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Novel predictors of mild paravalvular aortic regurgitation in SAPIEN 3 transcatheter aortic valve implantation

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KEYWORDS

- aortic stenosis
- paravalvular leak
- TAVI

Abstract

Aims: Paravalvular leak (PVL) remains an important issue in TAVI. The Edwards SAPIEN 3 (S3) valve has reduced PVL but in up to one third of patients mild leak remains. Our study aimed to identify predictors of mild PVL after TAVI with the S3 valve.

Methods and results: From October 2015 to May 2017, 122 consecutive patients underwent S3 TAVI for symptomatic severe aortic stenosis. Thirty-three patients with mild PVL on transthoracic echocardiography at 30-day follow-up were compared to 89 with none/trace PVL. Thirty-day mortality was 2.5% (n=3), with zero stroke and major vascular complications. There were no differences between the two groups in patient characteristics, annular and left ventricular outflow tract (LVOT) sizing, distribution and severity of annular calcification, valve implantation technique, post-dilatation and implant depth. Mild PVL was associated with higher annular eccentricity (p=0.04) and moderate-severe LVOT calcification (p=0.03). Independent predictors of mild PVL were LVOT eccentricity (OR 1.05 per % ellipticity, 95% CI: 1.02-1.09, p=0.005), discordant sizing (OR 3.08, 95% CI: 1.20-7.90, p=0.02) and three-leaflet calcification (OR 13.3, 95% CI: 2.66-66.7, p=0.002).

Conclusions: LVOT eccentricity and discordant sizing predict PVL after S3 TAVI. Further studies are needed to understand their mechanism and significance.

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Abbreviations

LBBB left bundle branch block
LVOT left ventricular outflow tract
MDCT multidetector computed tomography
PVL paravalvular leak
ROC receiver operating characteristic
S3 SAPIEN 3
TAVI transcatheter aortic valve implantation
TEE transoesophageal echocardiography
TTE transthoracic echocardiography
TVT transcatheter valve therapy
VARC Valve Academic Research Consortium

Introduction

Transcatheter aortic valve implantation (TAVI) has become the preferred treatment in patients with symptomatic severe aortic stenosis with high or prohibitive surgical risks[1]. More recently, TAVI was also approved in intermediate-risk patients[2,3], and randomised trials in low-risk patients are underway. Yet, paravalvular leak (PVL) remains a concern even with newer-generation valves. The incidence of moderate or greater (≥3+) PVL in the latest-generation balloon-expandable Edwards SAPIEN 3 (S3) transcatheter valve (Edwards Lifesciences, Irvine, CA, USA) is reduced compared to its predecessors[3-5]. However, at least 30% of patients in the PARTNER (Placement of AoRtic TraNscathetER valve) II S3 trial developed mild (2+) PVL[4-6]. As TAVI expands to lower-risk patients, the longer-term impact of PVL may become relevant[7,8]. Our study therefore aimed to identify predictors of mild PVL in S3 TAVI.

Methods

PATIENT POPULATION

From October 2015 to May 2017, 122 consecutive patients underwent S3 TAVI for symptomatic severe aortic stenosis. Patient data were prospectively collected in the American College of Cardiology/Society of Thoracic Surgeons (ACC/STS) US Transcatheter Valve Therapy (TVT) registry and retrospectively analysed. Our study was approved by the Institutional Review Board and patient consent was waived.

PREPROCEDURAL ASSESSMENT

All patients underwent transthoracic echocardiography (TTE) and multidetector computed tomography (MDCT) to evaluate aortic root dimensions, morphology and calcification, except two with severe kidney disease who underwent non-contrast CT and transoesophageal echocardiography (TEE).

MDCT ANALYSIS OF THE AORTIC ROOT

Aortic root analysis was performed at the end-systolic phase using 3mensio valve software, version 8.1 (Pie Medical Imaging, Maastricht, the Netherlands) to determine the largest dimensions at the annulus and left ventricular outflow tract (LVOT) (5 mm below the annulus, within the landing zone of most S3 implantations). Annular and LVOT eccentricities were defined as (1-minimal diameter/maximal diameter)×100%. Locations and severity of annular, LVOT and leaflet calcifications were semiquantitatively evaluated **(Figure 1)**[9]. Prosthesis sizing was according to manufacturer recommendations. S3 sizing to LVOT was calculated as

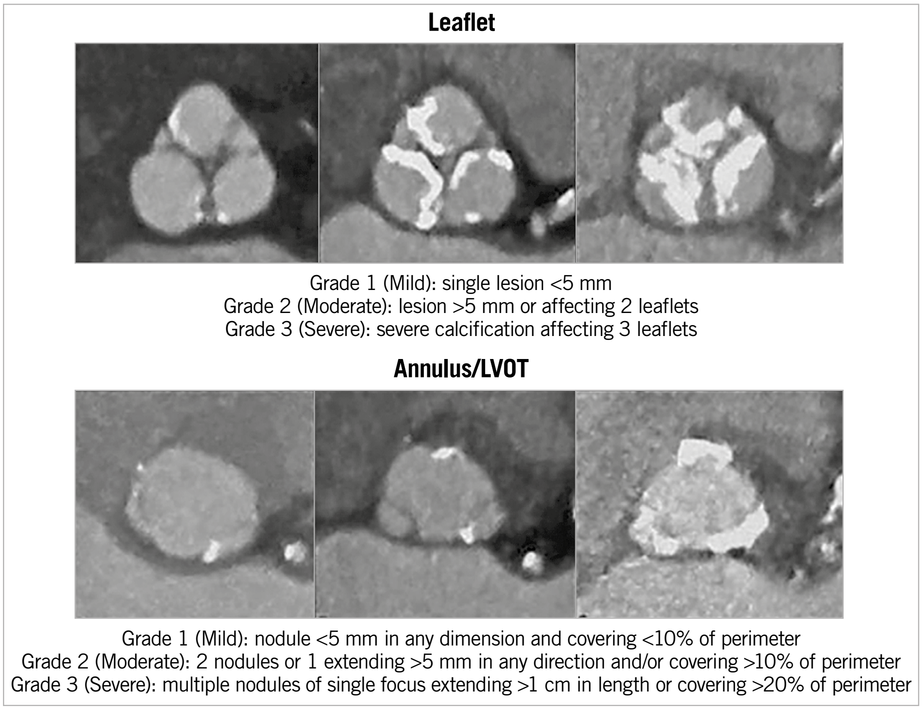


Figure 1. *Semiquantitative evaluation of aortic root calcification. Semiquantitative evaluation of aortic valve leaflet, annulus and left ventricular outflow tract calcifications performed in our study, as described by Barbanti and colleagues[9].*

([prosthesis area/LVOT area]–1)×100%. In cases where the anatomy lay between two sizes, balloon valvuloplasty with aortography was used to finalise valve size[10]. Annular sizing was compared to LVOT sizing and defined as "concordant" if the S3 was either oversized or undersized to both planes, and "discordant" if the S3 was oversized to one plane and undersized to the other. We derived four sizing combinations as:

– Concordant-undersized: annulus-undersized/LVOT-undersized
– Concordant-oversized: annulus-oversized/LVOT-oversized
– Discordant-undersized: annulus-undersized/LVOT-oversized
– Discordant-oversized: annulus-oversized/LVOT-undersized

S3 IMPLANTATION TECHNIQUE AND FOLLOW-UP

The S3 was implanted using standard techniques. In brief, balloon valvuloplasty using an Edwards balloon with aortography was performed in all cases[10]. Balloon volume was based on percent oversizing and aortic root calcification. Valve positioning was based on the top of the S3 frame relative to the sinotubular junction (STJ) and position of the bottom of the centre marker. When feasible, the marker bottom was positioned at or above the annulus (>0 mm) for a more aortic implantation. Valve deployment was preceded by aortography with a slow inflation technique. PVL severity was determined by TTE using the Valve Academic Research Consortium 2 (VARC-2) criteria[11], invasive haemodynamics and aortography. Post-dilatation was performed if PVL was mild or greater, with consideration of risk factors for annular injury.

The procedure was performed under conscious sedation by default with TTE evaluation by experienced echocardiographic sonographers. Patients at high procedural risk underwent general anaesthesia with TEE. S3 implant depth was analysed as previously described[12]. Thirty-day follow-up was 100% complete. PVL was graded by an expert echocardiographer (T. Dutta), blinded to procedure and valve selection. Outcomes were reported using the VARC-2 and US TVT Registry definitions.

STATISTICAL ANALYSIS

The clinical, anatomic, and procedural characteristics of patients with mild or greater PVL on TTE at 30 days were compared to those with none/trace PVL. Continuous variables were reported as means with standard deviations, while categorical variables were reported as proportions. Differences were detected using the t-test for continuous variables and chi-squared or Fisher's exact test for categorical variables. Univariate predictors of PVL were identified. In multivariate analysis, all univariate predictors with $p<0.10$ were considered, and only those with $p<0.05$ were included in the final model. Based on the number of events in our patient cohort, no more than three variables were included in the final model. To evaluate increasing odds associated with our multivariate predictors in a binary fashion, we assessed continuous variables included in the final multivariate model at incremental cut-offs via the c-statistic derived from the receiver operating characteristic (ROC) curve in logistic regression modelling. All statistical tests were two-tailed with $p<0.05$ considered significant. Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics are listed in **Table 1**. Mild PVL was seen in 27.0% of patients and none/trace in 73.0%. Mean age was 80.1±8.5 years and 41.0% were female. The STS score averaged 7.1±5.3%. There were no differences in patient characteristics between the two groups.

Table 1. Patient characteristics.

Variables expressed as N (%) or mean [SD]	Total N=122	None/trace PVL N=89	Mild PVL N=33	*p*-value
Age (yrs)	80.1 [8.5]	80.1 [7.8]	80.0 [10.3]	0.95
Female	50 (41.0%)	36 (40.4%)	14 (42.4%)	0.84
STS score	7.1 [5.3]	6.4 [4.4]	8.9 [7.1]	0.06
Coronary artery disease	60 (49.2%)	45 (50.6%)	15 (45.5%)	0.62
Diabetes	32 (26.2%)	27 (30.3%)	5 (15.2%)	0.09
TIA or stroke	16 (13.1%)	13 (14.6%)	3 (9.1%)	0.55
Peripheral vascular disease	28 (23.0%)	20 (22.5%)	8 (24.2%)	0.84
Moderate/severe COPD	49 (40.2%)	35 (39.3%)	14 (42.4%)	0.84
Atrial fibrillation	46 (37.7%)	30 (33.7%)	16 (48.5%)	0.13
Chronic kidney disease	39 (32.0%)	26 (29.2%)	13 (39.4%)	0.28
Pulmonary hypertension (PASP >60 mmHg)	21 (17.2%)	13 (14.6%)	8 (24.2%)	0.21
Prior permanent pacemaker	12 (9.8%)	8 (9.0%)	4 (12.1%)	0.73
Prior cardiac surgery	23 (18.9%)	14 (15.7%)	9 (27.3%)	0.15
Prior PCI	35 (28.7%)	28 (31.5%)	7 (21.2%)	0.37
Bicuspid aortic valve	8 (6.6%)	5 (5.6%)	3 (9.1%)	0.45
LVEF <35%	8 (6.6%)	5 (5.6%)	3 (9.1%)	0.45

COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; PASP: pulmonary arterial systolic pressure; PCI: percutaneous coronary intervention; PVL: paravalvular leak; SD: standard deviation; STS: Society of Thoracic Surgeons; TIA: transient ischaemic attack

ANATOMIC CHARACTERISTICS

There were no differences in annular and LVOT dimensions between the PVL groups **(Table 2)**. However, the mild PVL group had greater annular (29.2% vs. 25.7%, p=0.04) and LVOT eccentricities (43.4% vs. 36.1%, p=0.008). Increasing annular and LVOT eccentricity was associated with more mild PVL **(Figure 2)**, but mild PVL was not associated with decreasing annular or LVOT sizing **(Figure 3)**. There were no differences in mild PVL among valve sizes with increasing annular and LVOT eccentricities **(Supplementary Figure 1)**. The mild PVL group was associated with more three-leaflet calcification (90.9% vs. 61.8%, p=0.002), severe leaflet calcification (36.4% vs. 16.9%, p=0.02) and moderate-severe LVOT calcification (36.4% vs. 18.0%, p=0.03).

Table 2. Anatomic characteristics.

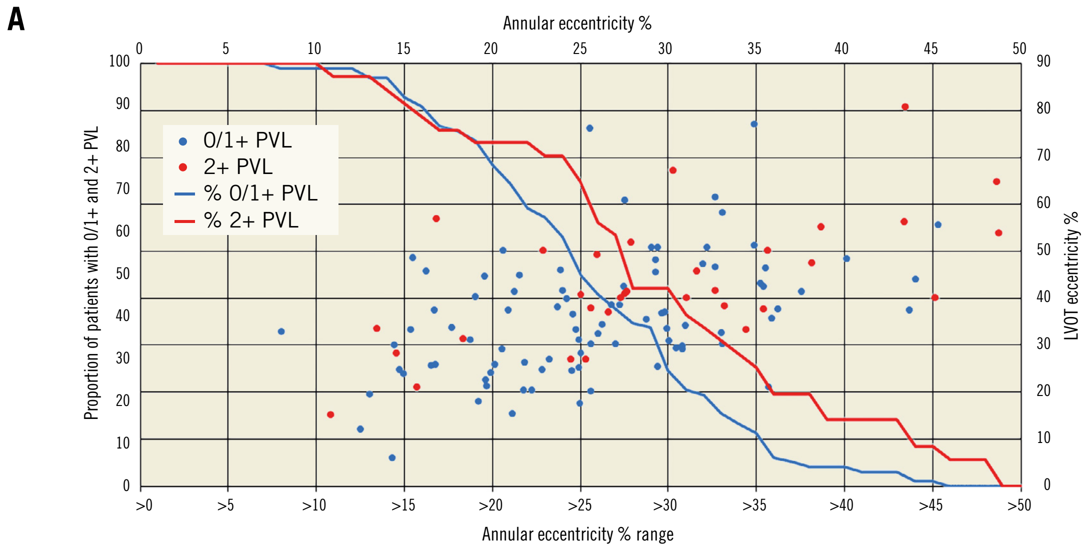
Variables expressed as N (%) or mean [SD]		Total	None/trace PVL	Mild PVL	*p*-value
Annulus		**N=122**	**N=89**	**N=33**	
Mean diameter (mm)		25.4 [2.4]	25.4 [2.4]	25.3 [2.3]	0.71
Area (mm^2)		504.4 [95.7]	506.3 [97.9]	499.4 [90.9]	0.73
Perimeter (mm)		80.5 [7.5]	80.5 [7.6]	80.3 [7.2]	0.86
% sized by area		2.3 [7.7]	2.6 [7.7]	1.4 [7.7]	0.45
Annulus-oversized		69 (56.6%)	53 (59.6%)	16 (48.5%)	0.31
Annulus-undersized		53 (43.4%)	36 (40.4%)	17 (51.5%)	
% eccentricity		26.6 [8.5]	25.7 [7.7]	29.2 [10.1]	0.04
LVOT*		**N=120**	**N=88**	**N=32**	
Mean diameter (mm)		24.8 [2.8]	24.8 [2.8]	24.6 [2.7]	0.68
Area (mm^2)		474.4 [112.7]	477.6 [112.8]	465.6 [113.6]	0.61
Perimeter (mm)		78.9 [8.9]	79.1 [8.9]	78.4 [8.9]	0.71
% sized by area*		10.5 [13.9]	10.2 [14.0]	11.4 [13.8]	0.67
LVOT-oversized		92/120 (76.7%)	67/88 (76.1%)	25/32 (78.1%)	1.00
LVOT-undersized		28/120 (23.3%)	21/88 (23.9%)	7/32 (21.9%)	
% eccentricity		38.0 [13.4]	36.1 [12.8]	43.4 [13.7]	0.008
Annulus and LVOT sizing combinations*		**N=120**	**N=88**	**N=32**	
Concordant sizing		79 (65.8%)	63 (71.6%)	16 (50.0%)	0.03
Discordant sizing		41 (34.2%)	25 (28.4%)	16 (50.0%)	
Concordant-undersized		20 (16.7%)	16 (18.2%)	4 (12.5%)	0.59
Concordant-oversized		59 (49.2%)	47 (53.4%)	12 (37.5%)	0.15
Discordant-undersized		33 (27.5%)	20 (22.7%)	13 (40.6%)	0.07
Discordant-oversized		8 (6.7%)	5 (5.7%)	3 (9.4%)	0.44
Calcification characteristics		**N=122**	**N=89**	**N=33**	
3-leaflet calcification		85 (69.7%)	55 (61.8%)	30 (90.9%)	0.002
Leaflet calcium grade	Mild-moderate	95 (77.9%)	74 (83.1%)	21 (63.6%)	0.02
	Severe	27 (22.1%)	15 (16.9%)	12 (36.4%)	
Annulus presence	LCC	40 (32.8%)	28 (31.5%)	12 (36.4%)	0.61
	RCC	25 (20.5%)	18 (20.2%)	7 (21.2%)	0.90
	NCC	33 (27.0%)	25 (28.1%)	8 (24.2%)	0.67
Annular calcium grade	None-mild	77 (63.1%)	58 (65.2%)	19 (57.6%)	0.44
	Mod-severe	45 (36.9%)	31 (34.8%)	14 (42.4%)	
LVOT presence	LCC	43 (35.2%)	32 (36.0%)	11 (33.3%)	0.79
	RCC	3 (2.5%)	1 (1.1%)	2 (6.1%)	0.18
	NCC	25 (20.5%)	17 (19.1%)	8 (24.2%)	0.61
LVOT calcium grade	None-mild	94 (77.0%)	73 (82.0%)	21 (63.6%)	0.03
	Mod-severe	28 (23.0%)	16 (18.0%)	12 (36.4%)	

*No LVOT measurements available in 2 patients with non-contrast CT-derived aortic root measurements. LCC: left coronary cusp; LVOT: left ventricular outflow tract; NCC: non-coronary cusp; RCC: right coronary cusp

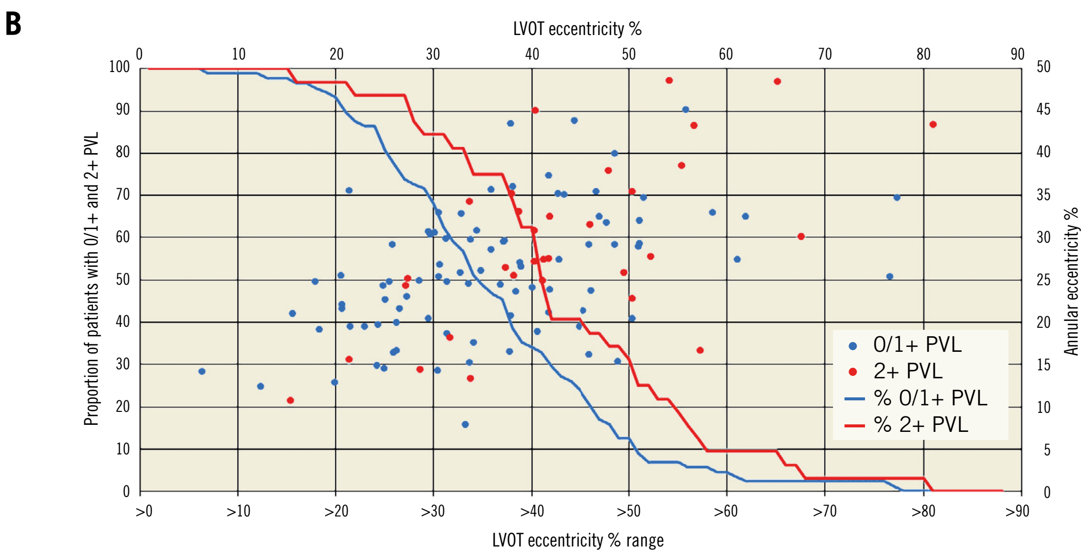
Figure 4 shows the distribution of PVL in concordant-sized, discordant-sized and the four annulus-LVOT sizing combinations. Although 43.4% were annulus-undersized (of which 20 [37.7%] were concordant-undersized and 33 [62.3%] discordant-undersized), our sizing criteria were all within manufacturer recommendations and targeted to <20% to annulus to reduce risks of annular injury and heart block. There were no differences in annular undersizing (p=0.31) between groups. Annulus-undersized patients had more balloon overfilling (71.7% vs. 27.5%, p<0.001) and post-dilatation (49.1% vs. 31.9%, p=0.06) than annulus-oversized, although no differences in balloon overfilling (p=0.31) and post-dilatation (p=0.40) were seen between groups. The mild PVL group had more discordant sizing (50.0% vs. 28.4%, p=0.03), and there were more mild PVL with discordant sizing overall (39.0% in discordant-sized vs. 20.3% in concordant-sized), and within the annulus-undersized subgroup (39.4% in discordant-undersized vs. 20.0% in concordant-undersized).

PROCEDURAL CHARACTERISTICS

All procedures were successful, with the transfemoral approach in 121 patients and left axillary in one **(Table 3)**; 81.1% had conscious sedation, with two conversions to general anaesthesia due



	>0	>5	>10	>15	>20	>25	>30	>35	>40	>45
2+ PVL	32 (100%)	32 (100%)	32 (100%)	29 (90%)	26 (81%)	23 (72%)	15 (47%)	9 (28%)	5 (16%)	3 (9%)
0/1+ PVL	88 (100%)	88 (100%)	87 (99%)	81 (92%)	67 (76%)	44 (50%)	24 (27%)	11 (13%)	4 (5%)	1 (1%)
p-value	1.00	1.00	1.00	0.073	0.63	***0.039***	***0.049***	*0.054*	*0.056*	*0.058*



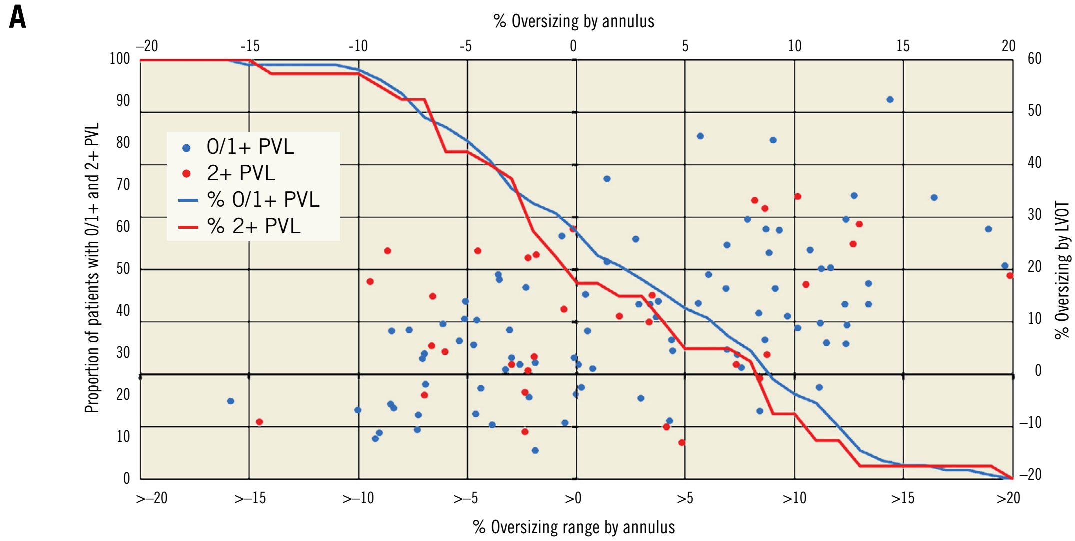
	>0	>10	>20	>30	>40	>50	>60	>70	>80
2+ PVL	32 (100%)	32 (100%)	31 (97%)	27 (84%)	20 (63%)	10 (31%)	3 (9%)	1 (3%)	1 (3%)
0/1+ PVL	88 (100%)	87 (99%)	82 (93%)	60 (68%)	30 (34%)	11 (13%)	4 (5%)	2 (2%)	0 (0%)
p-value	1.00	1.00	0.67	0.11	***0.007***	***0.03***	0.38	1.00	0.27

Figure 2. *Incidence of mild paravalvular leak with annular and LVOT eccentricity. Analysis of relationships between annular (A) and LVOT (B) eccentricity in association with none/trace (0/1+) and mild (2+) paravalvular leak. Increasing annular and LVOT eccentricity was associated with more mild PVL (A & B). LVOT: left ventricular outflow tract; PVL: paravalvular leak*

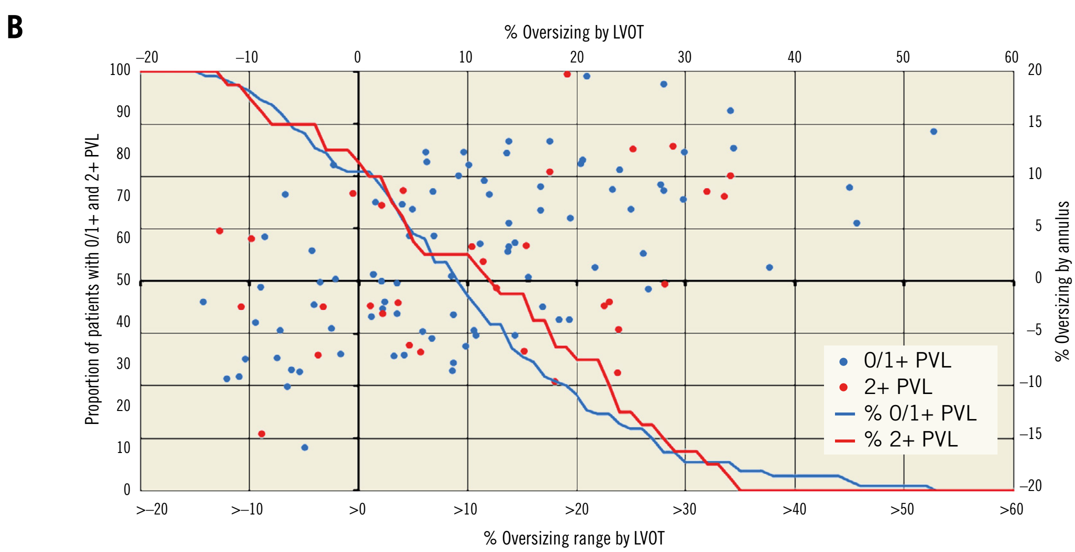
to patient anxiety and haemodynamic instability. No differences in S3 size distribution, balloon filling, contrast use and implant depth were observed.

OUTCOMES

There were no differences in ICU and hospital length of stay **(Table 4)**. One in-hospital mortality occurred in a patient who presented with cardiogenic shock but died of persistent renal failure and withdrawal of care. There were two 30-day mortalities, one from primary cardiac failure with a baseline ejection fraction of 15%, and one from intracranial haemorrhage after a fall. No stroke or vascular complication occurred, and 20 patients (16.4%) developed new left bundle branch block (LBBB). Of the 13 patients (10.7%) who required a new permanent pacemaker, nine had pre-existing right bundle branch block (RBBB). Mean follow-up was 10.7±5.8 months (range 0.1-20.8). All surviving patients had NYHA class improvements.



2+ PVL	32 (100%)	32 (100%)	31 (97%)	25 (78%)	15 (47%)	10 (31%)	5 (16%)	1 (3%)
0/1+ PVL	88 (100%)	87 (99%)	86 (99%)	71 (81%)	52 (59%)	36 (41%)	18 (20%)	3 (3%)
p-value	1.00	1.00	1.00	0.80	0.30	0.40	0.61	1.00



2+ PVL	32 (100%)	30 (94%)	25 (78%)	18 (56%)	10 (31%)	3 (9%)	0 (0%)	0 (0%)
0/1+ PVL	88 (100%)	84 (95%)	67 (76%)	41 (47%)	20 (23%)	6 (7%)	3 (3%)	1 (1%)
p-value	1.00	0.66	1.00	0.41	0.35	0.70	0.56	1.00

Figure 3. *Incidence of mild paravalvular leak with annular and LVOT prosthesis sizing. Analysis of relationships between SAPIEN 3 sizing to annulus (A) and LVOT (B) in association with none/trace (0/1+) and mild (2+) paravalvular leak. Mild PVL was not associated with increasing annular or LVOT sizing (A & B). LVOT: left ventricular outflow tract; PVL: paravalvular leak*

PREDICTORS OF MILD PARAVALVULAR LEAK

There was no moderate or greater PVL in our cohort. Mild PVL was associated with increasing annular eccentricity (OR 1.05, 95% CI: 1.001-1.10, p=0.04) and moderate-severe LVOT calcification (OR 2.61, 95% CI: 1.07-6.36, p=0.03) **(Table 5)**. The area under the ROC curve for the multivariate model was robust with a 0.80 c-statistic. Independent predictors of mild PVL were three-leaflet calcification (OR 13.3, 95% CI: 2.7-66.7, p=0.002), LVOT eccentricity (OR 1.05 per % LVOT eccentricity, 95% CI: 1.02-1.09, p=0.005), and discordant sizing (OR 3.08, 95% CI: 1.20-7.90, p=0.02).

We identified LVOT eccentricity >40% as the most predictive binary variable for the associated continuous variable based on the most robust area under the ROC curve in univariate modelling (0.63). Composed of this variable and discordant sizing and three-leaflet calcification, we created a composite variable. Compared to having 0 or 1 of these predictors, a patient with two predictors had

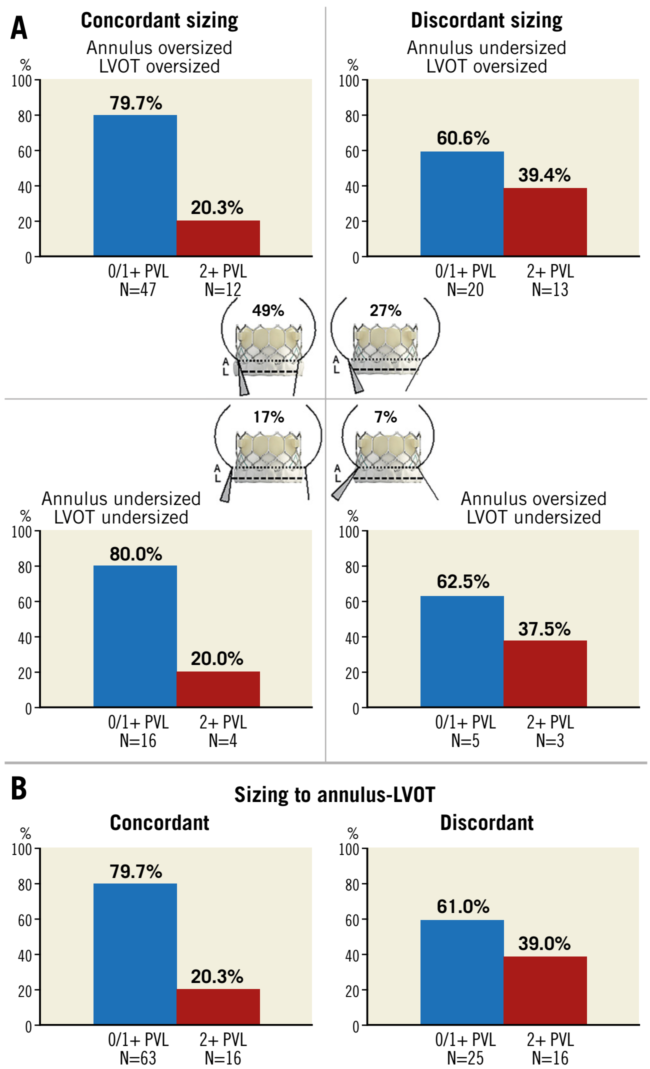


Figure 4. *Incidence of mild paravalvular leak (PVL) across annular and LVOT sizing composites. Distribution of patients with none/trace vs. mild PVL after SAPIEN 3 TAVI across four different annulus and LVOT sizing combinations (A) and between concordant and discordant sizing (B). Discordant sizing was predictive of mild PVL. 0/1+: none/trace; 2+: mild; LVOT: left ventricular outflow tract*

a 7.1-fold higher odds, and with all three had an 11.6-fold higher odds of developing mild PVL (p<0.001).

Discussion

Our main findings are: 1) mild PVL was seen in 27.0% of our S3 TAVI, with no differences in valve sizing, balloon filling, implantation technique, post-dilatation and implant depth; 2) annular and LVOT eccentricities, three-leaflet and moderate-severe LVOT calcification and discordant sizing were associated with PVL; 3) three-leaflet calcification, LVOT eccentricity and discordant sizing were independent predictors of PVL.

PVL remains an ongoing issue in TAVI. Mild PVL predicted mortality[6,7,13] with the SAPIEN/XT but not the S3[5]. More recent PARTNER 2A intermediate-risk data showed no higher two-year mortality with mild PVL in SAPIEN/XT[2]. Nonetheless, the longer-term impact of mild PVL on left ventricular remodelling and survival remains unknown in lower-risk patients. PVL predictors include valve undersizing, implant depth and aortic root calcification[6,14-17]. In the S3, less oversizing and annular/LVOT calcification

Table 3. Procedural characteristics.

Variables expressed as N (%) or mean [SD]	Total N=122	None/trace PVL N=89	Mild PVL N=33	*p*-value
Transfemoral approach	121 (99.2%)	89 (100%)	32 (97.0%)	0.27
Conscious sedation	99 (81.1%)	74 (83.1%)	25 (75.8%)	0.43
Valve size				
23 mm	42 (34.4%)	29 (32.6%)	13 (39.4%)	0.78
26 mm	48 (39.3%)	36 (40.4%)	12 (36.4%)	
29 mm	32 (26.2%)	24 (27.0%)	8 (24.2%)	
Post-dilatation	48 (39.3%)	33 (37.1%)	15 (45.5%)	0.40
Final balloon filling				
Nominal	58 (47.5%)	45 (50.6%)	13 (39.4%)	0.31
Underfill	7 (5.7%)	6 (6.7%)	1 (3.0%)	
Overfill	57 (46.7%)	38 (42.7%)	19 (57.6%)	
Contrast (mL)	65.2 [21.5]	65.3 [22.7]	64.8 [18.2]	0.92
Valve implant depth				
% ventricular, NCC	27.7 [12.3]	28.8 [12.4]	24.8 [12.0]	0.11
% ventricular, LCC	23.9 [10.9]	24.2 [11.9]	23.1 [8.2]	0.56
% ventricular, mean	25.8 [9.7]	26.5 [10.4]	24.0 [7.1]	0.13
LCC: left coronary cusp; NCC: non-coronary cusp				

Table 4. In-hospital and 30-day outcomes.

Variables expressed as N (%) or mean [SD]	Total N=122	None/trace PVL N=89	Mild PVL N=33	*p*-value
In-hospital outcomes				
ICU stay (hours)	40.7 [48.6]	40.5 [51.0]	41.2 [41.9]	0.95
Hospital stay (days)	3.6 [3.2]	3.4 [2.7]	4.2 [4.4]	0.32
New persistent LBBB	20 (16.4%)	14 (15.7%)	6 (18.2%)	0.79
New complete heart block	12 (9.8%)	7 (7.9%)	5 (15.2%)	0.30
New permanent pacemaker	13 (10.7%)	7 (7.9%)	6 (18.2%)	0.11
30-day outcomes				
Stroke	1 (0.8%)	1 (1.1%)	0 (0%)	1.00
Major vascular complication	0 (0%)	0 (0%)	0 (0%)	1.00
SAPIEN 3 valve haemodynamics				
Mean gradient (mmHg)	11.2 [5.6]	10.9 [5.5]	11.9 [5.7]	0.43
Peak gradient (mmHg)	21.3 [9.9]	20.5 [9.7]	23.2 [10.4]	0.25
Valve area (cm²)	1.76 [0.56]	1.78 [0.59]	1.71 [0.50]	0.64
LBBB: left bundle branch block				

EuroIntervention 2018;14:58-68

Table 5. Univariate and multivariate predictors of mild paravalvular leak.

Univariate predictors	OR	95% CI	*p*-value
Annular eccentricity (%)	1.05	1.001-1.10	0.04
LVOT eccentricity (%)	1.04	1.01-1.08	0.008
Discordant sizing to annulus-LVOT	2.41	1.06-5.50	0.03
3-leaflet calcification	6.18	1.75-21.8	<0.001
Moderate-severe LVOT calcification	2.61	1.07-6.36	0.03
Multivariate predictors			
LVOT eccentricity (%)	1.05	1.02-1.09	0.005
Discordant sizing to annulus-LVOT	3.08	1.20-7.90	0.02
3-leaflet calcification	13.3	2.66-66.7	0.002

CI: confidence interval; LVOT: left ventricular outflow tract; OR: odds ratio

were associated with PVL[15-18]. Compared to the PARTNER II intermediate-risk trial[17], our averaged annular oversizing was less at 2.3±7.7% with fewer patients (55.8%) oversized. Yet, our mild PVL rate was only 27.0% with none moderate/severe, consistent with those reported in S3 studies[3-5,15-18,20]. This could be due to our higher balloon overfilling and post-dilatation rates[4]. Similar to other studies[14,17,18], three-leaflet and moderate-severe LVOT calcification were associated with PVL, although our evaluation of calcification was limited by its semiquantitative nature.

LVOT ECCENTRICITY: INDEPENDENT PREDICTOR OF PVL

Eccentricities at both annulus and LVOT were associated with PVL, and increasing LVOT eccentricity was an independent predictor of PVL. This result has not been reported and was somewhat surprising given that balloon-expandable valves are known to circularise the annulus and LVOT[19]. It is conceivable that, in more elliptical LVOT, the S3 while stretching the LVOT short axis may not foreshorten the long axis sufficiently to seal against the LVOT. The long axis of the LVOT typically spans from non-coronary to left coronary sinuses, with a significant portion comprised of the aortomitral curtain. In undersized LVOT, the aortomitral curtain segment of the LVOT, being fibrous in nature, may not seal as well against the S3 frame after circularisation, compared to the muscular portion of the LVOT, which would provide better sealing. This hypothesis may be supported by Khalique and colleagues, who found that most of the PVL were located at non-coronary and left coronary portions of the annulus[14].

SIZING MISMATCH OF ANNULUS-LVOT: CONCEPT OF THE SAPIEN 3 SEAL ZONE

Unlike previous reports[6,15-17], annular undersizing did not predict PVL in our study, but discordant sizing did. This is the first study to have examined LVOT anatomy in predicting PVL in balloon-expandable TAVI. We conceptualised a seal zone at and below the annulus to explain the impact of discordant sizing on PVL **(Figure 5)**. It is conceivable that patients with discordant sizing have a more heterogeneous landing surface with a shorter seal zone **(Figure 4A, Figure 5)**, that may seal less optimally against the S3 frame after expansion. Concordant sizing provides a more homogenous landing surface with a longer seal zone that maintains contact more optimally with the S3 frame **(Figure 5)**. TEE to localise PVL and MDCT to examine valve geometry in relation to aortic root anatomy may help to evaluate the above hypothesis.

Previous studies have recommended 1-8% oversizing as optimal to minimise PVL in S3 TAVI[15,17,18]. Fifty-three percent (53%) of our 122 patients who were annulus-undersized had more balloon overfilling and post-dilatation, and those with concordant undersizing developed less PVL. It is conceivable that, when both annulus and LVOT are undersized, balloon overfilling and post-dilatation can more uniformly expand the S3 frame, to create a longer seal zone to minimise PVL. Interestingly, valve size had no effect on concordant versus discordant sizing, and PVL occurred more frequently in discordant sizing across all valve sizes **(Supplementary Figure 2)**.

The clinical impact of discordant sizing resulting in a shorter, more heterogeneous seal zone in S3 TAVI remains to be seen. Our group is currently evaluating different LVOT morphologies and their relationship to discordant sizing to quantify LVOT-annular mismatch and further the present study. Of note, there was no difference in the ratio of annulus to LVOT area between the none/trace and mild PVL groups (1.07±0.11 vs. 1.10±0.14, p=0.26), but discordant sizing was an independent predictor of PVL.

ESCALATING RISK OF PVL WITH MULTIPLE PREDICTORS

When LVOT eccentricity was analysed as a binary variable, having more than one independent predictor increased the odds of PVL after S3 TAVI. LVOT eccentricity >40%, three-leaflet calcification and discordant sizing increase the risk of PVL by 11.6-fold. The clinical implication of this large risk magnitude is unclear. What we suggest is that, during case planning, if two to three of the above risk factors are present, we would probably expect PVL after S3 implantation. In the absence of high-risk root anatomy, post-dilatation to reduce PVL may be beneficial, but residual mild PVL may be expected, given the underlying anatomic risk factors. Future innovations (e.g., SAPIEN Ultra) may address this limitation.

Limitations

Our study has limitations. It was retrospective and the sample size was relatively small. However, we feel confident of our multivariate analysis with a c-statistic of 0.80. Unlike a previous study[14], calcification was evaluated semiquantitatively. PVL severity was not core lab evaluated and PVL location was not determined. There was no moderate or severe PVL (which has been associated with mortality[20]), and the longer-term impact of mild PVL remains unknown. Further studies are needed to validate our predictive model in an independent cohort.

Conclusions

As TAVI expands to lower-risk patients, the longer-term impact of mild PVL may become important. We identified LVOT eccentricity and discordant sizing as novel predictors of PVL in

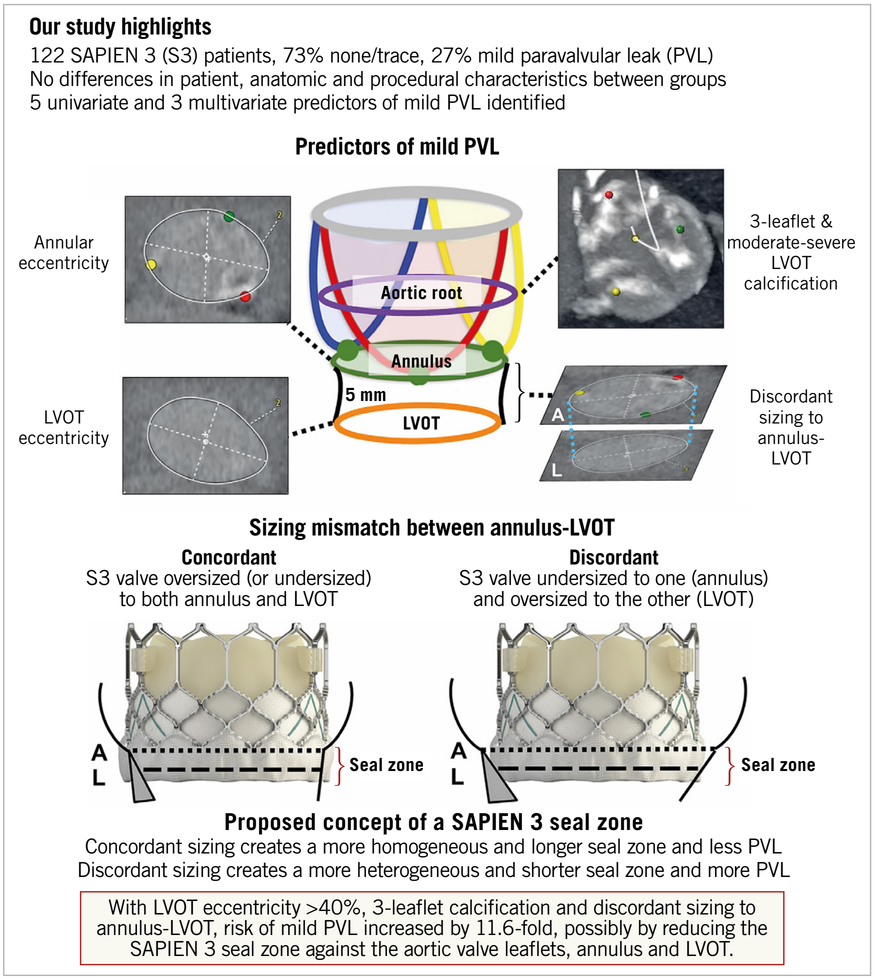


Figure 5. *Predictors of paravalvular leak after SAPIEN 3 TAVI.*

S3 implantation. Further studies should aim to understand their mechanism and significance, to minimise PVL in TAVI with balloon-expandable valves.

Impact on daily practice

Paravalvular leak remains an important issue in TAVI. The Edwards SAPIEN 3 valve has reduced PVL but >30% remain with mild PVL. The longer-term impact of mild PVL may be relevant as TAVI expands to lower-risk patients. In this retrospective analysis, mild PVL was associated with higher annular eccentricity and moderate-severe LVOT calcification. Independent predictors of mild PVL were LVOT eccentricity, discordant sizing and three-leaflet calcification. This study calls for a more routine evaluation of the LVOT anatomy, annular and LVOT eccentricity, and annulus-LVOT sizing mismatch when considering TAVI with balloon-expandable valves.

Conflict of interest statement

G. Tang is a physician proctor for Edwards Lifesciences and Medtronic. The other authors have no conflicts of interest to declare.

References

1. Holmes DR Jr, Brennan JM, Rumsfeld JS, Dai D, O'Brien SM, Vemulapalli S, Edwards FH, Carroll J, Shahian D, Grover F, Tuzcu EM, Peterson ED, Brindis RG, Mack MJ; STS/ACC TVT Registry. Clinical outcomes at 1 year following transcatheter aortic valve replacement. *JAMA*. 2015;313:1019-28.

2. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG; PARTNER 2 Investigators. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med*. 2016;374:1609-20.

3. Thourani VH, Kodali S, Makkar RR, Herrmann HC, Williams M, Babaliaros V, Smalling R, Lim S, Malaisrie SC, Kapadia S, Szeto WY, Greason KL, Kereiakes D, Ailawadi G, Whisenant BK, Devireddy C, Leipsic J, Hahn RT, Pibarot P, Weissman NJ, Jaber WA, Cohen DJ, Suri R, Tuzcu EM, Svensson LG, Webb JG, Moses JW, Mack MJ, Miller DC,

Smith CR, Alu MC, Parvataneni R, D'Agostino RB Jr, Leon MB. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. *Lancet.* 2016;387:2218-25.

4. Kodali S, Thourani VH, White J, Malaisrie SC, Lim S, Greason KL, Williams M, Guerrero M, Eisenhauer AC, Kapadia S, Kereiakes DJ, Herrmann HC, Babaliaros V, Szeto WY, Hahn RT, Pibarot P, Weissman NJ, Leipsic J, Blanke P, Whisenant BK, Suri RM, Makkar RR, Ayele GM, Svensson LG, Webb JG, Mack MJ, Smith CR, Leon MB. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. *Eur Heart J.* 2016;37:2252-62.

5. Herrmann HC, Thourani VH, Kodali SK, Makkar RR, Szeto WY, Anwaruddin S, Desai N, Lim S, Malaisrie SC, Kereiakes DJ, Ramee S, Greason KL, Kapadia S, Babaliaros V, Hahn RT, Pibarot P, Weissman NJ, Leipsic J, Whisenant BK, Webb JG, Mack MJ, Leon MB; PARTNER Investigators. One-Year Clinical Outcomes With SAPIEN 3 Transcatheter Aortic Valve Replacement in High-Risk and Inoperable Patients With Severe Aortic Stenosis. *Circulation.* 2016;134:130-40.

6. Athappan G, Patvardhan E, Tuzcu EM, Svensson LG, Lemos PA, Fraccaro C, Tarantini G, Sinning JM, Nickenig G, Capodanno D, Tamburino C, Latib A, Colombo A, Kapadia SR. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. *J Am Coll Cardiol.* 2013;61:1585-95.

7. Kodali S, Pibarot P, Douglas PS, Williams M, Xu K, Thourani V, Rihal CS, Zajarias A, Doshi D, Davidson M, Tuzcu EM, Stewart W, Weissman NJ, Svensson L, Greason K, Maniar H, Mack M, Anwaruddin S, Leon MB, Hahn RT. Paravalvular regurgitation after transcatheter aortic valve replacement with the Edwards sapien valve in the PARTNER trial: characterizing patients and impact on outcomes. *Eur Heart J.* 2015;36:449-56.

8. Kampaktsis PN, Ullal AV, Minutello RM, Feldman DN, Swaminathan RV, Voudris K, Baduashvili A, Pastella K, Pawar S, Kaple RK, Vavuranakis M, Bergman GS, Skubas NJ, Lin F, Salemi A, Devereux RB, Chiu Wong S. Impact of Paravalvular Aortic Insufficiency on Left Ventricular Remodeling and Mortality after Transcatheter Aortic Valve Replacement. *J Heart Valve Dis.* 2016;25:301-8.

9. Barbanti M, Yang TH, Rodès Cabau J, Tamburino C, Wood DA, Jilaihawi H, Blanke P, Makkar RR, Latib A, Colombo A, Tarantini G, Raju R, Binder RK, Nguyen G, Freeman M, Ribeiro HB, Kapadia S, Min J, Feuchtner G, Gurtvich R, Alqoofi F, Pelletier M, Ussia GP, Napodano M, de Brito FS Jr, Kodali S, Norgaard BL, Hansson NC, Pache G, Canovas SJ, Zhang H, Leon MB, Webb JG, Leipsic J. Anatomical and procedural features associated with aortic root rupture during balloon-expandable transcatheter aortic valve replacement. *Circulation.* 2013;128:244-53.

10. Shivaraju A, Thilo C, Ott I, Mayr PN, Schunkert H, von Scheidt W, Thoenes M, Byrne R, Kastrati A, Kasel AM. Tools and Techniques - Clinical: Fluoroscopic balloon sizing of the aortic annulus before transcatheter aortic valve replacement (TAVR) - follow the "right cusp rule". *EuroIntervention.* 2015;11:840-2.

11. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol.* 2012;60:1438-54.

12. Mauri V, Reimann A, Stern D, Scherner M, Kuhn E, Rudolph V, Rosenkranz S, Eghbalzadeh K, Friedrichs K, Wahlers T, Baldus S, Madershahian N, Rudolph TK. Predictors of Permanent Pacemaker Implantation After Transcatheter Aortic Valve Replacement With the SAPIEN 3. *JACC Cardiovasc Interv.* 2016;9:2200-9.

13. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, Kodali SK, Makkar RR, Fontana GP, Kapadia S, Bavaria J, Hahn RT, Thourani VH, Babaliaros V, Pichard A, Herrmann HC, Brown DL, Williams M, Akin J, Davidson MJ, Svensson LG; PARTNER 1 trial investigators. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomized controlled trial. *Lancet.* 2015;385:2477-84.

14. Khalique OK, Hahn RT, Yang TH, Gada H, Nazif TM, Vahl TP, George I, Kalesan B, Forster M, Williams MB, Leon MB, Einstein AJ, Pulerwitz TC, Pearson GD, Kodali SK. Quantity and location of aortic valve complex calcification predicts severity and location of paravalvular regurgitation and frequency of post-dilatation after balloon-expandable transcatheter aortic valve replacement. *JACC Cardiovasc Interv.* 2014;7:885-94.

15. Yang TH, Webb JG, Blank P, Dvir D, Hansson NC, Norgaard BL, Thompson CR, Thomas M, Wendler O, Vahanian A, Himbert D, Kodali SK, Hahn RT, Thourani VH, Schymilk G, Precious B, Berger A, Wood DA, Pibarot P, Rodés-Cabau J, Jaber WA, Leon MB, Walther T, Leipsic J. 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;8:462-71.

16. Kaneko H, Hoelschermann F, Tambor G, Yoon SH, Neuss M, Butter C. Predictors of Paravalvular Regurgitation After Transcatheter Aortic Valve Implantation for Aortic Stenosis Using New-Generation Balloon-Expandable SAPIEN 3. *Am J Cardiol.* 2017;119:618-22.

17. Blanke P, Pibarot P, Hahn R, Weissman N, Kodali S, Thourani V, Parvataneni R, Dvir D, Naoum C, Nørgaard BL, Douglas P, Jaber W, Khalique OK, Jilaihawi H, Mack M, Smith C, Leon M, Webb J, Leipsic J. Computed Tomography-Based Oversizing Degrees and Incidence of Paravalvular Regurgitation of a New Generation Transcatheter Heart Valve. *JACC Cardiovasc Interv.* 2017;10:810-20.

18. Maeno Y, Abramowitz Y, Jilaihawi H, Israr S, Yoon S, Sharma RP, Kazuno Y, Kawamori H, Miyasaka M, Rami T, Mangat G, Takahashi N, Okuyama K, Kashif M, Chakravarty T, Nakamura M, Cheng W, Makkar RR. Optimal sizing for SAPIEN 3 transcatheter aortic valve replacement in patients with or without left ventricular outflow tract calcification. *EuroIntervention.* 2017;12:e2177-85.

19. Kazuno Y, Maeno Y, Kawamori H, Takahashi N, Abramowitz Y, Babak H, Kashif M, Chakravarty T, Nakamura M, Cheng W, Friedman J, Berman D, Makkar RR, Jilaihawi H. Comparison of SAPIEN 3 and SAPIEN XT transcatheter heart valve stent-frame expansion: evaluation using multi-slice computed tomography. *Eur Heart J Cardiovasc Imaging.* 2016;17:1054-62.

20. Pibarot P, Hahn RT, Weissman NJ, Arsenault M, Beaudoin J, Bernier M, Dahou A, Khalique OK, Asch FM, Toubal O, Leipsic J, Blanke P, Zhang F, Parvataneni R, Alu M, Herrmann H, Makkar R, Mack M, Smalling R, Leon M, Thourani VH, Kodali S. Association of Paravalvular Regurgitation With 1-Year Outcomes After Transcatheter Aortic Valve Replacement With the SAPIEN 3 Valve. *JAMA Cardiol.* 2017;2:1208-16.

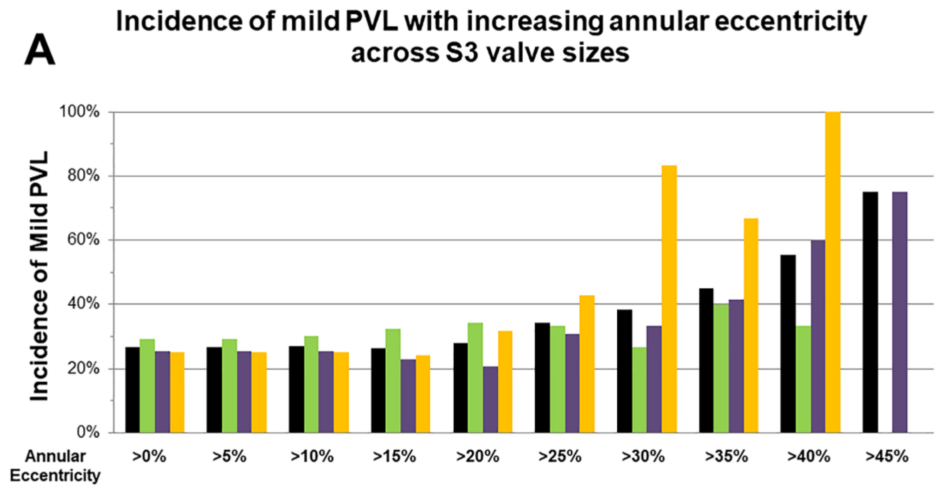
Supplementary data

Supplementary Figure 1. Mild paravalvular leak across valve sizes.

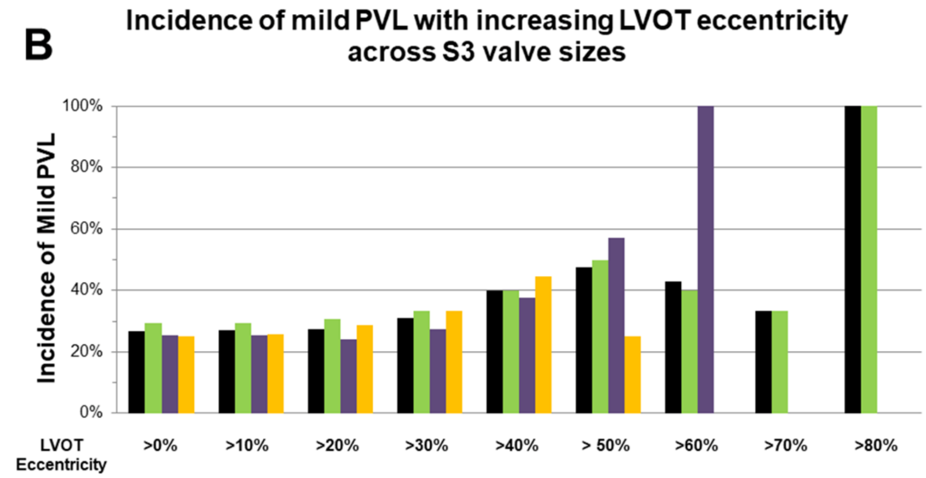
Supplementary Figure 2. Paravalvular leak according to concordant vs. discordant sizing across SAPIEN 3 valve sizes.

The supplementary data are published online at: http://www.pcronline.com/eurointervention/134th_issue/10

Supplementary data

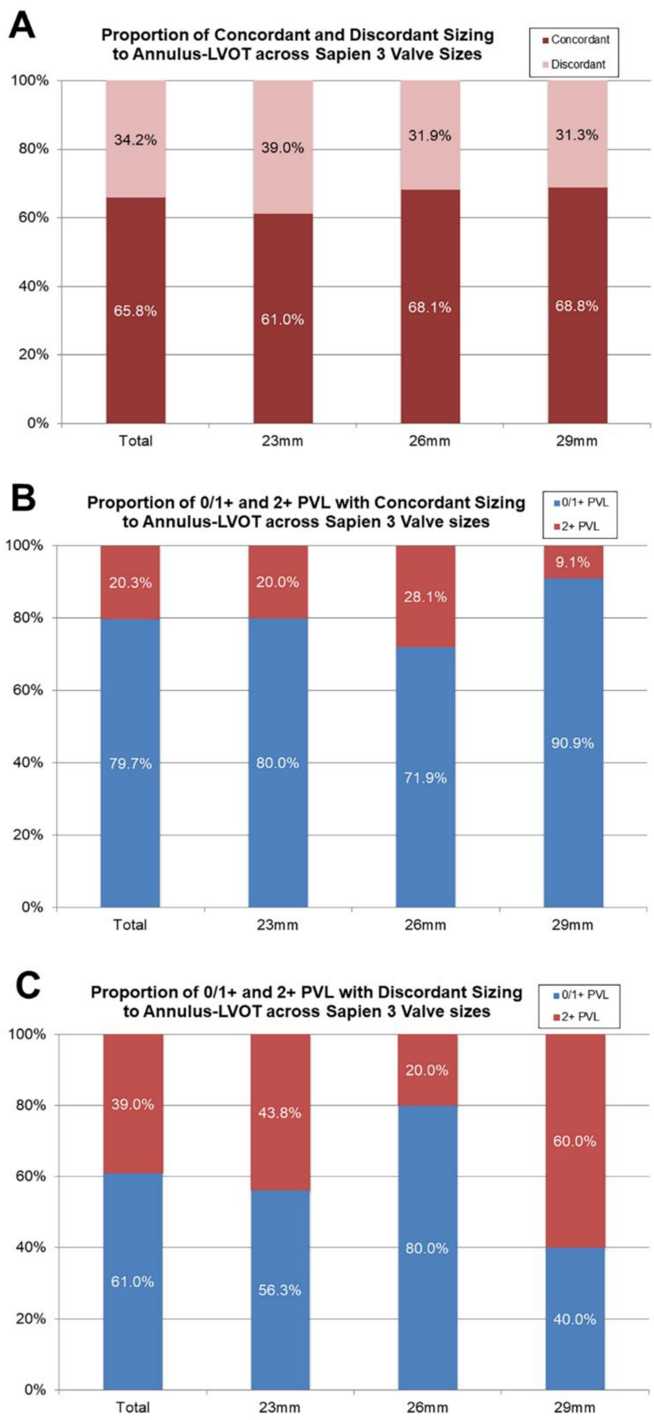


	>0%	>5%	>10%	>15%	>20%	>25%	>30%	>35%	>40%	>45%
Total PVL	32/120 (27%)	32/120 (27%)	32/119 (27%)	29/110 (26%)	26/93 (28%)	23/67 (34%)	15/39 (38%)	9/20 (45%)	5/9 (56%)	3/4 (75%)
23mm S3	12/41 (29%)	12/41 (29%)	12/40 (30%)	12/37 (32%)	11/32 (34%)	9/27 (33%)	4/15 (27%)	2/5 (40%)	1/3 (33%)	0/0 (-)
26mm S3	12/47 (26%)	12/47 (26%)	12/47 (26%)	10/44 (23%)	8/39 (21%)	8/26 (31%)	6/18 (33%)	5/12 (42%)	3/5 (60%)	3/4 (75%)
29mm S3	8/32 (25%)	8/32 (25%)	8/32 (25%)	7/29 (24%)	7/22 (32%)	6/14 (43%)	5/6 (83%)	2/3 (67%)	1/1 (100%)	0/0 (-)



	>0%	>10%	>20%	>30%	>40%	> 50%	>60%	>70%	>80%
Total PVL	32/120 (27%)	32/119 (27%)	31/113 (27%)	27/87 (31%)	20/50 (40%)	10/21 (48%)	3/7 (43%)	1/3 (33%)	1/1 (100%)
23mm S3	12/41 (29%)	12/41 (29%)	12/39 (31%)	12/36 (33%)	10/25 (40%)	5/10 (50%)	2/5 (40%)	1/3 (33%)	1/1 (100%)
26mm S3	12/47 (26%)	12/47 (26%)	11/46 (24%)	9/33 (27%)	6/16 (38%)	4/7 (57%)	1/1 (100%)	0/0 (-)	0/0 (-)
29mm S3	8/32 (25%)	8/31 (26%)	8/28 (29%)	6/18 (33%)	4/9 (44%)	1/4 (25%)	0/1 (0%)	0/0 (-)	0/0 (-)

Supplementary Figure 1. Mild paravalvular leak across valve sizes. Incidence of mild paravalvular leak (PVL) with increasing annulus (A) and LVOT (B) eccentricity was not different across SAPIEN 3 sizes.



Supplementary Figure 2. Paravalvular leak according to concordant vs. discordant sizing across SAPIEN 3 (S3) valve sizes. The proportion of concordant vs. discordant sizing was similar across S3 sizes (A). In concordant sizing (B), there were fewer mild PVL across valve sizes. However, milder PVL was observed across valve sizes in the discordant group (C).