UNIVERSITÀ DI ROMA "SAPIENZA"

DOTTORATO DI RICERCA IN

FISIOPATOLOGIA ED IMAGING CARDIO-TORACO-VASCOLARE

(XXXI CICLO)

Coordinatore: Prof. Federico Venuta

RISK FACTORS FOR PARAVALVULAR LEAK AFTER TRANSCATHETER AORTIC VALVE REPLACEMENT

Dottorando
Dott. Francesco Pollari

Tutore
Prof. Marco Anile

Supervisore
Ao. Prof. Steffen Pfeiffer

ANNO ACCADEMICO 2017/2018

TABLE OF CONTENTS

ABBREVIATIONS

DLZ = device landing zone

LCC = left coronary cusp

LVOT = left ventricular outflow tract

MDCT = multidetector computed tomography

NCC = non-coronary cusp

PCI = percutaneous coronary intervention

PVL = paravalvular leak

RCC = right coronary cusp

ROI = region of interest

TA = transapical

TAVI = transcatheter aortic valve implantation

TTE = transthoracic echocardiography

TEE = transesophageal echocardiography

TF = transfemoral

ABSTRACT

Objective. To assess risk factors for paravalvular leak (PVL) after transcatheter aortic valve implantation (TAVI) in a large single-center cohort, including measurement of aortic valve calcification using a reproducible method.

Methods. We retrospectively analyzed preoperative contrast-enhanced multidetector computed tomography (MDCT) scans of patients who underwent TAVI in our center between 2009 and 2016. Calcium volume was calculated for each aortic cusp in the aortic valve (AV), left ventricular outflow tract (LVOT) and device-landing zone (DLZ).

Results. Overall, 539 patients were included in the study (Edwards SapienXT, n=192; Edwards Sapien3, n=206; Medtronic CoreValve EvolutR, n=44; Symetis Acurate, n=97). Median calcium volume in the DLZ was 757 mm^3, with no significant differences among the four prosthesis groups. None of the patients had severe PVL. The overall incidence of mild-to-moderate PVL was 15.8% (95% CI: 12.8-19.1%). On multivariate logistic regression, DLZ calcification (p=0.00006; OR for an increase of 100 mm^3 1.08; 95% CI: 1.04-1.13) and use of the CoreValve (p=0.0028; OR 4.1; 95% CI: 1.6-10 with SapienXT as reference) prosthesis were found to be associated with ≥mild PVL. In contrast, degree of oversizing (p=0.002; OR 0.97; 95% CI: 0.95-0.99), and use of Sapien3 (p=0.00005; OR 0.23; 95% CI: 0.11-0.47 with SapienXT as reference) were associated with a lower incidence of ≥mild PVL.

Conclusions. Aortic calcification volume in the DLZ is associated with residual PVL after TAVI. When taking calcification into account, the balloon-expandable prosthesis Sapien3 seems to be associated with a lower incidence of PVL.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has emerged as a new standard for percutaneous treatment of severe aortic valve stenosis in intermediate and high surgical risk or inoperable patients [1]. However, its wide application is yet limited by the occurrence of postoperative paravalvular leak (PVL), which portends increased mortality during follow-up [2]. Aortic valve calcification has been found to be associated with PVL [3-6], but results from the available literature have been obtained in studies with limited sample sizes [7] or affected by several bias, including methods for calcium determination [8] or center effect in multicenter studies [9].

The aim of this study was to assess risk factors for PVL after TAVI in a large single-center cohort, including aortic valve calcification as measured by contrast-enhanced multidetector computed tomography (MDCT).

METHODS

Study population

We retrospectively analyzed our center experience with TAVI procedures between July 2009 and October 2016. All patients who underwent TAVI for symptomatic severe stenosis of the native aortic valve were included in the study. Severe aortic stenosis was defined in accordance with international guidelines [1]. Exclusion criteria were: bicuspid aortic valve, pure aortic regurgitation, and aborted procedures because of annulus diameter of >30 mm. Overall, 659 patients were eligible for the study. However, 108 patients had not a MDCT scan (by first patients was not yet a standard) or was performed 5 years previously and MDCT images were not retrievable from our "Picture Archiving and Communication System"; 4 patients had no preoperative contrast-enhanced MDCT because of severe renal impairment; 3 patients did not have ECG-triggered MDCT scans and were unsuitable for analysis; and 5 patients were treated with an experimental second-generation prosthesis. Thus, a total of 539 patients were evaluable (Figure 1). Clinical and operative data were prospectively collected in our institutional database. The following intraoperative outcomes were recorded based on the Valve Academic Research Consortium-2 recommendations [10]: unplanned cardiopulmonary bypass, conversion to surgery, coronary obstruction, prosthesis valve malpositioning, second prosthesis implantation, and intraoperative percutaneous coronary intervention (PCI). All patients provided written informed consent for the use of their data anonymously, and the study was approved from our institutional review board (IRB-2017-006). The study protocol conforms to the ethical guidelines in the Declaration of Helsinki.

The Heart Team

According to international guidelines [1], indication for TAVI is discussed within a Heart Team, composed of at least a cardiologist and a cardiac surgeon evaluating patients with severe aortic valve stenosis, including those referred to our center from peripheral hospitals, private practices, or

our emergency department. All patients with frailty factors who were judged inoperable or at high surgical risk (as defined by logistic EuroSCORE>20%) were considered eligible for TAVI.

MDCT Angiography and calcium quantification

All patients underwent contrast-enhanced ECG-gated MDCT (330 ms rotation, helical mode, 60-70% gating, 0.6x64 mm collimation, 50-100 ml of i.v. contrast agent [Solutrast 370, Bracco Imaging Deutschland GmbH] at 4 ml/s) for assessment of aortic root anatomy (suitability for TAVI) and the femoral axis (suitably for transfemoral [TF] approach). In our center, all MDCT studies were performed with a 64-slice SOMATOM Definition AS (Siemens Healthcare GmbH, Erlangen, Germany) and were analyzed by the Heart Team using 3mensio Structural Heart software (v.7.0 SP1, Medical Imaging BV, Bilthoven, the Netherlands), which allowed assessment of the basal plane (aortic annulus), defined as the virtual plane crossing the nadir of each aortic cusp in diastole.

Calcium volume in the aortic valve was retrospectively measured using 3mensio. After identification of the basal plane, the lower coronary ostium was determined and the region of interest (ROI) was set before the origin of the coronary vessel. 3mensio software automatically performs aortic valve cusp delineation and detects all calcified areas for the selected Hounsfield unit (HU) threshold at each of the three cusps. Correct boundary delineation of the left (LCC), right (RCC) and non-coronary cups (NCC) was checked at the coaptation point, with manual adjustment if necessary. Then, ROI was moved 10 mm below the basal plane in the left ventricular outflow tract (LVOT). For the purpose our study, calcium volume was assessed in three different ROIs: (i) in the aortic valve; (ii) in the LVOT—these two ROIs were considered either as a whole or for each cusp separately; (iii) in the device landing zone (DLZ), defined as the sum of the first two (Figure 2). The threshold for calcium detection was set to two different cut-off values depending on the average HU of blood in the ascending aorta. For values between 130 and 300 HU, a threshold of 500 HU was chosen, in line with previous studies [3,9]. In contrast, for values between 300 and 600

HU (46 patients), an empiric threshold of 800 HU was chosen. Measurements of calcium volume were performed by a cardiac surgeon experienced in TAVI and trained in the use of 3mensio (F.P.). Interobserver variability was tested for the first 20 cases by a second cardiac surgeon (S.P.) and was 4.8%.

The degree of over- or undersizing was calculated as prosthesis valve area (provided by the manufacturer)/MDCT annular area. Prosthesis valve area was derived according to the geometrical rule: $A= \pi (d/2)^2$, where d is the labeled prosthesis size. Aortic annulus eccentricity index was calculated as 1–(minimal diameter/maximal diameter) based on MDCT annular measurements [11].

Paravalvular leak quantification

PVL was quantified by intraoperative transesophageal echocardiography (TEE) performed by a dedicated cardiac anesthesiologist under supervision of a cardiologist. In order to obtain maximum accuracy, a multiwindow and multiparametric (qualitative and quantitative) approach was applied to assess PVL severity [12]. The PVL was categorized as 0=none, 0.5=trace, 1=mild, 1.5=mild to moderate, 2=moderate, 2.5=moderate to severe, and 3=severe.

Procedure

TF-TAVI was preferred as first choice in all patients without severe peripheral artery disease and with suitable femoral axis. Alternatively, the transapical (TA-TAVI) access was used. All procedures were conducted in a hybrid operating room under fluoroscopic control (Artis Zeego System, Siemens AG, Erlangen, Germany), general anesthesia, periprocedural TEE, and a cardiac perfusionist with ready-to-use cardiopulmonary bypass on site. All implants were performed by a multidisciplinary team composed of at least a cardiologist (procedure leader in case of TF-TAVI) and a cardiac surgeon (procedure leader in case of TA-TAVI). Four different prostheses are routinely implanted in our center: SapienXT and Sapien3 (Edwards Lifesciences Inc., Irvine, CA), CoreValve/EvolutR (Medtronic, Minneapolis, MN), and Acurate TA/NeoTF (Symetis SA,

Ecublens, Switzerland). Selection of prosthesis type is agreed preoperatively with the cardiologist and cardiac surgeon on the basis of several parameters, including need for elective PCI after TAVI, annulus dimension, and distance from the aortic annulus to the coronary ostia. Definitive selection of prosthesis size is usually agreed intraoperatively by the Heart Team after evaluation of MDCT (annular perimeter-derived dimensions), TEE and angiographic parameters (e.g. contrast reflux during valvuloplasty, balloon sizing).

Statistical analysis

Data consistency was checked and data were screened for outliers and normality by using quantile plots. Continuous variables were also tested for normality by using Kolmogrov-Smirnov test. Categorical variables are expressed as frequencies (percentages) and continuous variables as mean (±standard deviation) or median (interquartile range). In order to assess the performance of different prosthetic valves in different calcification patterns, the study population was divided into four groups according to the implanted prosthesis. Differences between groups were determined by ANOVA testing with Bonferroni correction and Kruskal-Wallis test. Cross tabulation tables with Kruskal-Wallis test for singly ordered variables. Potential risk factors for the occurrence of ≥mild PVL, including CT, baseline and operative parameters of patients were entered in the univariate and multivariate logistic regression models. The dependent variable of the logistic model was the occurrence of PVL. A univariate analysis was first performed. Variables with $p<0.2$ were included in a multivariable logistic model regression analysis using stepwise selection algorithm (hierarchical forward with switching) to identify the predictors of PVL. Odds ratios with corresponding 95% confidence intervals were computed in each model. The discrimination achieved was assessed with the C statistic, which is equivalent to the area under the receiver operating characteristic curve. A generalized linear model for PVL location was built to analyze the relation between calcium distribution across the aortic cusps (based on the multinomial distribution for PVL location).

Clinical, procedural, echocardiographic, and preoperative MDCT variables were entered into univariate analysis. A receiver operating characteristic (ROC) curve was calculated from the DLZ, allowing assessment of cutoff values defining ≥mild PVL. All reported tests were two-sided, and p-values <0.05 were considered as statistically significant. All statistical analyses in this report were performed by use of NCSS (NCSS 10, NCSS, LLC. Kaysville, UT), STATISTICA 13 (Hill, T. & Lewicki, P. Statistics: Methods and Applications. StatSoft, Tulsa, OK) and PASW 23 (IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY).

RESULTS

Patient clinical and procedural characteristics are shown in Table 1, and MDCT measurements including calcium volume are listed in Table 2, according to the implanted prosthesis. The TF access route was most frequently used for TAVI (67% of cases). All groups had a mean logistic EuroSCORE>20%. Calcium volume in the DLZ varied from a minimum of 17.5 mm^3 to a maximum of 4523 mm^3. Significant differences among the prosthesis groups were observed in New York Heart Association class, size of prosthesis used, valve area, annulus perimeter, distance between the coronary ostia and annuli, and oversizing. Calcium volume in the DLZ and in the diverse subsectors did not significantly differ among groups.

Figure 3A shows the incidence of PVL by prosthesis group. Overall, 199 (36.9%) patients had an intraoperative leak (from trace to moderate). No patient presented severe or moderate to severe PVL. Patients implanted with the Sapien3 valve had the lowest incidence and degree of PVL. The distribution of calcium volume in the DLZ for patients with none, trace, mild and moderate PVL are showed in supplementary figure 1 according to valve prosthesis. Logistic regression model (C-statistic=0.809; 95% CI 0.771-0.843; Table 3), based on preoperative variables of Table 1 and 2, identified DLZ calcification and use of CoreValve/EvolutR prosthesis as associated with ≥mild PVL. On the other hand degree of oversizing and use of Sapien3 were associated with a lower incidence of ≥mild PVL. The discriminating power of DLZ calcification was evaluated by C-statistic and ROC curve analysis. The area under the ROC curve (Supplementary Figure 2) was 0.66 (95% confidence interval 0.617–0.699, p=0.0001) for ≥mild PVL. The ROC analysis identified the cutoff value of 1079 mm^3 (sensitivity 53%; specificity 75%) for DLZ calcification, above which a significantly increased risk of ≥mild PVL was observed. Differences in PVL incidence for DLZ higher or lower than 1079 mm^3 are shown in Figure 3B for each prosthesis group. A DLZ calcium volume >1079 mm^3 was associated with a significantly higher incidence of ≥mild PVL in all prosthesis groups ($p<0.05$).

Table 1. Baseline and procedural characteristics

	Total (=539)			Sapien XT (=192)			Sapien 3 (=206)			CoreValve/EvolutR (=44)			Symetis (=97)			
	N	Mean-%	SD	N	Mean-%	SD	N	Mean-%	SD	N	Mean-%	SD	N	Mean-%	SD	p
Age (years)		81.70	6.04		81.82	6.43		81.97	5.48		80.09	7.72		81.62	5.51	0.30
Female gender	272	50%		96	50%		103	50%		21	48%		52	54%		0.91
BMI (kg/m^2)		27.18	4.82		27.07	4.75		27.02	4.78		27.05	4.86		27.79	5.05	0.59
Creatinine (mg/dl)		1.50	0.95		1.47	0.89		1.47	0.79		1.28	0.54		1.71	1.38	0.06
Creatinine clearance (ml/min)		44.71	19.46		44.67	19.34		44.29	18.38		50.26	20.49		43.16	21.25	0.23
Extracardiac arteriopathy	145	27%		50	26%		55	27%		8	18%		32	33%		0.31
Previously cardiac surgery	111	21%		47	24%		33	16%		10	23%		21	22%		0.21
Previously CABG	94	17%		36	19%		28	14%		10	23%		20	21%		0.28
Chronic lung disease	101	19%		40	21%		38	18%		7	16%		16	16%		0.77
NYHA		3.02			3.11			2.96			2.98			3.01		0.02
Ejection fraction (%)		52.62	12.97		53.14	13.68		52.47	12.85		49.05	12.30		53.55	11.94	0.24
Recent myocardial infarction	16	3%		10	5%		4	2%		0	0%		2	2%		0.13
Severe PHT (>60 mmHg)	181	34%		68	35%		75	36%		12	27%		26	27%		0.31
Additive EuroSCORE		10.41	2.56		10.59	2.65		10.40	2.62		9.77	2.74		10.37	2.10	0.30
Logistic EuroSCORE		23%	0.15		24%	0.16		23%	0.16		21%	0.15		22%	0.13	0.41
EuroSCORE II		9%	0.07		9%	0.08		9%	0.08		8%	0.06		8%	0.06	0.36
TF access	360	67%		118	61%		155	75%		44	100%		43	44%		<0.001
Prosthesis size																<0.001
23 mm	175	32.5%		61	31.8%		84	40.8%		0			30	30.9%		
25 mm	33	6.1%											33	34%		
26 mm	192	35.6%		91	47.4%		91	44.2%		10	22.7%					
27 mm	34	6.3%											34	35%		
29 mm	83	15.4%		40	20.8%		31	15%		12	27.3%					
31 mm	22	4.1%								22	50%					
Valvuloplasty pre-implant	527	97.8%		189	98.4%		202	98.1%		40	90.9%		96	99%		0.01
Implant rapid pacing	413	76.6%		192	100%		206	100%		4	9.1%		11	11.3%		<0.001
Balloon dilation post-implant	184	34.1%		75	39.1%		53	25.7%		14	31.8%		42	43.3%		0.01

BMI=body mass index; CABG=coronary artery bypass graft; Chronic lung disease=use of bronchodilators; NYHA=New York Heart Association; PHT=pulmonary hypertension; TF=transfemoral.

Table 2. MDCT measurements.

	Total		Sapien XT		Sapien 3		CoreValve/EvolutR		Symetis		
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	p
Annulus area (cm^2)	4.60	3.9-5.28	4.51	3.82-5.12	4.64	4.08-5.42	5.39	4.15-6.03	4.49	3.78-4.98	<0.001
Annulus perimeter (mm)	77.50	71.8-83.5	76.55	70.95-82.8	78.60	72.75-84.3	83.70	74.37-88.77	76.50	70.45-81.35	<0.001
Distance annulus-RCA (mm)	15.40	13-18	17.00	14.32-19.2	14.55	12.6-17.2	15.00	12-17.7	14.40	11.8-17.5	<0.001
Distance annulus-LCA (mm)	13.40	11.6-15	13.60	12-15.5	14.00	11.05-15	12.90	11-15.37	13.00	11-15	0.04
Oversizing (%)	12%	3.2-23	15%	6.1-27.2	7%	-0.65-14.3	34%	21.9-45.5	11%	6.8-20.4	<0.001
Eccentricity index	0.19	0.14-0.23	0.19	0.13-0.23	0.19	0.15-0.23	0.19	0.13-0.22	0.19	0.15-0.24	0.51
DLZ calcium (mm^3)	757.00	442-1176	748.10	419-1171	756.10	477-1174	976.80	561-1446	649.00	391-1086	0.06
Total calcium-AV (mm^3)	683.00	412-1082	655.20	409-1023	698.2	433-1094	917.45	482-1323	633.60	356-1073	0.07
LCC calcium-AV (mm^3)	188.80	95-327	173.60	84-305	186.4	102-337	251.60	104-363	176.80	104-308	0.26
RCC calcium-AV (mm^3)	178.70	89-312	181.85	84-313	188.4	120-303	190.40	85-417	139.20	67-296	0.15
NCC calcium-AV (mm^3)	289.60	161-452	273.50	155-439	290.75	171-460	390.35	155-578	276.60	157-439	0.05
Total calcium-LVOT (mm^3)	18.00	1.37-85	12.70	0.025-77	17.70	2-68.85	48.30	6.1-190.8	22.70	1.6-91.25	0.26
LCC calcium-LVOT (mm^3)	2.05	0-34	0.40	0-23.82	1.60	0-31.1	5.2	0-88.57	5.1	0.1-48.45	0.34
RCC calcium-LVOT (mm^3)	0.00	0-1.2	0.00	0-0.1	0.10	0-2.75	0.05	0-6.87	0.00	0-0.55	0.49
NCC calcium-LVOT (mm^3)	2.00	0-24	0.90	0-20.75	2.20	0-24.55	15.95	0.22-62.07	1.80	0-18.6	0.05

AV=aortic valve; DLZ=device landing zone; LCA=left coronary artery; LCC=left coronary cusp; LVOT=left ventricular outflow tract; NCC=non-coronary cusp; RCA=right coronary artery; RCC=right coronary cusp.

Table 3. Independent factors for paravalvular leak at logistic regression analysis.

	Univariate model				Multivariate model (stepwise)			
	p-value	**OR**	**95% CI**		**OR**	**95% CI**		**p-value**
Ejection fraction (%)	0.14	0.99	0.97	1.00	-	-	-	-
Annulus diameter Max (mm)	0.002	1.14	1.05	1.24	-	-	-	-
Annulus diameter Min (mm)	0.02	1.12	1.02	1.23	-	-	-	-
Annulus area (cm^2)	0.001	1.51	1.18	1.93	-	-	-	-
Annulus perimeter (mm)	0.004	1.05	1.01	1.08	-	-	-	-
Oversizing (%)	0.039	0.98	0.97	1.00	0.97	0.95	0.99	0.002
LCC calcium-AV (mm^3)	0.00003	1.00	1.00	1.00	-	-	-	-
NCC calcium-AV (mm^3)	0.00001	1.00	1.00	1.00	-	-	-	-
LCC calcium-LVOT (mm^3)	0.054	1.00	1.00	1.00	-	-	-	-
NCC calcium-LVOT (mm^3)	0.0003	1.01	1.00	1.01	-	-	-	-
Female gender[a]	0.011	0.54	0.33	0.87	-	-	-	-
Dialysis (preoperative)	0.19	0.26	0.03	1.95	-	-	-	-
TA access[b]	0.015	1.79	1.12	2.88	-	-	-	-
Sapien XT[c]	-	1	-	-	1	-	-	-
Sapien 3	0.001	0.34	0.18	0.65	0.23	0.11	0.47	0.00005
CoreValve/EvolutR	0.019	2.69	1.17	6.17	4.09	1.62	10.3	0.003
Symetis	0.23	1.44	0.80	2.62	1.29	0.68	2.43	0.44
DLZ calcium (mm^3)[d]	< 0.00001	1.09	1.05	1.13	1.08	1.04	1.12	0.00006

[a)] reference is male. [b)] reference transfemoral. [c)] reference is Sapien XT. [d)] OR is rescaled to 100 mm^3. AV=aortic valve. DLZ=device landing zone; LCC=left coronary cusp; LVOT=left ventricular outflow tract; NCC=non-coronary cusp; TA=transapical.

Among the 199 patients with PVL, data on annular leak location were missing in 33. In the remaining 166 patients, the lowest incidence of PVL was detected in the RCC (5.4%), which also had less calcium volume in the LVOT. PVL was located more frequently in the LCC (59.6%), followed by the NCC (26.5%). In the remaining 8.4% of cases, it occurred at the commissure level (LCC/NCC 5.4%; NCC/RCC 0.6%; RCC/LCC 2.4%). On generalized linear model (multinomial model) no significant relations were found between PVL location and calcium distributions across the aortic cusps.

Other intraoperative complications and outcome

Prosthesis migration or malpositioning occurred in 6 cases (3 SapienXT [TA-access], 2 Symetis [TA-access], 1 CoreValve [TF-access]), seemingly unrelated to calcium volume (mean DLZ calcium 785 mm^3; 171–1338) but to a low level of oversizing (median 9.7%). Three patients underwent emergent surgical aortic valve replacement (AVR) following explantation of the TAVI device. Three patients underwent emergency valve-in-valve implantation with good results in 2 and conversion to surgical AVR in 1. All 6 patients survived the procedure.

Annular rupture occurred in 2 patients (DLZ calcium of 2828 and 613 mm^3, respectively, with intraprocedural death in one case, and discharge to home in the other). Coronary obstruction as isolated complication (unrelated to prosthesis migration) occurred in 2 cases (DLZ calcium of 1044 and 156 mm^3, with Sapien XT), requiring emergency PCI in one case and coronary artery bypass graft in the other case. Overall, immediate and 30-day mortality was 0.93% (n=5) and 5.38% (n=29), respectively.

DISCUSSION

Our study evaluated post-implant PVL occurrence and grade using a multimodality approach that included measurement of aortic valve calcification. On the basis of our results:

(i) DLZ calcification plays a key role in PVL occurrence after TAVI, and routine determination of calcium volume with a quantitative and reproducible measurement may provide additional useful information for planning interventions;

(ii) in presence of extensive DLZ calcifications and increased risk of PVL, the procedural strategy should be modified accordingly, trying to reduce the burden of other contributing but controllable factors (e.g.: oversizing and choice of prosthesis);

(iii) CoreValve prosthesis is more vulnerable and perform less efficiently in the presence of severe calcification.

The use of MDCT has become routine for transcatheter heart valve sizing and procedural planning [1]. Given the availability of improved imaging software and the widespread use of TAVI, we adopted a new approach to extract the most information from MDCT and achieve the best possible outcome.

The presence of even mild residual PVL in high-risk patients was found to be associated with a significantly worse survival compared to that of patients who did not exhibit such complication, up to 5-year follow-up [2]. In intermediate-risk patients, this tendency was also observed for ≥moderate PVL [13]. The incidence of ≥mild PVL varies across studies, ranging from 44% to 77%, with ≥moderate PVL ranging from 3.1% to 21.6% [14,15]. In our study, greater than mild PVL was observed in 15.76% of patients, with 1.4% of them experiencing moderate PVL and none severe PVL, which is significantly lower than the incidence reported in the literature. In our opinion, two factors may account for this discrepancy. First, the use of new prostheses: a direct comparison between SapienXT and Sapien3, where the latter is a further development of the former and was

used in the majority of our study patients, seems to confirm that the improvements introduced in the newer generation valves (e.g. annular skirt) have fulfilled the predetermined purpose of reducing PVL occurrence, as also demonstrated in the SOURCE-3 Registry [14]. Second, the higher use of balloon post-dilation (34.13%): this is the result of our team's choice of low tolerance of ≥moderate PVL, which proved to be safe, with only one case of annular rupture among patients who underwent balloon post-dilation.

Our study aimed at identifying a practical method for pre-procedural calcification assessment. The critical value above which all prosthesis models proved to be vulnerable seems >1000 mm^3, taking as reference PVL of mild or greater degree. Despite the sensitivity and specificity of this threshold are not optimal, this finding is consistent with previous research [3]. In every case, the low incidence of other intraoperative complications, apparently unrelated to the degree of calcification, confirms that TAVI remains a safe procedure.

To the best of our knowledge, this study is the largest to assess calcium volume in patients undergoing TAVI. Studies based on reproducible and quantitative methods (or dedicated software) for quantification of aortic valve calcification have so far been scant, with limited sample size or several potential biases.

In 123 patients implanted with an Edwards Sapien/SapienXT valve (23 and 26 mm), Jilaihawi and colleagues [4] tested the reliability of contrast-enhanced MDCT for calcium quantification at multiple thresholds for detection compared with the traditional Agatston scoring used for non-contrast MDCT scans. On multivariate analysis, prosthesis undersizing and presence of LVOT calcium were predictors of PVL.

In a retrospective study, Koh et al. [7] evaluated 56 patients who underwent TAVI with TA or transaortic delivery of an Edwards Sapien valve (no longer commercially available). Calcium volume was significantly higher in patients with PVL, but no correlation was found with PVL grade. However, these findings were not supported by multivariate analysis.

Seiffert and colleagues [9] evaluated the impact of calcium volume on PVL using a similar method to ours and reported comparable median calcium volumes (619 mm^3 in the aortic valve and 11 mm^3 in the LVOT). DLZ calcium, particularly if located in the LVOT, was predictive of PVL. In the Seiffert study, however, a higher incidence of PVL was observed. As this was a two-center study, one possible reason accounting for this finding is a center effect, which was also identified at linear regression analysis. Another aspect that deserves consideration is the low number of implants of 23 mm valves performed in their patients. In addition, in their study, only next-generation transcatheter aortic prostheses for TA access (e.g. JenaValve, Engager) were used, equipped with a peculiar implant system. Further, no balloon-expandable Sapien3 prosthesis was used in their study, which on the contrary accounts for 38% of the prostheses used in our study and implanted via TF access in 75% of cases. Similarly to the experience of Seiffert et al. [9], the CoreValve prosthesis was associated with a higher incidence of PVL. Although no small-sized CoreValve prostheses (23 mm) were used in our population, multivariate analysis has ruled out annular size as a risk factor for PVL. This means that the high incidence of PVL in this group cannot be explained solely by its use in large aortic annuli. Additionally, the CoreValve group was the one with the highest degree of oversizing, which was found to be a protective factor for subsequent PVL. An explanation may lie in the peculiar radial forces of the CoreValve Nitinol stent. The Figure 4 shows an emblematic example of how a severe calcification, despite 34% of oversizing, can result in a non-correctable PVL, even after post-dilatation, in a CoreValve prosthesis. It should be noted that only intraoperative TEE was evaluated as it is highly accurate in discriminating PVL from central regurgitation and our study was focused solely on the acute outcome. However, it has been demonstrated that incidence and severity of PVL after CoreValve implantation tend to diminish over time, showing a significant reduction after 1 year [16]. Incidence of PVL at discharge (assessed through TTE) in our series is showed in Supplementary Figure 3 and Supplementary Table 1. Bearing in mind the inferiority of the TTE with respect to the TEE, we did not observe any reduction in the incidence of ≥mild PVL.

Localization of PVL

Although our analysis confirmed that aortic calcification is crucial in determining post-implant PVL, less clear conclusions can be drawn regarding PVL location. A very low incidence of PVL was observed in the RCC. One possible explanation for this finding is that the RCC is positioned above the interventricular septum, which is probably a more stable cardiac structure allowing better sealing compared with the left and right fibrous trigone with which the LCC and NCC, respectively, are in direct continuity. However, the fact that PVL was found to be most frequently located in the LCC despite higher calcium volume along the NCC, remains unexplained. This may be due to (i) confounding factors (e.g. radial force distribution of the different stent designs) that, along with calcification, may contribute to determine the location of PVL, or (ii) a bias in reporting localization of PVL. Given that the valve systems used in our study do not provide an anatomical orientation of the prosthesis into the aortic annulus, the exact recognition of the native cusps is difficult after implantation. Fluoroscopy provides only a two-dimensional projection, and the use of intraoperative three-dimensional TEE is not routine practice in our institution. Notwithstanding this, future prospective studies using intraoperative three-dimensional imaging are required to address the issue of PVL localization.

Study limitations

Several limitations should be acknowledged in this study. First, the method used for assessing aortic calcification. Previous studies investigated the reliability of contrast-enhanced MDCT and different thresholds with non-enhanced MDCT [4]. Unfortunately, the results of contrast-enhanced MDCT remain strongly dependent on the selected HU threshold. Indeed, the choice of testing blood HU in the ascending aorta was intended to avoid relevant mistakes deriving from the indiscriminate use of the same threshold for all study patients. The selected threshold of 500 HU (and 800 HU in some cases) is arbitrary and needs to be validated, although adopted in previous similar studies [3,4,9].

Second, differences in prosthesis groups, where a greater expertise in balloon-expandable prostheses was likely. Third, extended calcifications may be hiding undetected bicuspid aortic valves that could be account as confounding factors [17]. Fourth, the retrospective nature of our study, which calls for the need of randomized prospective studies to validate our findings. Until then, suggesting a specific prosthesis for a particular calcification pattern would be imprudent. Moreover, the importance of other perioperative complications (e.g. vascular complications, stroke and need for permanent pacemaker implantation) should not be underestimated and is currently the subject of dedicated studies from our team.

Conclusions

In conclusion, aortic calcification volume in the DLZ is associated with residual PVL after TAVI. When taking calcification into account, the balloon-expandable prosthesis Sapien3 seems to be associated with a lower incidence of PVL.

REFERENCES

1. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease: The Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2017;38:2739-91.
2. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015;385:2477-84.
3. Khalique OK, Hahn RT, Gada H, Nazif TM, Vahl TP, George I, et al. Quantity and location of aortic valve complex calcification predicts severity and location of paravalvular regurgitation and frequency of post-dilation after balloon-expandable transcatheter aortic valve replacement. JACC Cardiovasc Interv 2014;7:885-94.
4. Jilaihawi H, Makkar RR, Kashif M, Okuyama K, Chakravarty T, Shiota T, et al. A revised methodology for aortic-valvar complex calcium quantification for transcatheter aortic valve implantation. Eur Heart J Cardiovasc Imaging 2014;15:1324-32.
5. Ewe SH, Ng ACT, Schuijf JD, van der Kley F, Colli A, Palmen M, et al. Location and severity of aortic valve calcium and implications for aortic regurgitation after transcatheter aortic valve implantation. Am J Cardiol 2011;108:1470-7.
6. Leber AW, Kasel M, Ischinger T, Ebersberger UH, Antoni D, Schmidt M, et al. Aortic valve calcium score as a predictor for outcome after TAVI using the CoreValve revalving system. Int J Cardiol 2013;166:652-7.
7. Koh EY, Lam KY, Bindraban NR, Cocchieri R, Planken RN, Koch KT, et al. Aortic valve calcification as a predictor of location and severity of paravalvular regurgitation after transcatheter aortic valve implantation. Interact Cardiovasc Thorac Surg 2015;20:345-50.

8. Unbehaun A, Pasic M, Dreysse S, Drews T, Kukucka M, Mladenow A, et al. Transapical aortic valve implantation: incidence and predictors of paravalvular leakage and transvalvular regurgitation in a series of 358 patients. J Am Coll Cardiol 2012;59:211-21.
9. Seiffert M, Fujita B, Avanesov M, Lunau C, Schön G, Conradi L, et al. Device landing zone calcification and its impact on residual regurgitation after transcatheter aortic valve implantation with different devices. Eur Heart J Cardiovasc Imaging 2016;17:576-84.
10. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. Eur Heart J 2012;33:2403-18.
11. Hansson NC, Nørgaard BL, Barbanti M, Nielsen NE, Yang TH, Tamburino C, et al. The impact of calcium volume and distribution in aortic root injury related to balloon-expandable transcatheter aortic valve replacement. J Cardiovasc Comput Tomogr 2015;9:382-92.
12. Pibarot P, Hahn RT, Weissman NJ, Monaghan MJ. Assessment of paravalvular regurgitation following TAVR: a proposal of unifying grading scheme. JACC Cardiovasc Imaging 2015;8:340-60.
13. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al; PARTNER 2 Investigators. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 2016;374:1609-20.
14. Wendler O, Schymik G, Treede H, Baumgartner H, Dumonteil N, Ihlberg L, 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;135:1123-32.
15. Gerckens U, Tamburino C, Bleiziffer S, Bosmans J, Wenaweser P, Brecker S, et al. Final 5-year clinical and echocardiographic results for treatment of severe aortic stenosis with a self-expanding bioprosthesis from the ADVANCE Study. Eur Heart J 2017;38:2729-38.

16. Oh JK, Little SH, Abdelmoneim SS, Reardon MJ, Kleiman NS, Lin G, et al. Regression of paravalvular aortic regurgitation and remodeling of self-expanding transcatheter aortic valve: an observation from the CoreValve U.S. Pivotal Trial. JACC Cardiovasc Imaging 2015;8:1364-75.
17. Popma JJ, Ramadan R. CT Imaging of Bicuspid Aortic Valve Disease for TAVR. JACC Cardiovasc Imaging. 2016;9:1159-1163.

FIGURES

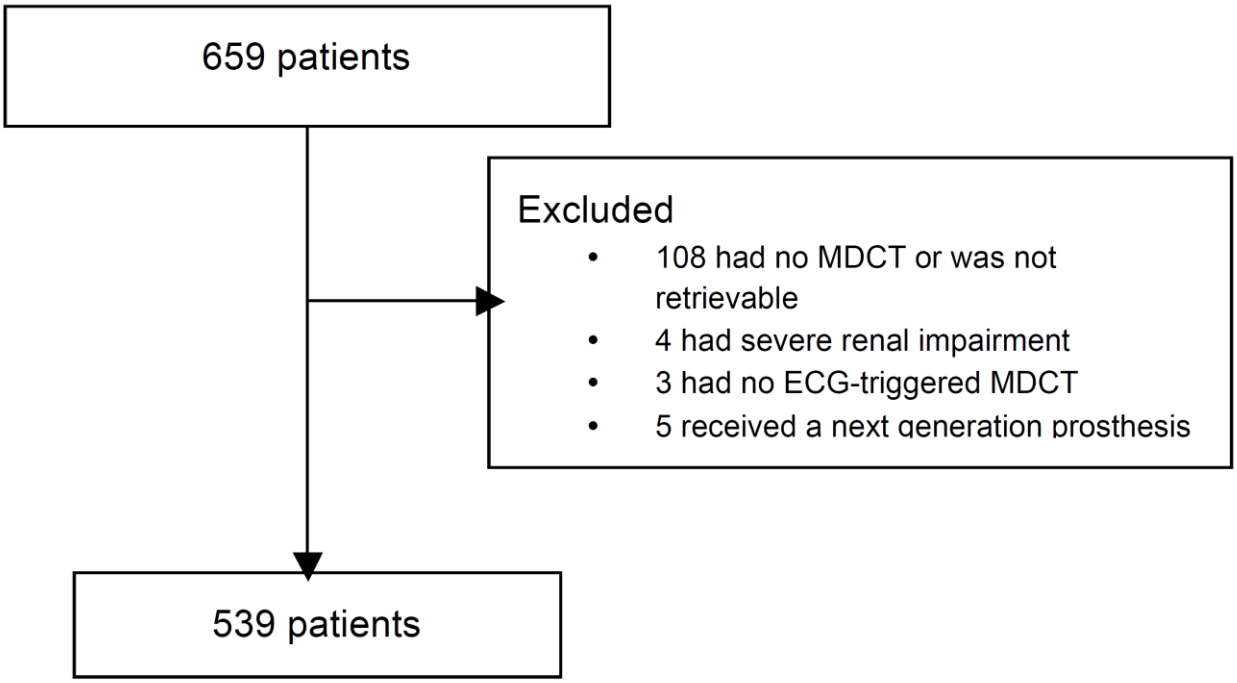


Figure 1. Flowchart showing the selection process of the study population.

Figure 2. Aortic calcium volume quantification on 3mensio Structural Heart. A: stretched vessel view of the aortic valve and ascending aorta with highlighting of the region of interest. The blue line identifies the basal plane (aortic annulus). B: transverse view of the native aortic valve with the three cusps (yellow=right coronary cusp; cyan=left coronary cusp; magenta=non-coronary cusp). AV=aortic valve; DLZ=device landing zone; LVOT=left ventricular outflow tract.

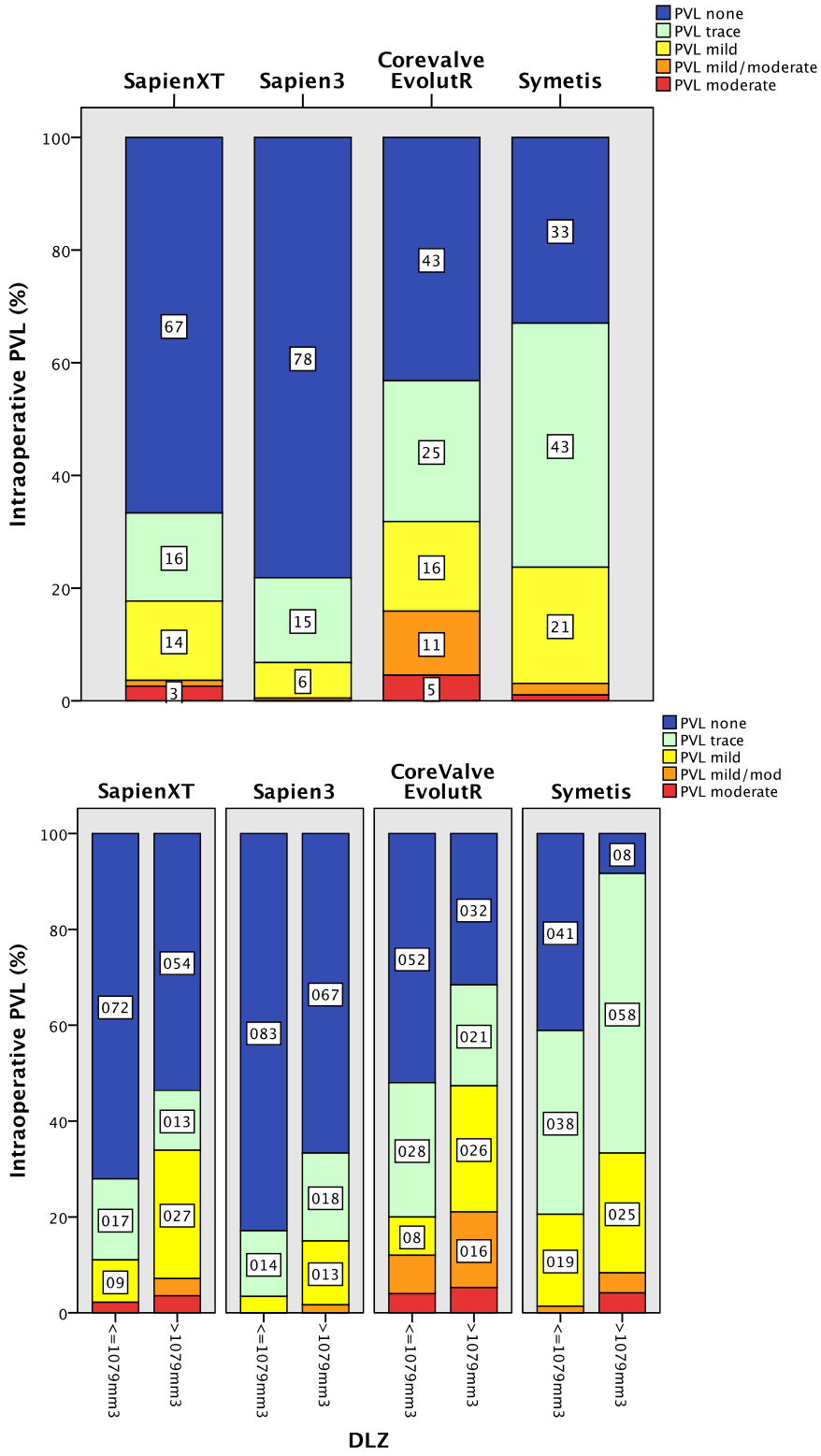


Figure 3. A: Incidence of residual paravalvular leak (PVL) in the four prosthesis groups (blue=none; green=trace; yellow=mild; orange=mild/moderate; red=moderate) assessed by intraoperative transesophageal echocardiography. B: Differences in residual paravalvular leak

(PVL) in the four prosthesis groups according to DLZ calcium volume higher or lower than the cut-off value of 1079 mm^3.

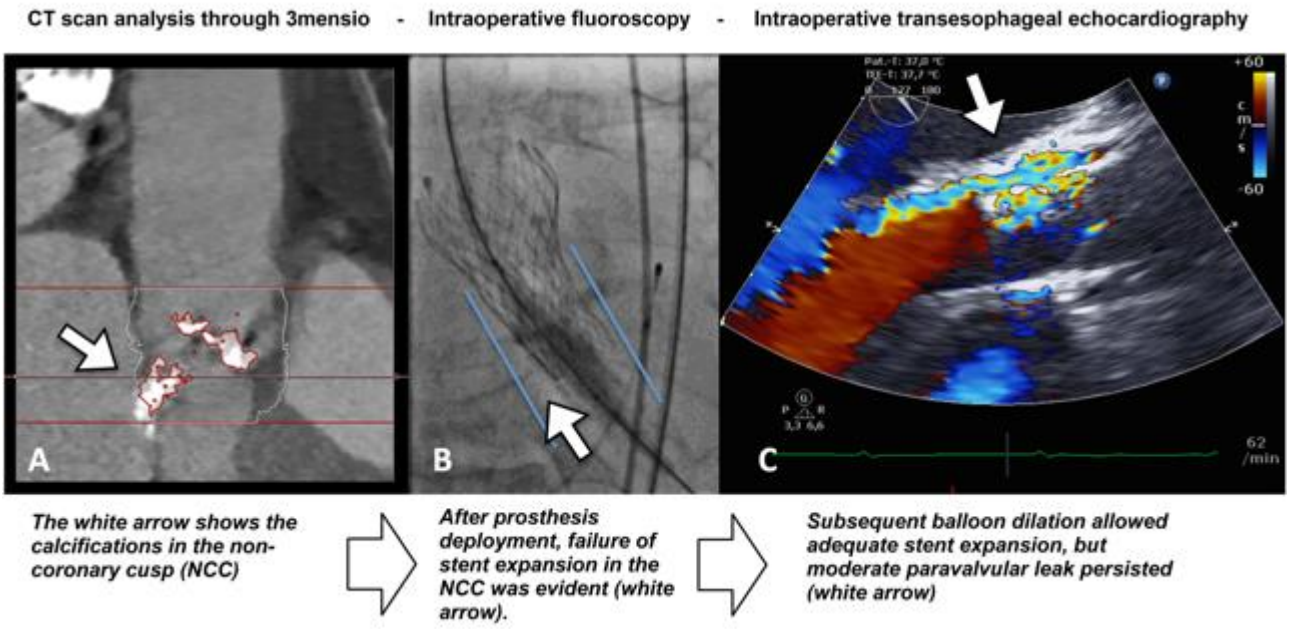
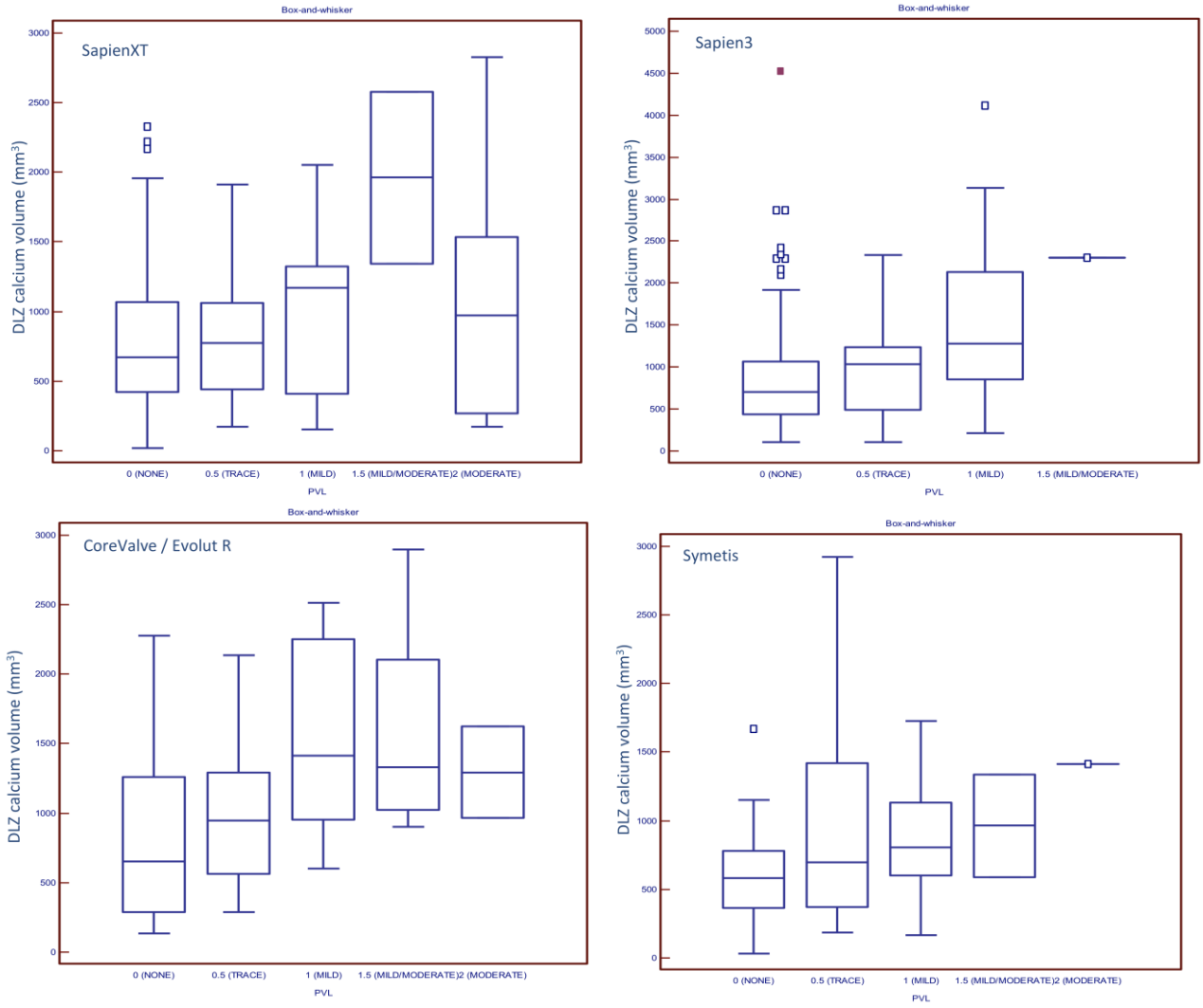
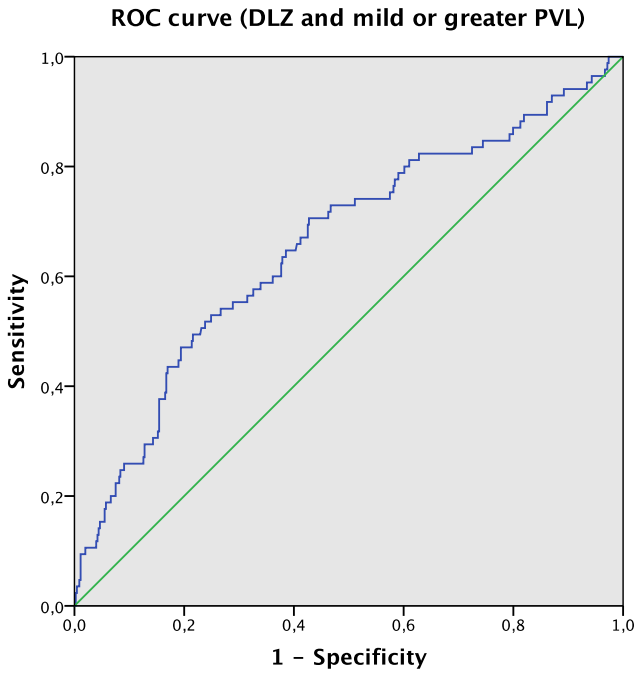


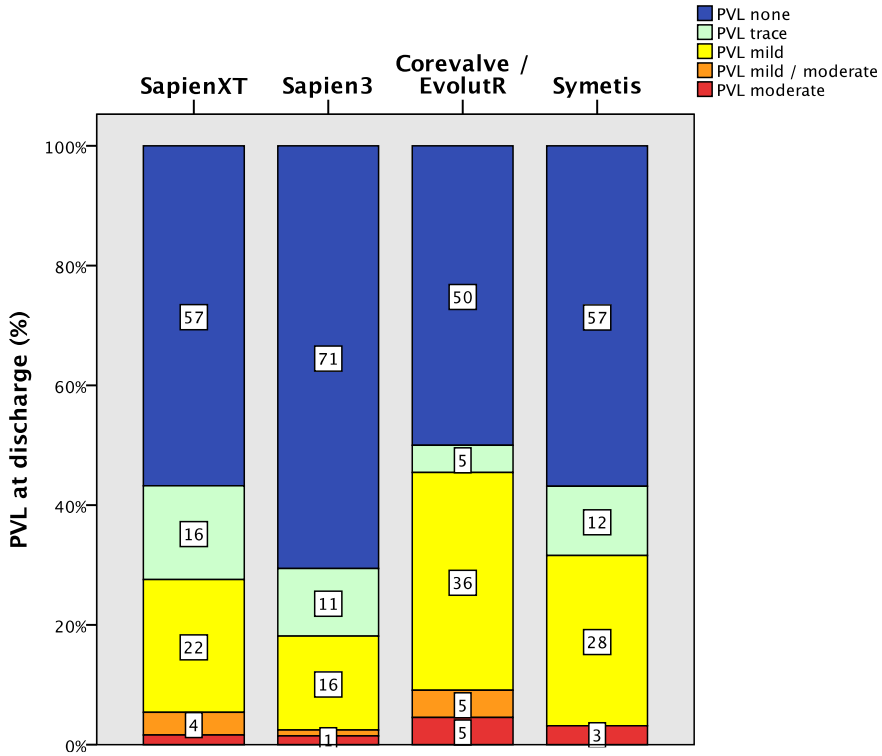
Figure 4. An emblematic example showing onset of paravalvular leak (PVL) during implantation of a 29 mm CoreValve EvolutR prosthesis in an 82-year-old woman with extremely calcified aortic valve. A) Calcification of aortic valve on 3mesio multidetector computed tomography scan (Device Landing Zone calcium volume: 1622 mm^3; Non coronary cusp [NCC]-LVOT calcium volume: 223 mm^3; oversizing: 34%). The white arrow shows NCC-LVOT. B) Intraoperative fluoroscopy: after prosthesis deployment, failure of stent expansion in the NCC was evident (white arrow). Subsequent balloon dilation allowed adequate stent expansion, but moderate paravalvular leak persisted (C, white arrow) at intraoperative transesophageal echocardiography.



Supplementary Figure 1. Side-by-side boxplot showing the distribution of calcium volume in the DLZ for patients with none, mild, mild/moderate and moderate PVL for each of the implanted prosthesis.



Supplementary Figure 2. Receiver operating characteristic (ROC) curve analysis for the accuracy of device landing zone calcium in predicting ≥ mild paravalvular leak.



Supplementary Figure 3. Incidence of residual paravalvular leak (PVL) in the four prosthesis groups (blue=none; green=trace; yellow=mild; orange=mild/moderate; red=moderate) assessed by transthoracic echocardiography at discharge from hospital.

ACKNOWLEDGMENTS

La ricerca illustrata è stata condotta sotto la supervisione dell'Ao. Prof. Steffen Pfeiffer presso la clinica universitaria di cardiochirurgia del Klinikum Nürnberg (Norimberga, Germania) ed accettata per la pubblicazione su The Journal of Thoracic and Cardiovascular Surgery (ISSN 0022-5223) sotto il titolo:

- Pollari F, Dell'Aquila AM, Söhn C, Marianowicz J, Wiehofsky P, Schwab J, Pauschinger M, Hitzl W, Fischlein T, Pfeiffer S. Risk factors for paravalvular leak after transcatheter aortic valve replacement. J Thorac Cardiovasc Surg. 2018 [Accepted for publication on 01st August 2018].

This research has been conducted under the supervision of Ao. Prof. Steffen Pfeiffer in the department of cardiac surgery of Klinikum Nürnberg (Nuremberg. Germany). Partial results of the presented work have been accepted for publication in The Journal of Thoracic and Cardiovascular Surgery (ISSN 0022-5223):

- Pollari F, Dell'Aquila AM, Söhn C, Marianowicz J, Wiehofsky P, Schwab J, Pauschinger M, Hitzl W, Fischlein T, Pfeiffer S. Risk factors for paravalvular leak after transcatheter aortic valve replacement. J Thorac Cardiovasc Surg. 2018 [Accepted for publication on 01st August 2018].