THV. *Textured polyethylene terephthalate outer skirt, which is approximately 40% higher than the SAPIEN 3 skirt and is designed to improve annular sealing.*

pairs. This was done by means of a non-parsimonious multivariable logistic regression including the following covariates: age, sex, body mass index (BMI), body surface area (BSA), hypertension, Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score, NYHA Functional Class III or IV, diabetes, chronic obstructive pulmonary disease (COPD), severe liver disease, atrial fibrillation (AF), peripheral vascular disease, prior stroke, coronary artery disease, prior myocardial infarction, prior percutaneous coronary intervention (PCI), previous coronary artery bypass graft (CABG), other previous cardiac surgery, estimated glomerular filtration rate (eGFR), dialysis, porcelain aorta, cerebrovascular disease, prior permanent pacemaker implantation (PPI), baseline left bundle branch block (LBBB), baseline right bundle branch block (RBBB), baseline first degree atrioventricular (AV) block, left ventricular ejection function (LVEF), transaortic mean gradient, aortic valve area (AVA), moderate to severe mitral regurgitation, moderate to severe aortic regurgitation, severe pulmonary hypertension, THV size, anaesthesia type, left ventricular outflow tract (LVOT) and aortic valve calcium distribution at the pre-TAVI computed tomography (CT). Matching was performed within each imputed dataset using the observed and imputed covariate values. The balance on the matched datasets was assessed by computing the standardised mean difference (SMD) for each covariate. Finally, the treatment effects estimated in each of the matched datasets were pooled together using Rubin's rules[19].

Prespecified primary and secondary outcomes were compared between the S3 and S3U valve groups in both the overall and PS-matched cohorts. The risk of adverse events 1 year after TAVI was compared for both cohorts using Cox proportional hazards regression and Kaplan-Meier analysis.

Statistical analysis was performed using R software, version 4.2.0 (R Foundation for Statistical Computing) and SPSS Statistics, version 25 for Macintosh (IBM). Propensity score and matching procedures were conducted using the MatchThem package in R[19].

Results

BASELINE CHARACTERISTICS

A total of 1,692 patients who underwent transfemoral TAVI with the S3U (n=519) or S3 (n=1,173) THV were included. Baseline characteristics of the entire study population stratified according to the THV type are presented in **Table 1**.

Before matching, most characteristics were already well balanced, with the exception of patients treated with an S3U who had a lower mean STS-PROM score (4.0±2.7 vs 4.93±3.82; p<0.01) and more frequently had coronary artery disease (50.4% vs 44.4%; p=0.02), while the degree of calcification of the aortic valve and LVOT was higher in the S3 group.

From the entire cohort, a 1-to-1 propensity score matching analysis (including clinical and anatomical characteristics, THV size and anaesthesia type) resulted in 496 matched pairs. There was no significant difference in any baseline characteristic among the propensity-matched S3U and S3 groups **(Figure 2)**, including the degree of AV and LVOT calcification.

PROCEDURAL CHARACTERISTICS, IN-HOSPITAL AND 30-DAY OUTCOMES

Procedural characteristics and in-hospital outcomes of the unadjusted and PS-matched populations are listed in **Table 2**. In the propensity-matched population, both predilatation and post-dilatation were less frequently performed with S3U compared to S3 (odds ratio [OR] 0.56, 95% confidence interval [CI]: 0.41 to 0.78; p<0.01; OR 0.23, 95% CI: 0.10 to 0.52; p<0.01). There were no significant differences between the two groups in the use of general anaesthesia (p=0.555). In-hospital mortality during the index admission was comparable in both groups (OR 0.74; 95% CI: 0.22 to 2.46; p=0.619).

There were no differences with respect to major vascular complications (OR 0.72, 95% CI: 0.28 to 1.86; p=0.497), life-threatening bleeding (OR 0.43, 95% CI: 0.14 to 1.32; p=0.140), cardiac tamponade (OR 0.77, 95% CI: 0.17 to 3.49; p=0.728) or conversion to open heart surgery (OR 1.68, 95% CI: 0.16 to 18.20; p=0.662) between the 2 groups. The rates of both annulus rupture and acute coronary obstruction were extremely low in the entire cohort (only 2 and 3 cases, respectively).

The rate of device success was similar between the two groups (90.6% S3U vs 92.2% S3; p=0.340).

The S3 group were hospitalised for significantly more days in the unadjusted analysis (S3U 4.51±4.50 vs S3 5.52±5.50; p<0.01), but this difference was not apparent in the adjusted analysis (mean difference −0.41, 95% CI: −1.38 to 0.50; p=0.368). There was also no significant difference in the rate of new PPI between patients in the S3U and S3 groups (OR 0.83, 95% CI: 0.49 to 1.41; p=0.360).

Table 1. Baseline characteristics of registry patients before PS matching.

		Missing (%)	Overall (n=1,692)	SAPIEN 3 (n=1,173)	SAPIEN 3 Ultra (n=519)	*p*-value
Age, yrs		-	81.7±6.4	81.5±6.4	82±6.5	0.222
Female		-	958 (56.6)	646 (55.1)	31 (60.1)	0.054
Height, cm		-	161.9±8.9	161.8±8.9	161.9±8.7	0.845
Weight, kg		-	71.6±14.5	71.7±14.7	71.2±13.9	0.469
Body mass index, kg/m^2		-	27.28±5.07	27.33±5.15	27.16±4.88	0.509
Body surface area, m^2		-	1.78±0.20	1.78±0.20	1.77±0.20	0.480
STS score		1.6	4.65±3.55	4.93±3.82	4.0±2.70	<0.001
NYHA Class III or IV		-	914 (54.0)	627 (53.5)	277 (53.4)	0.709
Hypertension		-	1,423 (84.1)	976 (83.2)	447 (86.1)	0.130
Diabetes		-	494 (29.1)	351 (29.9)	143 (27.5)	0.323
COPD		-	292 (17.2)	214 (18.2)	78 (15)	0.107
Severe liver disease		-	27 (1.6)	20 (1.7)	7 (1.3)	0.590
Porcelain aorta		-	75 (4.4)	57 (4.8)	18 (3.4)	0.200
Atrial fibrillation		-	457 (27.0)	323 (27.5)	134 (25.8)	0.463
Prior PCI		-	390 (23.0)	280 (23.8)	110 (21.2)	0.228
Peripheral vascular disease		-	188 (11.1)	138 (11.8)	50 (9.6)	0.198
Previous stroke		-	158 (9.3)	115 (9.8)	43 (8.3)	0.322
CAD		-	783 (46.2)	521 (44.4)	262 (50.4)	0.021
Prior MI		-	247 (14.6)	162 (13.8)	85 (16.4)	0.168
Prior CABG		-	147 (8.6)	110 (9.3)	37 (7.1)	0.130
Other prior cardiac surgery		-	133 (7.8)	100 (8.5)	33 (6.3)	0.127
Dialysis		-	22 (1.3)	17 (1.4)	5 (0.9)	0.416
eGFR <30 ml /min/1.73 m^2		0.2	203 (11.9)	133 (11.3)	70 (13.5)	0.210
eGFR, ml/min/1.73 m^2		0.2	53.72±23.58	54.03±23.68	53.07±23.36	0.441
Severe pulmonary hypertension		1.0	138 (9.9)	101 (10.0)	37 (9.4)	0.663
Previous pacemaker		-	159 (9.4)	111 (9.4)	48 (9.2)	0.898
RBBB		32.4	131 (11.4)	90 (9.5)	41 (8.0)	0.344
First degree AV block		32.4	161 (11.1)	111 (11.8)	50 (9.8)	0.258
LBBB		32.4	115 (10.0)	72 (7.7)	43 (8.5)	0.585
Peak gradient, mmHg		7.7	72.97±23.04	73.67±23.33	71.34±22.29	0.068
Mean gradient, mmHg		2.3	48.66±17.74	49.10±17.77	47.64±17.64	0.127
AVA, cm²		14.3	0.69±0.20	0.69±0.20	0.68±0.19	0.444
LVEF, %		0.6	57.20±10.87	57.35±11.05	56.85±10.45	0.376
Moderate or severe AR		8.2	321 (20.6)	224 (20.0)	97 (22.3)	0.308
Moderate or severe MR		2.9	439 (26.7)	300 (25.8)	139 (28.8)	0.227
Aortic annulus area, mm²		21.5	433±67	433±66	432±68	0.914
Aortic valve calcification	None	26.6	48 (3.8)	26 (2.9)	22 (6.5)	0.02
	Mild	26.6	179 (14.4)	128 (14.0)	51 (15.0)	
	Moderate	26.6	589 (47.5)	428 (47.3)	161 (48.5)	
	Heavy	26.6	917 (34.2)	321 (35.5)	104 (30.8)	
LVOT calcification	None	28	875 (71.8)	619 (68.8)	256 (80.5)	0.01
	Mild	28	198 (11.7)	164 (13.9)	34 (6.5)	
	Moderate	28	79 (4.6)	67 (5.7)	12 (2.3)	
	Severe	28	65 (3.8)	49 (4.1)	16 (3.0)	

Values are n (%) or mean±standard deviation. AR: aortic regurgitation; AV: atrioventricular; AVA: aortic valve area; CABG: coronary artery bypass graft; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; eGFR: estimated GFR; GFR: glomerular filtration rate; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; MI: myocardial infarction; MR: mitral regurgitation; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; PS: propensity score; RBBB: right bundle branch block; STS: Society of Thoracic Surgeons
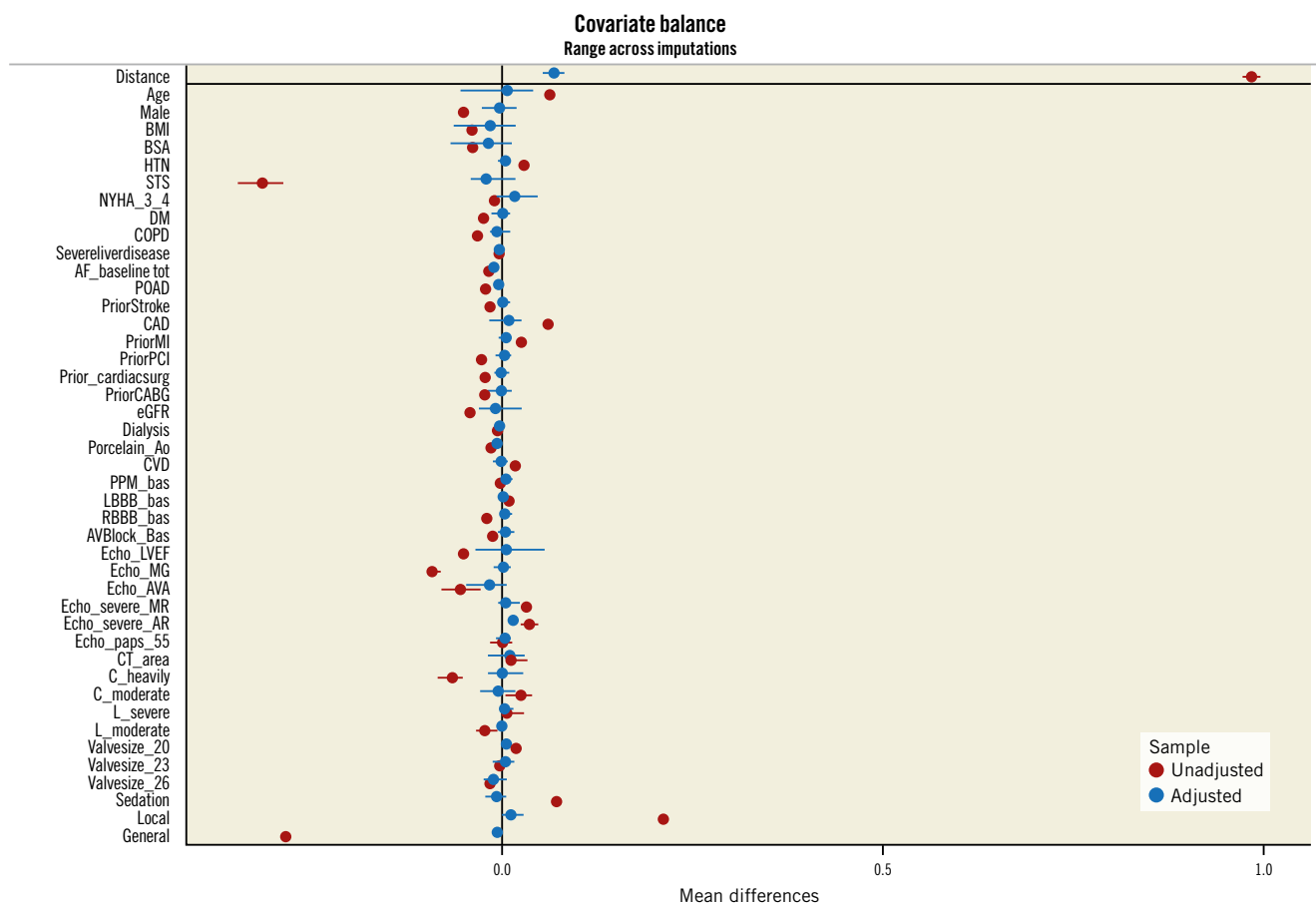
Figure 2. *Covariate balance plot. Baseline differences before propensity score matching (red circles) were adequately balanced after matching (blue circles).*

At 30 days, no significant differences were observed between patients treated with the S3U and S3 for all-cause mortality, disabling stroke, repeat hospitalisation for HF or rate of new PPI **(Table 3)**.

CLINICAL OUTCOMES AT 1 YEAR
Clinical outcomes at 1 year are shown for the unadjusted and propensity-matched populations in **Table 4**.

At 1 year, the rate of death from any cause was 4.9% in the S3U compared with 6.3% in the S3 group (hazard ratio [HR] 0.99, 95% CI: 0.61 to 1.41; p=0.745) **(Central illustration)**. Similarly, there was no significant difference in the rate of the composite endpoint of death from any cause, stroke, or rehospitalisation at 1 year after the procedure **(Central illustration)**. The unadjusted rate of new PPI was higher with the S3 compared to the S3U (HR 0.70, 95% CI: 0.50 to 0.99; p=0.045). The propensity-matched analysis confirmed that there were no significant differences in the rates of any death (HR 0.89, 95% CI: 0.53 to 1.53; p=0.691), cardiac death (HR 0.58, 95% CI: 0.24 to 1.38; p=0.218), disabling stroke (HR 0.55, 95% CI: 0.16 to 1.82; p=0.323) or heart failure hospitalisation (HR 0.71, 95% CI: 0.32 to 1.55; p=0.391). Moreover, the rate of new PPI at 1 year was similar in both groups (HR 0.75, 95% CI: 0.50 to 1.13; p=0.168).

ECHOCARDIOGRAPHIC OUTCOMES
Early echocardiographic data after TAVI (before discharge) of the unadjusted and propensity-matched cohorts are shown in **Table 2**. In the unadjusted population, the S3U more frequently achieved none/trivial PVL compared to its predecessor (OR 1.94, 95% CI: 1.50 to 2.52; p<0.01), whereas the rate of mild PVL was higher in the S3 group (OR 0.53, 95% CI: 0.43 to 0.73; p<0.01). The S3U was associated with a lower incidence of moderate or greater PVL compared with the S3 (0.8% for S3U vs 3.1% for S3; p<0.01). Moreover, the S3U yielded a slightly higher mean post-procedural aortic valve gradient than the S3 (12.5 mmHg vs 11.2 mmHg, respectively; p<0.01). However, the rate of device success did not differ between the two groups (S3U 90.8% vs S3 92.5%; p=0.340).

In the propensity-matched analysis, the S3U confirmed a lower incidence of PVL compared to the S3, but there was no difference in the rate of moderate or greater PVL (OR 0.34, 95% CI: 0.09 to 1.25; p=0.110). Post-procedural transprosthetic gradients were slightly higher in the S3U group (mean difference 1.31, 95% CI: 0.83 to 1.80; p<0.01; S3 group: mean difference 1.71; 95% CI: 0.82 to 2.61; p<0.01), but there was no difference in the rate of device success (OR 0.99; 95% CI: 0.64 to 1.51; p=0.952).

At 1 year, in both the unadjusted and the propensity-matched population **(Supplementary Table 1)**, absence of PVL was significantly

Table 2. Procedural and in-hospital outcomes of unadjusted and propensity-matched cohorts.

		SAPIEN 3 (n=1173)	SAPIEN 3 Ultra (n=519)	Unadjusted		Propensity-matched	
				OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Conscious sedation		377 (32.1)	204 (39.3)	1.36 (1.20-1.69)	0.04	0.97 (0.75-1.26)	0.840
General anaesthesia		414 (35.3)	36 (6.9)	0.14 (0.09-0.19)	<0.01	0.92 (0.70-1.20)	0.555
Local		382 (32.6)	279 (53.8)	2.40 (1.94-2.97)	<0.01	1.05 (0.81-1.35)	0.708
Predilatation		267 (22.7)	76 (14.6)	0.58 (0.43-0.76)	<0.01	0.56 (0.41-0.78)	<0.01
Post-dilatation		99 (8.4)	8 (1.5)	0.17 (0.07-0.33)	<0.01	0.23 (0.10-0.52)	<0.01
In-hospital death		18 (1.5)	5 (0.9)	0.62 (0.20-1.57)	0.354	0.74 (0.22-2.46)	0.619
Cardiac tamponade		8 (0.7)	4 (0.8)	1.13 (0.30-3.60)	0.841	0.77 (0.17-3.49)	0.728
Conversion to open heart surgery		5 (0.4)	3 (0.6)	1.35 (0.27-5.55)	0.676	1.68 (0.16-18.20)	0.661
Sepsis		14 (1.2)	10 (1.9)	1.62 (0.69-3.65)	0.244	0.99 (0.33-2.93)	0.988
Second THV implanted		6 (0.5)	1 (0.2)	0.375 (0.02-2.20)	0.365	0.55 (0.02-10.45)	0.685
Vascular complications	Major	29 (2.5)	12 (2.3)	0.93 (0.45-1.80)	0.843	0.86 (0.38-1.98)	0.734
Bleeding	Life threatening	21 (1.8)	5 (1.0)	0.53 (0.17-1.31)	0.209	0.41 (0.16-1.38)	0.169
	Major	45 (3.8)	9 (1.7)	0.44 (0.20-0.87)	0.03	0.48 (0.21-1.12)	0.09
New pacemaker		101 (8.6)	36 (6.9)	0.79 (0.53-1.17)	0.268	0.83 (0.49-1.41)	0.497
New onset of AF		66 (5.6)	18 (3.4)	0.60 (0.34-1.00)	0.06	0.67 (0.31-1.45)	0.301
New LBBB		67 (5.7)	25 (4.8)	0.83 (0.51-1.32)	0.455	0.62 (0.36-1.08)	0.09
Device success		1,082 (92.2)	471 (90.8)	0.82 (0.58-1.19)	0.340	0.99 (0.64-1.51)	0.952
LOS (days)		5.51±5.50	4.51±4.50	−0.96 (−1.52 to −0.39)	<0.01	−0.41 (−1.38 to 0.50)	0.360
Peak gradient, mmHg		21.43 ±8.09	23.17±8.7	1.71 (0.83-2.61)	<0.01	1.71 (0.82-2.61)	<0.01
Mean gradient, mmHg		11.21±4.45	12.55±4.9	1.35 (0.86-1.84)	<0.01	1.31 (0.83-1.80)	<0.01
AVA, cm²		1.68±0.45	1.55±0.34	0.04 (−0.06 to 0.13)	0.472	−0.07 (−0.13 to 0.02)	0.111
Non-trace PVL		802 (69.8)	412 (81.7)	1.94 (1.50-2.52)	<0.01	1.77 (1.27-2.45)	<0.01
Mild PVL		312 (27.1)	88 (17.4)	0.56 (0.43-0.73)	<0.01	0.62 (0.44-0.86)	<0.01
Moderate PVL or greater		36 (3.1)	4 (0.8)	0.25 (0.07-0.62)	0.008	0.34 (0.09-1.25)	0.110
LVEF, %		57.89±10.75	57.66±9.43	−0.21 (−1.33 to 0.90)	0.703	-0.31 (-1.72 to 1.09)	0.609

Values are n (%) or mean±standard deviation. AF: atrial fibrillation; AVA: aortic valve area; CI: confidence interval; LBBB: left bundle branch block; LOS: length of stay; LVEF: left ventricular ejection fraction; OR: odds ratio; PVL: paravalvular leak; THV: transcatheter heart valve

more frequent with the S3U compared with the S3 (OR 1.71, 95% CI: 1.28 to 2.28; p<0.01), whereas there was no significant difference in the rate of moderate or greater PVL (OR 0.88, 95% CI: 0.42 to 1.85; p=0.738). Mild PVL was more frequent in the S3 group (OR 0.63, 95% CI: 0.44 to 0.88; p<0.01). No patients experienced severe PVL. Transprosthetic gradients were similar in the two groups (mean difference −0.64, 95% CI: −2.19 to 0.90; p=0.389) **(Supplementary Figure 1, Supplementary Figure 2)**.

Discussion

The present study investigated the 1-year clinical and echocardiographic outcomes of TAVI with the SAPIEN 3 Ultra, compared with its predecessor the SAPIEN 3, in an unselected, real-world population from an international multicentre registry. We assessed the effect of THV design on clinical outcomes after taking into account the potential confounding factors by using a pre-specified propensity score method, which was performed with

Table 3. Clinical outcomes of unadjusted and propensity-matched populations at 30 days.

	Unadjusted				Propensity-matched	
	SAPIEN 3	SAPIEN 3 Ultra	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
All-cause death	19 (1.6)	7 (1.4)	0.93 (0.61-1.41)	0.743	1.0 (0.38-2.67)	0.928
Disabling stroke	1 (0.1)	3 (1.0)	0.63 (0.17-2.30)	0.481	0.89 (0.14-1.75)	0.901
Hospitalisation for HF	9 (0.8)	3 (0.6)	0.77 (0.24-2.39)	0.652	0.63 (0.18-2.25)	0.473
New pacemaker implantation	125 (10.7)	37 (7.8)	0.70 (0.50-1.01)	0.06	0.79 (0.54-1.26)	0.377
Repeat procedure	-	-	-	-	-	-

Values are n (%). Data are reported as Kaplan-Meier estimates at the specific timepoint. CI: confidence interval; HF: heart failure; HR: hazard ratio

Table 4. Clinical outcomes of unadjusted and propensity-matched populations at 1 year.

	Unadjusted				Propensity-matched	
	SAPIEN 3	SAPIEN 3 Ultra	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
All-cause death	69 (6.3)	22 (4.9)	0.93 (0.61-1.41)	0.743	0.89 (0.53-1.53)	0.691
Composite endpoint*	104 (9.5)	30 (6.6)	0.77 (0.54-1.18)	0.162	0.73 (0.46-1.17)	0.197
Cardiac death	39 (3.5)	7 (1.4)	0.57 (0.29-1.17)	0.102	0.58 (0.24-1.38)	0.218
Disabling stroke	20 (2.0)	3 (1.0)	0.45 (0.17-1.18)	0.107	0.55 (0.16-1.82)	0.323
Hospitalisation for HF	32 (3.0)	10 (2.2)	0.80 (0.42-1.55)	0.520	0.71 (0.32-1.55)	0.391
New pacemaker implantation	139 (12.1)	43 (8.5)	0.70 (0.50-0.99)	0.045	0.75 (0.50-1.13)	0.168
Repeat procedure	-	-	-	-	-	-

Values are n (%). Data are reported as Kaplan-Meier estimates at the specific timepoint. *Any death, disabling stroke, or repeat hospitalisation for heart failure. CI: confidence interval; HF: heart failure; HR: hazard ratio

a non-parsimonious approach including baseline characteristics, anatomical features (calcium burden and distribution), THV size and anaesthesia type.

The major findings of our study are as follows: 1) the S3U was associated with significantly lower rates of mild PVL compared with the S3, and this result was maintained at 1-year follow-up; 2) the rate of moderate or greater PVL was overall low and comparable in both groups at 1 year; 3) the S3U was comparable to the S3 with respect to 1-year rates of death from any cause, cardiac

death, disabling stroke, PPI and repeat hospitalisation due to heart failure.

It is recognised that moderate to severe PVL is associated with increased mortality and poor prognosis[6]. However, it remains controversial whether mild PVL affects clinical outcomes[8,9].

Recently, as the TAVI procedure expands to treat a younger and lower-risk population, technological advancements of new-generation THV have been focused on minimising PVL, even mild PVL, with the aim of approaching those rates achieved with surgical

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CENTRAL **ILLUSTRATION** 1-year clinical and echocardiographic outcomes of TAVI with the SAPIEN 3 Ultra or the SAPIEN 3.

Kaplan-Meier curves of (A) all-cause mortality and (B) death from any cause, disabling stroke and repeat hospitalisation for heart failure. (C) Rate of paravalvular leak (PVL) at 1 year according to THV design. CI: confidence interval; HF: heart failure; HR: hazard ratio

prostheses[4-5]. Our study results show a very low rate of PVL associated with the S3U suggesting that the main distinguishing features of the new-generation S3U have a significant preventive role. The absence of PVL was significantly higher in the S3U compared to the S3 group at discharge (69.8% S3 vs 81.7% S3U) and, more importantly, the results were confirmed at 1-year follow-up (67.1% S3 vs 80% S3U). The rate of mild PVL was significantly lower in the S3U group at both discharge (27.1% S3 vs 17.4% S3U) and 1-year follow-up (29.5% S3 vs 17.2% S3U). In both groups, the rate of moderate or greater PVL was overall low and similar **(Supplementary Figure 1)**. Recently, in a single-centre comparison of the S3U and S3 in 155 propensity-matched pairs of patients, Rheude et al[15] reported similar results in terms of a none/trivial PVL rate (77.3% S3U vs 50% S3) at 1 year. In comparison to previous registries using the SAPIEN, SAPIEN XT (also Edwards Lifesciences) and SAPIEN 3[20-22], our S3 Ultra registry results demonstrate that the rate of PVL at 1 year has progressively reduced in recent years **(Figure 3)**. The innovative features of the latest-generation S3U balloon-expandable valve represent a further significant technological advance in minimising PVL. However, in our study, a reduction of the PVL rate did not affect survival at 1 year. Future studies with longer follow-up beyond 5 years are warranted to evaluate the impact of reduced PVL on clinical outcomes.

In contrast, the presence of the textured polyethylene terephthalate and the higher external skirt had no negative impact on device success, PPI or adverse events at 30-day and 1-year follow-up, all of which had similar rates to those obtained with the S3. The rate of any death at 1 year in our propensity-matched cohort was similar in the S3U and S3 groups. Our results are in line with those reported by Rheude et al[15] (S3U 6% vs S3 8.6%). Similarly, no

differences in the primary composite endpoint, cardiac death or repeat procedure were detected between the two groups at 1 year. Moreover, we did not observe a significant difference in the rate of new PPI between the two prostheses; this result is in agreement with that reported by Rheude et al[15]. However, the PPI rate at 1 year in the S3U group was lower than that observed in our study (6.5% vs 8.5%). The reasons for this discrepancy are uncertain but might be explained by the small cohort size of their single-centre study, or it might have occurred by chance.

In comparison to previous registries and trials[4,22], the SAPIEN 3 Ultra registry results show a lower rate of 1-year all-cause mortality and a lower rate of composite endpoint of any death, disabling stroke and HF hospitalisation **(Central illustration)**. This is certainly a result of multiple factors, including device improvement, lower-risk patients and the learning curve of physicians in terms of patient selection, valve sizing and implantation techniques.

Of note, in terms of in-hospital outcomes, both predilatation and post-dilatation were less frequently performed with the S3U compared with the S3. These results coupled with a very low rate of major complications are in line with the observations made in previous studies[13] and confirm that TAVI with an S3U can be safely and effectively performed without predilatation and with a lower need for post-dilatation. Finally, the overall rates of all-cause mortality (2.8%) and disabling stroke (2.1%) at 30 days were very low in our study, consistent with previous studies evaluating S3U and S3 devices[13,14].

Limitations

This study has the inherent limitations of non-randomised, observational, retrospective studies without independent adjudication
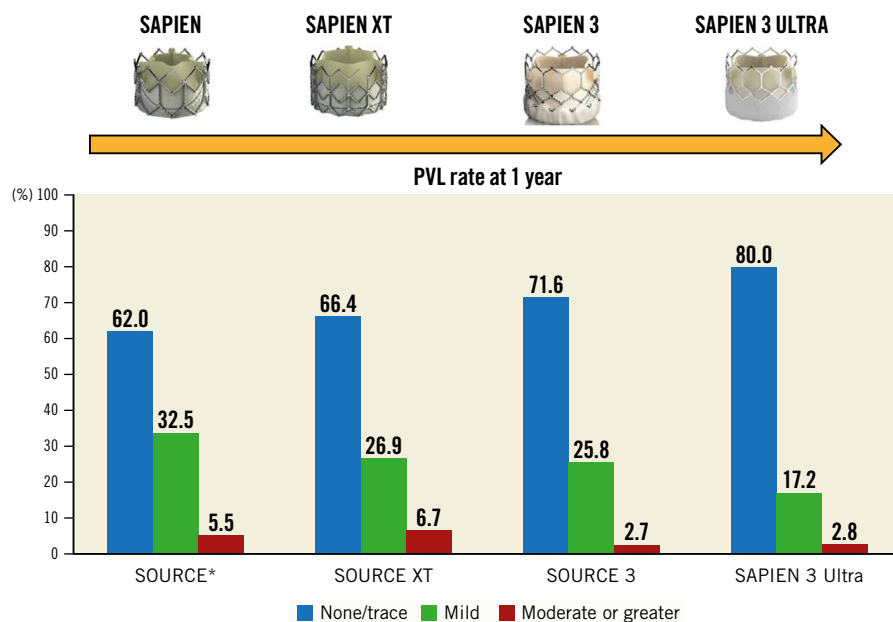

Figure 3. *Paravalvular leak (PVL) incidence at 1 year. PVL rate in the SAPIEN 3 Ultra (S3U) registry in comparison with the main registries of the SAPIEN transcatheter heart valve family: SOURCE (SAPIEN), SOURCE XT (SAPIEN XT), SOURCE 3 (SAPIEN 3). *For the SOURCE registry, the PVL rate was evaluated at discharge.*

of clinical events or an independent core laboratory to assess the PVL severity. We applied a propensity-matched approach to overcome differences in baseline characteristics and potential confounders; however, residual confounding remains a source of bias that cannot be excluded. Moreover, our data are derived from European centres only and may not be representative of other settings. Finally, the use of two different delivery systems with the S3U may affect the generalisability of our results.

Conclusions

This large multicentre experience of real-world patients treated by transfemoral TAVI with the new S3U THV shows excellent haemodynamic performance and clinical outcomes at 1 year. Further validation of our findings and longer-term follow-up are necessary to demonstrate the potential impact of reduced PVL rates on clinical outcomes.

Impact on daily practice

Limited data exist on 1-year outcomes after TAVI with the latest balloon-expandable SAPIEN 3 Ultra THV. In this real-world, multicentre European study we found that the SAPIEN 3 Ultra was associated with a lower rate of PVL compared to its predecessor (S3), a result that was maintained at 1 year. However, no difference in clinical outcomes was observed. Future randomised trials and larger observational studies are needed to further explore the benefit of reduced PVL on long-term outcomes after TAVI with the SAPIEN 3 Ultra.

Appendix. Authors' affiliations

1. Unit of Interventional Cardiology, Department of Cardiothoracic Surgery, IRCCS-ISMETT (Mediterranean Institute for Transplantation and Advanced Specialized Therapies), UPMC, Palermo, Italy; 2. Division of Cardiology, Department of Medicine, University of Verona, Verona, Italy; 3. Department of Cardiology, Erasmus University Medical Center, Thorax Center, Rotterdam, the Netherlands; 4. Department of Medical Sciences and Uppsala Clinical Research Center, Uppsala University Hospital, Uppsala, Sweden; 5. Division of Cardiology, AOU Policlinico "G. Rodolico − San Marco", Catania, Italy; 6. UOC Cardiologia Diagnostica e Interventistica, Fondazione C.N.R. Reg. Toscana G. Monasterio, Massa, Italy; 7. Hospital de Santa Cruz, CHLO, Nova Medical School, CEDOC, Lisbon, Portugal; 8. Centro Cardiologico Monzino IRCCS, University of Milan, Milan, Italy; 9. Department of Cardiology, Mauriziano Hospital, Turin, Italy; 10. Interventional Cardiology, Ospedali Riuniti di Ancona, Ancona, Italy; 11. Cardiovascular Institute, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria San Carlos, Madrid, Spain; 12. Cardiology Unit, Cardio-Thoracic-Vascular Department, IRCCS University Hospital of Bologna, Policlinico S. Orsola, Bologna, Italy; 13. Interventional Cardiology Unit, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua, Padua, Italy.

Guest editor

This paper was guest edited by Franz-Josef Neumann, MD; *Department of Cardiology and Angiology II, University Heart Center Freiburg - Bad Krozingen, Bad Krozingen, Germany.*

Conflict of interest statement

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Supplementary data

Supplementary Appendix 1. List of participating centres.

Supplementary Table 1. Echocardiographic outcomes of unadjusted and propensity-matched populations at 1 year.

Supplementary Figure 1. Rate of paravalvular leak (PVL) at 1 year.

Supplementary Figure 2. Mean gradient before and after TAVI.

The supplementary data are published online at:
https://eurointervention.pcronline.com/
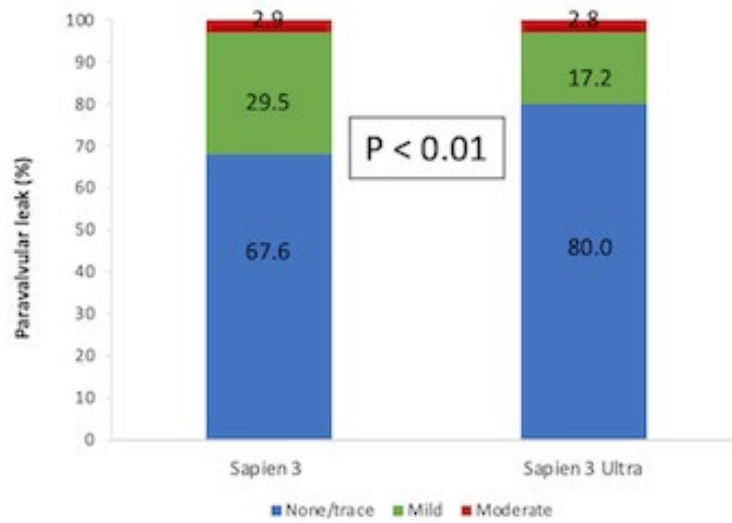*doi/10.4244/EIJ-D-22-01022*

Supplementary data

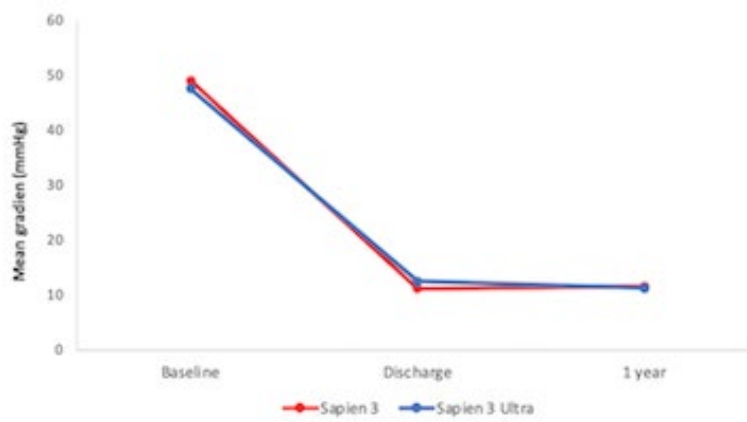**Supplementary Appendix 1. List of participating centres.**

- CCS-ISMETT (Mediterranean Institute for Transplantation and Advanced Specialized Therapies), UPMC, Palermo- Italy

- Cardio-Thoracic-Vascular Department, IRCCS University Hospital of Bologna, Policlinico S. Orsola, Bologna, Italy;

- Division of Cardiology, Department of Medicine, University of Verona, Verona, Italy

- Erasmus University Medical Center, Thoraxcenter, Rotterdam, the Netherlands

- Fondazione C.N.R. Reg. Toscana G. Monasterio, Massa, Italy

- A.O.U. Policlinico "G. Rodolico-San Marco", Catania, Italy

- Hospital de Santa Cruz, CHLO, Nova Medical School, CEDOC, Lisbon, Portugal

- Centro Cardiologico Monzino, I.R.C.C.S., University of Milan, Via Carlo Parea, 4, Milan, Italy

- Cardiovascular Institute, Hospital Clínico San Carlos, Madrid, Spain

- Mauriziano Hospital, Turin, Italy

- Ospedali Riuniti di Ancona, Ancona, Italy:

- Interventional Cardiology Unit, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua, Padua, Italy

Supplementary Table 1. Echocardiographic outcomes of unadjusted and propensity-matched populations at 1 year.

	Unadjusted				Propensity matched	
	Sapien 3	Sapien 3 Ultra	OR (95% CI)	p value	OR (95% CI)	p value
Peak gradient (mmHg)	20.9±8.74	20.73±8.06	0.93 (0.61-1.41)	0.807	-0.73 (-3.17-1.85)	0.558
Mean gradient (mmHg)	11.55±9.37	11.26±4.47	0.52 (0.26-1.04)	0.666	-0.64 (-2.19-0.90)	0.389
AVA (cm^2)	1.49±0.39	1.53±0.38	0.45 (0.17-1.18)	0.472	0.07 (-0.09-0.10)	0.08
None-trace PVL	496 (67.6)	173 (80.0)	1.88 (1.31-2.74)	<0.01	1.71 (1.28-2.28)	<0.01
Mild PVL	216 (29.5)	37 (17.2)	0.50 (0.34 -0.73)	<0.01	0.63 (0.44-0.88)	<0.01
Moderate or greater PVL	21 (2.9)	6 (2.8)	0.98 (0.36-2.33)	0.975	0.88 (0.42-0.1.85)	0.738
LVEF (%)	58.68±9.04	57.62±8.55	-1.05 (-2.43-0.32)	0.133	-0.48 (-2.06-1.09)	0.533

Supplementary Figure 1. Rate of paravalvular leak (PVL) at 1 year.

Supplementary Figure 2. Mean gradient before and after TAVI.