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ORIGINAL STUDIES

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Hemodynamic comparison of transcatheter aortic valve replacement with the SAPIEN 3 Ultra versus SAPIEN 3: The HomoSAPIEN registry

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Abstract

Objectives: The study aims to compare the hemodynamic and clinical outcomes of the SAPIEN 3 Ultra (S3-Ultra) with the SAPIEN 3 (S3) system in patients who underwent transfemoral transcatheter aortic valve replacement (TF-TAVR).

Background: The new balloon-expandable S3-Ultra system incorporates new features to reduce paravalvular leakage (PVL). However, the data after the S3-Ultra implantation is very limited.

Methods: A total of 282 consecutive patients who underwent TF-TAVR with the S3-Ultra and the S3 were evaluated. The primary outcome of this study was to compare the incidence of ≥mild PVL after the S3-Ultra and S3 implantation.

Results: Between June 2017 and November 2019, 141 patients with the S3-Ultra and 141 patients with the S3 were identified with similar baseline and preprocedural imaging characteristics (mean age: 79.6 ± 6.7 years and mean aortic annulus area: 492.5 ± 91.2 mm^2). In total, 83 patients (29.4%) were treated with 29-mm valve. Predischarge echocardiography demonstrated a significantly lower incidence of ≥mild PVL (the total cohort: 7.2 vs. 22.3%, $p < .001$, and the cohort excluding 29-mm valve: 4.0 vs. 21.4%, $p = .03$) for the S3-Ultra. The S3-Ultra system, especially 20-, 23-, and 26-mm valve, was associated with significantly lower risk of ≥mild PVL compared with the S3 system in multivariate analysis. There were no significant differences in clinical outcomes at 30-day between these groups, except for the lower incidence of major vascular complication (4.5 vs. 11.4%, $p = .05$) in patients with the S3-Ultra.

Conclusions: In this registry, the S3-Ultra system performed superiorly to the S3, as demonstrated by reduced ≥mild PVL, with comparable safety.

KEYWORDS

paravalvular leakage (PVL), transcatheter aortic valve replacement (TAVR), transcatheter heart valve (THV), transfemoral (TF)

1 | INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is an established treatment of severe aortic stenosis (AS).[1,2] Although proven noninferior and even superior to surgical aortic valve replacement in terms of all-cause mortality and/or stroke, TAVR is associated with a higher incidence of postoperative paravalvular leakage (PVL).[3-5] The expanding indication of TAVR to low risk populations with long life-expectancy requires minimization of adverse events including PVL, partly depending on technological improvements in transcatheter heart valves (THVs).

Recently, the new balloon-expandable SAPIEN 3 Ultra THV (S3-Ultra THV: Edwards Lifesciences, Irvine, CA) has become commercially available with CE mark and new features including an improved external-sealing skirt to mitigate PVL and lower delivery system profile to simplify the transfemoral (TF) TAVR. Initial data from a single-arm, multicenter registry retrospectively evaluating the performance of the S3-Ultra system seemed highly promising, especially in terms of mitigating PVL.[6] Comparative studies on the hemodynamic and clinical outcomes between the S3-Ultra and SAPIEN 3 (S3) are not currently available.

Therefore, we aimed to compare the hemodynamic performance and early clinical outcomes of TF-TAVR with the S3-Ultra versus S3 in patients with severe AS.

2 | MATERIALS AND METHODS

2.1 | Patient selection

A total of consecutive 282 patients with severe AS underwent TF-TAVR with the S3-Ultra or S3 in two centers (Helsinki and Oulu University Hospital, Finland) between June 2017 and November 2019 were retrospectively reviewed. All TF-TAVR were planned after the evaluation of contrast-enhanced multidetector computed tomography (MDCT) and coronary angiography. All patients were evaluated as eligible for TF-TAVR by a multidisciplinary heart team.[7,8] The study excluded patients who underwent TAVR with alternative approach other than TF-approach and TAVR in failed surgical aortic valve. For this study, consecutive 141 patients with S3-Ultra system and 141 patients with S3 system were evaluated to compare the clinical outcomes and post-TAVR hemodynamics (Figure 1).

Written informed consent was obtained about alternative treatment methods in all patients with the procedure. The study protocol was conformed to the Declaration of Helsinki and approved by the Helsinki and Oulu University Institutional Review Boards.

2.2 | Transcatheter heart valve devices

The S3 and its new iteration, S3-Ultra, are both balloon-expandable valves that consist of a tri-leaflet bovine pericardial valve sewn into a cobalt-chromium flame. The S3-Ultra THV received CE mark approval in November 2018. The new features to the S3-Ultra are with a lower delivery profile, higher radial strength and higher outer skirt height in comparison to the S3. The S3-Ultra differences compared with the S3 are summarized in Figure 2. The most important improvement to the S3-Ultra is the external textured polyethylene terephthalate (PET) skirt and 40% higher height than that of the S3 considered to have better sealing potential. Currently, the S3-Ultra valve is available in the three sizes (20-, 23-, and 26-mm), whereas the 29-mm THV is the S3 29-mm mounted on the Ultra delivery system. Moreover, the Axela sheath replaced the eSheath with new features. It is a 14 Fr expandable sheath for all THV size including the S3-Ultra 29-mm with a new delivery system.[6]

2.3 | MDCT and echocardiographic image assessment

All MDCT examinations were reviewed by two experienced interventional cardiologists (N.M., and H.L.) using 3mensio Structure Heart software (3mensio Medical Imaging B.V., Bilthoven, The Netherlands) and Syngo.via (Siemens Healthineers, Germany). Planimetry of the

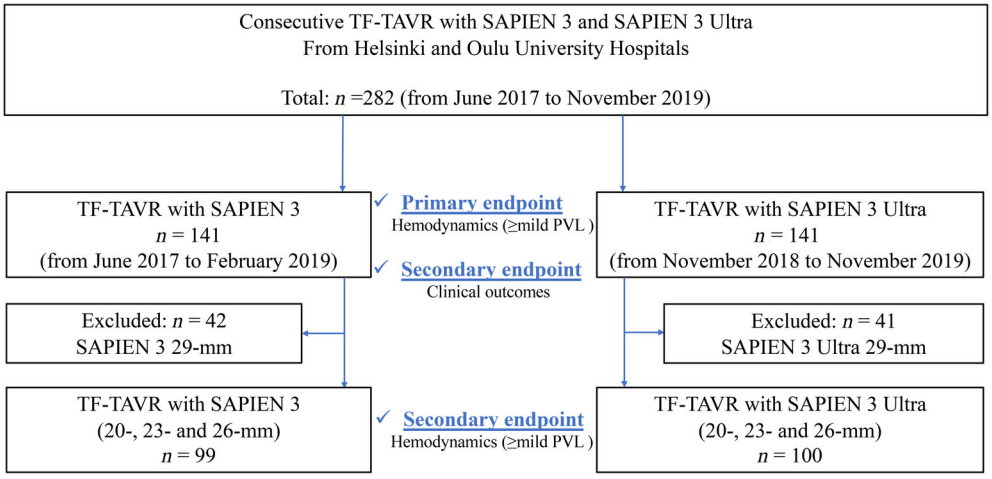

FIGURE 1 Study flow. The hemodynamic and clinical outcomes were compared between patients who underwent TF-TAVR with the SAPIEN 3 Ultra or SAPIEN 3. TF-TAVR, transfemoral transcatheter aortic valve; THV, transcatheter heart valve

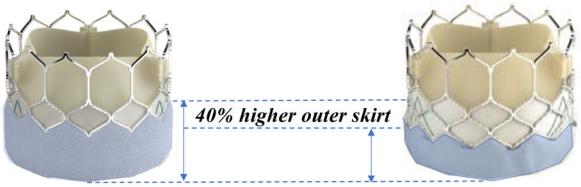

FIGURE 2 The SAPIEN 3 Ultra system. The SAPIEN 3 Ultra system (Edwards Lifesciences, Irvine, California) consists the SAPIEN 3 Ultra THVs 20-, 23-, and 26-mm including an improved outer sealing skirt and the SAPIEN 3 29-mm THV. Abbreviation as in Figure 1

	SAPIEN 3 Ultra system (S3-Ultra)				SAPIEN 3 system (S3)			
	20-mm	23-mm	26-mm	29-mm	20-mm	23-mm	26-mm	29-mm
Outer sealing skirt height, mm	7.3	9.0	9.7	8.1	5.2	6.6	7.0	8.1
Transfemoral sheath size, Fr	14	14	14	14	14	14	14	16
Nominal area sealing zone, mm^2	328	409	519	649	328	409	519	649
Inner skirt height, mm	7.9	9.3	10.2	11.6	7.9	9.3	10.2	11.6
Expanded height, mm	15.5	18	20	22.5	15.5	18	20	22.5
THV design	SAPIEN 3 Ultra - THV				SAPIEN 3 - THV			

annulus contours yielded area, major diameter, and minor diameter. Annulus area was measured by manually tracking the luminal contours on double-oblique transverse plane. The percentage of oversizing (positive percentage) (%OS) was calculated using the following formula: % OS = (S3-Ultra or S3 nominal area/MDCT annular area − 1) × 100. The nominal external valve areas of an expanded S3-Ultra and S3 THV are shown in Figure 2. The annulus was analyzed for degree of calcification. If present, the distribution of calcification and extension into the left ventricular outflow tract were also assessed in a semiquantitative fashion as follows: mild, one nodule of calcium extending <5 mm in any direction; moderate, two nodules of calcification, or one extending >5 mm in any direction; severe, multiple nodules of calcification of single focus extending >1 cm in length.[9]

Pre-TAVR and post-TAVR transthoracic echocardiography (TTE) were performed by experienced echocardiographers who are independent from TAVR operators at each participating center. Paravalvular leakage (PVL) was graded as none-trace, mild, moderate, and severe according to the Valve Academic Research Consortium 2 (VARC-2) criteria.[10]

2.4 | Definitions and outcome measures

All patients were severe AS defined by standard criteria. The operative risk was evaluated according to the Society of Thoracic Surgeons (STS) risk scoring methods.[11] Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) greater than 60 ml/min/1.73 m^2.[12] Clinical outcomes were registered based on VARC-2 criteria.[10]

The primary outcome of this study was to assess and compare the incidence of ≥mild PVL between the S3-Ultra and S3 system (20-, 23-, 26-, and 29-mm) at discharge. Secondary outcomes were to assess the all clinical outcomes including device success and hemodynamics other than PVL based on VARC-2 criteria at discharge and 30-day after TF-TAVR in the total cohort and to compare the severity of PVL between the S3-Ultra and S3 20-, 23-, and 26-mm at discharge (Figure 1).

2.5 | Statistical analysis

Categorical variables are presented as counts and/or percentages and were compared using the chi-square test. Continuous variables are presented as the mean ± standard deviation (*SD*) and were compared using the Student's *t*-test or the Wilcoxon rank sum test based on their distributions. The power calculation for the primary endpoint was based on the following assumptions: (a) the incidence of ≥mild PVL of 26.4% in the S3-THV group[13]; (b) the incidence of ≥mild PVL of 11.5% in the S3-Ultra-THV group[6]; and (c) a power of 80% and an α-level of 0.05. The calculated sample size was a total of 214 patients (107 patients per group). To determine the adjusted odds ratio (OR) of ≥mild PVL, a Cox regression analysis including baseline clinical, MDCT data and procedural covariates was used to obtain the OR and 95% confidence interval (CI) for the development of endpoints. A *p* value <.2 on univariate analysis and a generation of THV, predilatation, MDCT % OS, and severity of annular calcification were selected for the multivariate model. A *p*-value <.05 was considered statistically significant. All statistical tests were two-tailed and performed using JMP version 10.0 (SAS Institute Inc., Cary, North Carolina).

3 | RESULTS

3.1 | Baseline characteristics and procedural data

Our analysis included consecutive 141 patients who underwent the S3-Ultra implantation and 141 patients who underwent the S3 implantation (Figure 1). The mean age was 79.6 ± 6.7 years, 38.3%

were female and the average STS score was 3.8 ± 2.5% in the total cohort. The baseline characteristics of the study population are summarized in Table 1. There were no significant differences in the baseline characteristics. Preprocedural TTE and MDCT data are provided in Table 2. Mean aortic gradient was 45.5 ± 14.5 mmHg, 23.1% were bicuspid aortic valve and the mean aortic annulus area was 492.5 ± 91.2 mm^2. There was no significant difference between groups regarding preprocedural TTE and MDCT variables. The procedural characteristics are also listed in Table 2. In total, 83 patients (29.4%) were treated with 29-mm THV. No significant difference was observed in the THV sizes between the S3-Ultra and S3 groups. The sheath size used was significantly smaller in patients with the S3-Ultra in comparison to those with the S3 (14.1 ± 0.49 vs. 14.9 ± 1.0 Fr, $p < .001$). Regardless of the similar severity of AS between groups in terms of mean aortic gradient, the rate of predilation was significantly higher in patients with the S3-Ultra compared with those with the S3 (48.9 vs. 17.7%, $p < .001$). The incidence of vascular closure success (97.8 vs. 91.3%, $p = .016$) was more frequent in

TABLE 1 Baseline clinical characteristics

	SAPIEN 3 Ultra*n* = 141	SAPIEN 3*n* = 141	*p* value
Age, year	79.8 ± 6.7	79.5 ± 6.7	.78
Female	58 (41.1)	50 (35.5)	.33
BMI, kg/m^2	26.6 ± 5.0	27.1 ± 5.0	.35
BSA, m^2	1.85 ± 0.20	1.89 ± 0.21	.09
Hypertension	126 (89.4)	128 (90.8)	.69
Diabetes mellitus	41 (29.2)	33 (24.3)	.42
CKD[a]	48 (34.0)	43 (30.5)	.52
Atrial fibrillation	58 (41.1)	61 (43.3)	.72
COPD	34 (24.1)	32 (22.7)	.78
Peripheral artery disease	19 (13.5)	22 (15.6)	.61
Prior PCI	37 (26.2)	47 (33.3)	.19
Prior CABG	15 (10.6)	13 (9.2)	.69
Prior CVA/TIA	16 (11.4)	12 (8.6)	.43
Prior PMI	14 (9.9)	15 (10.6)	.84
NYHA class ≥ III	107 (75.9)	101 (71.6)	.42
STS-PROM, %	3.7 ± 2.1	3.9 ± 3.0	.51
Laboratory data			
Hemoglobin, g/L	128.6 ± 16.7	130.7 ± 16.3	.14
Creatinine, μmol/L	103.8 ± 5.4	95.2 ± 5.4	.26
eGFR, ml/min/1.73 m^2	59.3 ± 17.3	61.2 ± 16.7	.34
Electrocardiogram			
PR duration, ms	191.5 ± 32.6	187.6 ± 31.5	.40
QRS duration, ms	113.2 ± 30.1	112.4 ± 27.6	.82
First degree atrioventricular block	38 (27.0)	38 (27.0)	>.90
Right bundle branch block	12 (8.5)	15 (11.0)	.49
Left bundle branch block	15 (10.6)	11 (8.0)	.46
Medical therapy			
Aspirin	63 (44.7)	56 (39.7)	.40
ADP receptor blocker	23 (16.3)	24 (17.0)	.87
Vitamin K antagonist	24 (17.0)	36 (25.5)	.09
DOAC	29 (20.6)	21 (14.9)	.21

Notes: Values are *n* (%) or mean ± *SD*.

Abbreviations: ADP, adenosine-diphosphate; BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CVA/TIA, cerebrovascular attack/transient ischemic attack; DOAC, direct oral anticoagulants; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PMI, pacemaker implantation.

[a]Estimated glomerular filtration rate <60 ml/min/1.73 m^2.

TABLE 2 Aortic valve assessment and procedural characteristics

	SAPIEN 3 Ultra *n* = 141	SAPIEN 3 *n* = 141	*p* value
Echocardiogram			
Left ventricular ejection fraction, %	54.9 ± 11.8	54.8 ± 12.6	.96
Peak aortic velocity, m/s	4.2 ± 1.6	4.5 ± 2.4	.20
Aortic valve area, cm^2	0.69 ± 0.18	0.70 ± 0.17	.52
Peak aortic gradient, mmHg	71.7 ± 20.7	73.6 ± 22.0	.45
Mean aortic gradient, mmHg	44.7 ± 14.3	46.4 ± 14.8	.34
MDCT			
Bicuspid aortic valve	33 (23.6)	32 (22.7)	.86
Aortic annulus minor diameter, mm	22.2 ± 2.3	23.7 ± 1.9	.35
Aortic annulus major diameter, mm	28.0 ± 2.9	28.6 ± 2.6	.27
Aortic annulus mean diameter, mm	25.1 ± 2.3	26.1 ± 2.6	.21
Eccentricity index	0.20 ± 0.06	0.17 ± 0.11	.53
Aortic annulus area, mm^2	488.1 ± 93.9	497.0 ± 88.5	.41
Aortic annulus area derived diameter, mm	24.8 ± 2.5	25.1 ± 2.2	.37
Annular calcification severity			.32
None	90 (63.8)	83 (59.0)	
Mild	32 (22.7)	38 (26.9)	
Moderate	11 (7.8)	12 (8.6)	
Severe	8 (5.7)	8 (5.8)	
Procedural data			
General anesthesia	3 (2.1)	2 (1.4)	.65
Sheath, Fr	14.1 ± 0.49	14.9 ± 1.0	<.001
Labeled THV size			.99
20-mm	2 (1.4)	2 (1.4)	
23-mm	38 (27.0)	36 (25.5)	
26-mm	60 (42.6)	61 (42.3)	
29-mm	41 (29.1)	42 (29.8)	
MDCT % area oversizing, %	7.8 ± 4.3	6.4 ± 10.2	.12
Predilation	69 (48.9)	25 (17.7)	<.001
Balloon size, mm	21.7 ± 1.8	21.8 ± 2.1	.82
Post-dilation	2 (1.4)	0 (0)	.25
THV balloon burst during deployment	2 (1.4)	1 (0.70)	.56
Second valve implantation	0 (0)	0 (0)	>.90
Coronary obstruction	1 (0.71)	0 (0)	.32
Annulus rupture	0 (0)	1 (0.70)	.32
Cardiac tamponade	2 (1.4)	2 (1.4)	>.90
Conversion to cardiac surgery	2 (1.4)	0 (0)	.16
Access vascular closure success	136 (97.8)	126 (91.3)	.016
Contrast volume, ml	72.2 ± 32.4	75.8 ± 41.6	.39
Intraprocedural death	1 (0.70)	1 (0.70)	>.90

Notes: Values are *n* (%) or mean ± *SD*.
Abbreviations: Fr, French; MDCT, multislice-detector computed tomography; THV, transcatheter heart valve. Other abbreviations as in Table 1.

patients who underwent the S3-Ultra implantation. The description of cases with balloon burst and coronary obstruction in patients with the S3-Ultra in detail are displayed in Table S1 and Videos S1 and S2. Baseline and MDCT data, and procedural characteristics in patients who received the S3-Ultra and S3 20-, 23-, and 26-mm are displayed in Table S2.

3.2 | Early outcomes

3.2.1 | Hemodynamics

Hemodynamics improved after TAVR, with a significant decrease in mean aortic valve gradients from 45.4 ± 14.5 mmHg to 9.9 ± 3.9 mmHg (p < .001). Although there was no significant difference in post-TAVR mean aortic gradient between the S3-Ultra and S3 groups (10.3 ± 3.8 vs. 9.6 ± 3.9, p = .14), the rate of ≥mild PVL was significantly lower in patients with the S3-Ultra (total cohort: 7.2 vs. 22.3%, p = .002; 20-, 23-, and 26-mm cohort: 4.0 vs. 21.4%, p = .03). No cases of severe PVL were reported in any groups (Table 3; Figure 3). One case of the S3-Ultra with moderate PVL probably due to deep implantation is shown in Figure S1. In Figure 4, the

TABLE 3 Predischarge echocardiography and in-hospital and 30-day clinical outcomes

	SAPIEN 3 Ultra*n* = 141	SAPIEN 3*n* = 141	*p* value
Echocardiogram			
Peak aortic velocity, m/s	2.0 ± 0.38	2.0 ± 0.40	.58
Peak aortic gradient, mmHg	19.0 ± 6.8	17.8 ± 6.9	.14
Mean aortic gradient, mmHg	10.3 ± 3.8	9.6 ± 3.9	.14
PVL			
≥Mild	10 (7.2)	31 (22.3)	.002
Moderate or severe	1 (0.72)	4 (2.9)	.18
In-hospital and 30-day clinical outcomes			
All-cause mortality	3 (2.1)	3 (2.1)	>.90
Stroke or TIA	2 (1.4)	2 (1.4)	>.90
Bleeding complication			
Life-threatening or disabling	2 (1.4)	6 (4.3)	.15
Major	5 (5.7)	9 (6.4)	.62
Major vascular complication	7 (4.5)	16 (11.4)	.05
Hemoglobin drop (before-after), g/L	16.2 ± 8,9	19.3 ± 13.9	.03
AKI	1 (0.7)	3 (2.1)	.32
Stage 1	1 (0.7)	3 (2.1)	.32
Stage 2	0 (0)	0 (0)	>.90
Stage 3	0 (0)	0 (0)	>.90
Creatinine change (after-before), μmol/L	−11.8 ± 21.9	−7.2 ± 22.1	.08
Creatinine change (after / before)	0.89 ± 0.11	0.93 ± 0.20	.03
PMI	8 (5.7)	7 (5.0)	.80
PMI without prior PMI	8 (6.3)	7 (5.6)	.80
PMI with prior first-degree block	3 (7.9)	3 (7.9)	>.90
PMI with prior right bundle branch block	2 (16.7)	4 (26.7)	.53
Post PR duration, ms	199.5 ± 40.4	191.0 ± 39.3	.15
PR duration (after-before), ms	8.4 ± 32.5	6.0 ± 31.0	.42
Post QRS duration, ms	119.7 ± 30.3	118.5 ± 33.8	.77
QRS duration (after-before), ms	7.5 ± 21.9	6.3 ± 20.5	.65
New left bundle branch block	19 (13.7)	22 (16.7)	.49
LOS, days	2.7 ± 3.0	3.7 ± 4.3	.017
LOS after TAVR, days	2.0 ± 2.2	2.5 ± 2.5	.05
Device success	135 (95.7)	132 (93.6)	.43
Any device failure requiring reintervention within 30-days	0 (0)	1 (0.71)	.32
30-days mortality	3 (2.1)	3 (2.1)	>.90

Notes: Values are *n* (%) or mean ± *SD*.

Abbreviations: AKI, acute kidney injury; LOS, length of hospital stay; PVL, paravalvular leakage; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack. Other abbreviations as in Table 1.

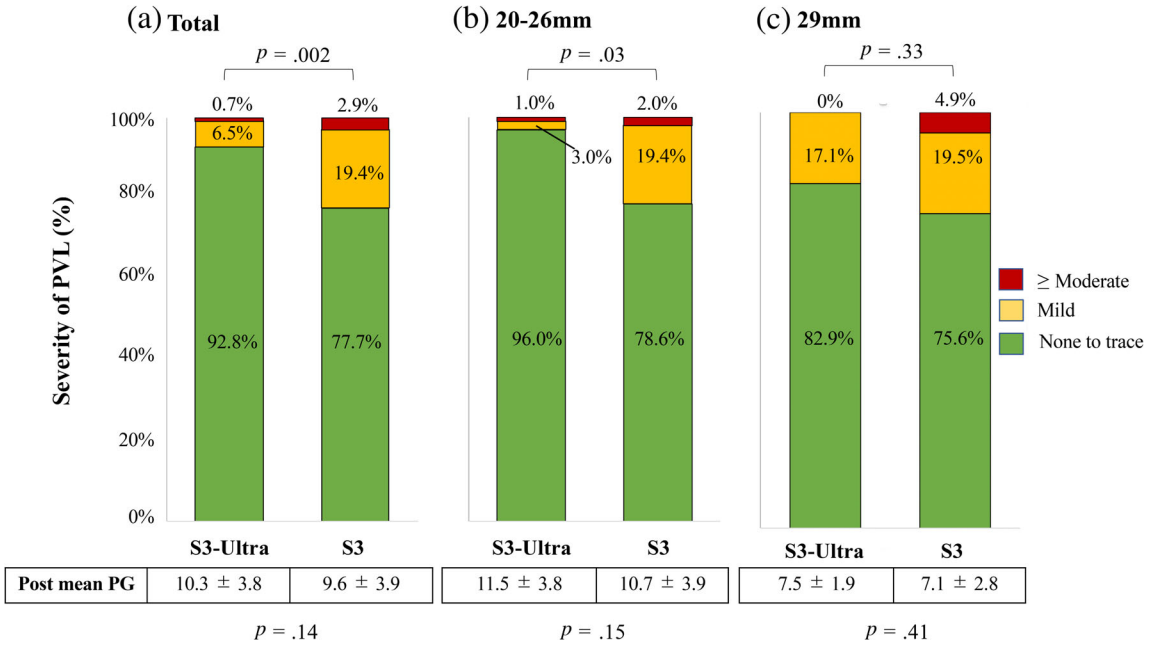

FIGURE 3 Paravalvular leakage evaluated by transthoracic echocardiography at discharge. (a) THV with 20-, 23-, 26-, and 29-mm; (b) THV with 20-, 23-, and 26-mm; and (c) THV with 29-mm. PVL, paravalvular leakage

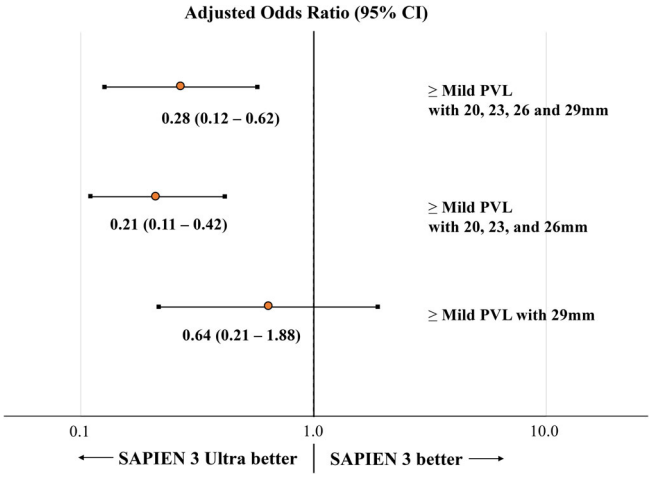

FIGURE 4 Comparative risk for ≥mild paravalvular leakage with the SAPIEN 3 Ultra and SAPIEN 3. The SAPIEN 3 Ultra system is associated with significantly lower risk of ≥mild PVL in comparison to the SAPIEN 3 system, which is derived from the performance of the SAPIEN 3 Ultra 20-, 23-, and 26-mm THV. PVL, paravalvular leakage. Other abbreviations as in Figure 1

comparative risk of ≥mild PVL on TTE at discharge is displayed. The S3-Ultra system implantation had significantly lower risk of ≥mild PVL in comparison to the S3 (THV size: 20-, 23-, 26-, and 29-mm, OR: 0.28, 95% CI: 0.12–0.62, THV size: 20-, 23-, and 26-mm, OR: 0.21, 95% CI: 0.11–0.42). There was no significant difference in the risk of ≥mild PVL between patients with the S3-Ultra 29-mm and the S3 29-mm (OR: 0.64, 95% CI: 0.21–1.88). In case of none to mild annular calcification, significantly less frequent incidence of ≥mild PVL was observed in patients with the S3-Ultra in comparison to those with the S3 (5.7 vs. 22.3%, p = .01), but not significant in case of moderate to severe annular calcification (15.8 vs. 20.0%, p = .63). In case of tricuspid valve morphology, the incidence of ≥mild PVL was significantly less frequent in patients with the S3-Ultra (5.5 vs. 20.2%, p = .001) (Table 4).

3.2.2 | Clinical outcomes

All-cause mortality at discharge and 30-day were comparable between two groups (at discharge: 2.1 vs. 2.1%, p > .90; at 30-day: 2.1 vs. 2.1%, p > .90, respectively). Although bleeding complications were not different between the cohort, major vascular complication was less common (4.5 vs. 11.4%, p < .05) and length of hospital stay (LOS) was shorter after the S3-Ultra implantation (LOS: 2.7 ± 3.0 days vs. 3.7 ± 4.3 days, p = .017; LOS after TAVR: 2.0 ± 2.2 days vs. 2.5 ± 2.5 days, p = .05). There was no significant difference in the device success between groups (S3-Ultra: 95.7% vs. S3: 93.6%, p = .43).

No significant differences were observed in hemodynamic and clinical outcomes in patients who underwent TF-TAVR with the S3-Ultra between two participating centers in this study (Table S3).

4 | DISCUSSION

We performed a retrospective comparison of outcomes in patients who underwent TF-TAVR with the S3-Ultra or S3. Our main findings were: (a) significantly lower incidence of ≥mild PVL for the S3-Ultra system, (b) comparable clinical outcomes based on VARC-2 between

TABLE 4 The impact of degree of annulus calcification, % oversizing, and aortic valve morphology on ≥mild PVL

	S3-Ultra system (*n* = 141)	S3 system (*n* = 141)	*p* value
≥Mild PVL	10 (7.2)	31 (22.3)	.002
Annular calcification			
None to mild(S3-Ultra: *n* = 122, S3: *n* = 121)	7 (5.7)	27 (22.3)	.01
Moderate to severe(S3-Ultra: *n* = 19, S3: *n* = 20)	3 (15.8)	4 (20.0)	.63
(*p* value)	.12	.21	–
% oversizing			
<0% (S3-Ultra: *n* = 31, S3: *n* = 41)	3 (9.7)	6 (14.6)	.38
0–10% (S3-Ultra: *n* = 60, S3: *n* = 46)	3 (5.0)	11 (23.9)	.004
> 10% (S3-Ultra: *n* = 50, S3: *n* = 54)	4 (8.0)	14 (25.9)	.003
(*p* value)	.61	.39	–
Aortic valve morphology			
Tricuspid(S3-Ultra: *n* = 108, S3: *n* = 109)	6 (5.5)	22 (20.2)	.001
Bicuspid(S3-Ultra: *n* = 33, S3: *n* = 32)	4 (12.1)	9 (28.2)	.12
(*p* value)	.19	.37	–

Notes: Values are *n* (%). Abbreviations as in Table 3.

patients who received the S3-Ultra and S3, with less frequent major vascular complication for the S3-Ultra system, and (c) the S3-Ultra was significantly associated with the less frequent ≥mild PVL compared with the S3 in multivariate analysis. This finding was mainly attributed to the better sealing performance of the S3-Ultra 20-, 23-, and 26-mm. New sealing-skirt of the S3-Ultra THV may play an important role of mitigating PVL. Our data indicate that TF-TAVR with the novel balloon-expandable S3-Ultra THV is clinically safe with a better hemodynamic result.

4.1 | Paravalvular leakage

Even since the introduction of TAVR, postprocedural PVL has been one of major issues of this treatment. The reduction of PVL established with the S3-THV is of importance because several studies and meta-analysis showed decreased survival rates for patients even with mild PVL.[14,15] In the PARTNER trials with the S3-THV, 26.3–29.5% of ≥mild PVL and 0.8–3.7% of moderate or severe PVL were reported.[4,16] Identically, in the largest registry reflecting real-world clinical practice, 26.4% of ≥mild PVL including 3.1% of moderate or severe PVL was observed with the S3-THV.[13] The results of the present study showed an extremely low rate of ≥mild PVL associated with the S3-Ultra (7.2%), much lower than the previous those with the S3 and also significantly lower than that of our control arm of the S3 (≥mild PVL: 22.3%). The result of ≥mild PVL following the S3 implantation in this study was in line with those in the previous study.[13-16] The incidence of ≥mild PVL was reduced by 67% in comparison to the S3 arm, leading to an incidence of residual leakage close to that reported in recent studies with surgical valve replacement and TAVR with the mechanical-expandable valve.[4,17] Saia et al. also reported 11.5% of ≥mild PVL with the S3-Ultra in the multicenter registry.[6] These data could support the advantage of new sealing-skirt of the S3-Ultra over that of the S3.

Previously, several anatomical factors associated with ≥mild PVL in patients with the S3 were reported. Moderate or severe annulus calcification was known as a risk factor of PVL in the usage of S3-THV.[18] In this study, the patients with moderate to severe annulus calcification, who underwent the S3-Ultra implantation, had a numerically higher incidence of ≥mild PVL in comparison to those with none to mild calcification (16.7 vs. 5.7%, p = .12) (Table 4). Compared with the S3, significantly lower incidence of ≥mild PVL was observed in the S3-Ultra group with none to mild calcifications (5.7 vs. 22.3%, p = .01), but not significant in moderate to severe calcification (15.8 vs. 20.0%, p = .63). These findings might suggest that the S3-Ultra with new sealing-skirt is highly effective to mitigate PVL in patients with minor annulus calcification. On the other hand, it is important to understand that the impact of moderate to severe annulus calcification still appears to be similar between these THVs, even with new improvement features of the S3-Ultra. Therefore, an optimal patient selection could be essential to further reduce the incidence of significant PVL. The cutoff value of % OS for the prediction of ≥mild PVL was previously investigated with use of the S3-THV.[9] Patients with 0–10% OS could be the goal of %OS with the S3. Our data also suggested that 0–10% OS with the S3-Ultra appears to be the proper range to mitigate PVL (≥mild PVL: %OS <0% = 9.7%, 0–10%OS = 5.0% and >10%OS = 8.0%). Furthermore, in patients with bicuspid aortic valve, the incidence of ≥mild PVL following the S3-Ultra implantation was also numerically higher than those with tricuspid aortic valve (Table 4). Considering relatively small population involved in this study, larger study is warranted to be investigated our findings in detail. Moreover, the current study did not investigate the association between implantation depth and PVL. The study including data on implantation depth following the S3-Ultra deployment may reveal how new and improved sealing-skirt has impact on mitigating PVL.

4.2 | Procedural and early clinical outcomes

Although the main objective of this study was to analyze the hemodynamic results of the S3-Ultra, it should be noted that any of VARC-2 clinical outcomes are statistically similar between both groups, with the exception of lower incidence of major vascular complication in patients with the S3-Ultra. These findings might support the safety of the S3-Ultra, in terms of early clinical outcomes. Significant reduction of vascular complication could be partially explained by lower profile Axela sheath. However, during the period after introduction of the S3-Ultra, we developed a novel technique of percutaneous vascular closure leading to extremely low rate of access-related vascular complication.[19] As a result, the rate of vascular closure success was higher in the S3-Ultra group. Moreover, our study does not include data on MDCT-derived iliofemoral artery features, such as degree of calcification, lumen diameter and sheath to femoral artery ratio, potentially associated with vascular complication. Therefore, the result of major vascular complication in this study should be carefully interpreted.

Unfortunately, unexpected issues during procedure with the S3-Ultra system were reported as shown in Table 2 and Table S1. After introduction of the S3-Ultra, the need of predilation significantly increased from 17.7% in the S3 system to 48.9%. The frequent predilation may indicate the cautionary step with the new device based on operators' preference or poorer crossing ability through native aortic valve with the new S3-Ultra delivery system in comparison to the Commander delivery system. However, no significant association was found between the predilation and mitigating PVL in the multivariable analysis (OR: 1.88, 95% CI: 0.75–5.38, p = .28). Furthermore, predilation did not affect hemodynamics following the S3-Ultra implantation (Table S4). During the study period, the US Food and Drug Administration announced a class I recall of the S3-Ultra delivery system,[20] because of several cases of balloon rupture during valve deployment leading to vascular and bleeding complication requiring surgical treatment (Table S1 and Video S1). Therefore, the manufacture decided to support the use of the S3-Ultra THV with the Commander delivery system and 14 or 16 Fr expandable eSheath.

5 | LIMITATIONS

Firstly, our study has limitations typical of those with a retrospective design. Secondly, there were few patients in our study that met the indications for the 20-mm bioprosthesis. Therefore, our data does not support the performance of the S3-Ultra 20-mm THV. Thirdly, outcomes were self-reported by participating centers. There was no core laboratory evaluation of echocardiographic results. The external validity of these results should be evaluated in larger trials. Fourthly, we calculated sample size needed to evaluate our primary endpoint. The results of other endpoints should be carefully interpreted because of relatively small sample size. Finally, all S3-Ultra cases were performed with the Axela sheath or eSheath, and the Ultra delivery system. However, the S3-Ultra THV is currently implanted using the S3 delivery system including the eSheath and the Commander delivery catheter. Further study is needed to confirm our findings with the S3-Ultra THV on the S3 delivery system.

6 | CONCLUSIONS

In the HomoSAPIEN registry, the new S3-Ultra THV demonstrated lower rate of ≥mild PVL compared with the preceding the S3 THV. The new improvement of outer-sealing skirt of the S3-Ultra might play an important role to reduce the severity and incidence of PVL. Furthermore, we found that TF-TAVR with the S3-Ultra system is similarly safe, in terms of early clinical outcomes within 30 days based on VARC-2, compared with that with the S3 system. Larger clinical studies with the S3-Ultra THV mounted on the Commander delivery system including more detailed information on post-procedural TTE evaluated by core laboratory are needed to elucidate the findings observed in the current study.

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CONFLICTS OF INTEREST

N.M. reports receiving consultant fee from Teleflex and is a clinical proctor of Boston Scientific (LOTUS Edge and ACURATE neo) and Edwards Lifesciences (SAPIEN 3 series). M.L. reports receiving non-regulatory research grants from Teleflex and consultant fee from Boston Scientific, Edwards Lifesciences and Medtronic, and is a clinical proctor of Boston Scientific (LOTUS Edge and ACURATE neo) and Edwards Lifesciences (SAPIEN 3 series). H.L., H.M., J.P., and M.N. report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

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REFERENCES

1. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011; 364:2187-2198.
2. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med. 2014; 370:1790-1798.
3. Thyregod HG, Steinbrüchel DA, Ihlemann N, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. J Am Coll Cardiol. 2015;65:2184-2194.
4. Mack MJ, Leon MB, Thourani VH, et al. PARTNER 3 investigators. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med. 2019;380:1695-1705.
5. Popma JJ, Deeb GM, Yakubov SJ, et al. Evolut low risk trial investigators. Transcatheter aortic-valve replacement with a self-

expanding valve in low-risk patients. N Engl J Med. 2019;380:1706-1715.
6. Saia F, Gandolfo C, Palmerini T, et al. Thirty-day outcomes of the SAPIEN 3 ultra balloon-expandable Transcatheter aortic valve: the S3U registry. EuroIntervention. 2020;15:1240-1247.
7. Lauck SB, Wood DA, Baumbusch J, et al. Vancouver transcatheter aortic valve replacement clinical pathway: minimalist approach, standardized care, and discharge criteria to reduce length of stay. Circ Cardiovasc Qual Outcomes. 2016;9:312-321.
8. Babaliaros V, Devireddy C, Lerakis S, et al. Comparison of transfemoral aortic valve replacement performed in the catheterization laboratory (minimalist approach) versus hybrid operating room (standard approach): outcomes and cost analysis. J Am Coll Cardiol Intv. 2014;7:898-904.
9. Yang TH, Webb JG, Blanke P, et al. Incidence and severity of paravalvular aortic regurgitation with multidetector computed tomography nominal area oversizing or undersizing after transcatheter heart valve replacement with the Sapien 3: a comparison with the Sapien XT. JACC Cardiovasc Interv. 2015;8:462-471.
10. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the valve academic research Consortium-2 consensus document. J Am Coll Cardiol. 2012;60:1438-1454.
11. Online STS Adult Cardiac Surgery Risk Calculator. http://riskcalc.sts.org/stswebriskcalc/calculate. Accessed April 12, 2020.
12. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145:247-254.
13. Wendler O, Schymik G, Treede H, et al. SOURCE 3 registry: design and 30-day results of the European Postapproval registry of the latest generation of the SAPIEN 3 transcatheter heart valve. Circulation. 2017;135:1123-1132.
14. Athappan G, Patvardhan E, Tuzcu EM, et al. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. J Am Coll Cardiol. 2013;61:1585-1595.
15. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med. 2012;366:1686-1695.
16. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med. 2016;374:1609-1620.
17. Feldman TE, Reardon MJ, Rajagopal V, et al. Effect of mechanically expanded vs self-expanding transcatheter aortic valve replacement on mortality and major adverse clinical events in high-risk patients with aortic stenosis: the REPRISE III randomized clinical trial. Jama. 2018;319:27-37.
18. Feuchtner G, Plank F, Bartel T, et al. Prediction of paravalvular regurgitation after transcatheter aortic valve implantation by computed tomography: value of aortic valve and annular calcification. Ann Thorac Surg. 2013;96:1574-1580.
19. Moriyama N, Dahlbacka S, Vähäsilta T, et al. The efficacy of the ultrasound-navigated MANTA deployment following transfemoral transcatheter aortic valve replacement. JACC Cardiovasc Interv. 2019;12:2564-2566.
20. https://www.fda.gov/medical-devices/medical-device-recalls/2019-medical-device-recalls. Accessed March 7, 2020.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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