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ORIGINAL RESEARCH

STRUCTURAL

Incidence, Predictors, and Outcomes of Paravalvular Regurgitation After TAVR in Sievers Type 1 Bicuspid Aortic Valves

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ABSTRACT

BACKGROUND Transcatheter aortic valve replacement (TAVR) in patients with bicuspid aortic valve (BAV) stenosis is technically challenging and is burdened by an increased risk of paravalvular regurgitation (PVR).

OBJECTIVES The aim of this study was to identify the incidence, predictors, and clinical outcomes of PVR after TAVR in Sievers type 1 BAV stenosis.

METHODS Consecutive patients with Sievers type 1 BAV stenosis undergoing TAVR with current-generation transcatheter heart valves (THVs) in 24 international centers were enrolled. PVR was graded as none/trace, mild, moderate, and severe according to echocardiographic criteria. The endpoint of major adverse events (MAEs), defined as a composite of all-cause death, stroke, or hospitalization for heart failure, was assessed at the last available follow-up.

RESULTS A total of 946 patients were enrolled. PVR occurred in 423 patients (44.7%)—mild, moderate, and severe in 387 (40.9%), 32 (3.4%), and 4 (0.4%) patients, respectively. Independent predictors of moderate or severe PVR were a larger virtual raphe ring perimeter (adjusted OR: 1.07; 95% CI: 1.02-1.13), severe annular or left ventricular outflow tract calcification (adjusted OR: 5.21; 95% CI: 1.45-18.77), a self-expanding valve (adjusted OR: 9.01; 95% CI: 2.09-38.86), and intentional supra-annular THV positioning (adjusted OR: 3.31; 95% CI: 1.04-10.54). At a median follow-up of 1.3 years (Q1-Q3: 0.5-2.4 years), moderate or severe PVR was associated with an increased risk of MAEs (adjusted HR: 2.52; 95% CI: 1.24-5.09).

CONCLUSIONS After TAVR with current-generation THVs in Sievers type 1 BAV stenosis, moderate or severe PVR occurred in about 4% of cases and was associated with an increased risk of MAEs during follow-up.

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Transcatheter aortic valve replacement (TAVR) has emerged as a valuable treatment strategy for patients with severe aortic stenosis. However, pivotal randomized clinical trials (RCTs) comparing TAVR with surgical aortic valve replacement excluded patients with bicuspid aortic valve (BAV) stenosis because of the perceived anatomic challenges for TAVR such as a large elliptical annulus; fibrotic or calcified raphe; and severe calcification involving the leaflets, the annulus, and/or the left ventricular outflow tract (LVOT).[1] Iterative advances in TAVR techniques with the advent of new-generation transcatheter heart valves (THVs) have tackled previous anatomical concerns, and emerging data suggest a reasonable safety of TAVR in BAV stenosis.[2] Nevertheless, BAVs still encompass a high rate of TAVR-related issues, such as postprocedural paravalvular regurgitation (PVR).[3] Notably, previous evidence demonstrated that PVR after TAVR is associated with an increased risk of morbidity and mortality.[4] However, there is still limited evidence on the relevance of PVR after TAVR in BAV stenosis. In particular, raphe-type BAV represents a distinctive phenotype associated with worse outcomes and more frequent procedural TAVR complications compared with no-raphe BAV.[5] With this background, this study aimed to evaluate the incidence, predictors, and clinical outcomes of PVR after TAVR in Sievers type 1 BAV stenosis.

METHODS

STUDY POPULATION. The AD HOC (Characteristics, Sizing, and Outcomes of Stenotic Raphe-Type Bicuspid Aortic Valves Treated with Trans-catheter Device Implantation) is an observational, retrospective, international, multicenter registry designed to describe the phenotypical characteristics of severe, Sievers type 1 BAV stenosis undergoing TAVR and to assess the safety and efficacy of contemporary-generation THVs. Between January 2016 and October 2023, all consecutive patients with Sievers type 1 BAV stenosis treated with transfemoral TAVR in 24 international centers were enrolled (Supplemental Table 1). The inclusion criteria were age ≥18 years, severe aortic valve stenosis, type 1 BAV pattern based on Sievers' classification,[6] and the availability of preprocedural multislice computed tomography (MSCT). The exclusion criteria were Sievers type 0 or type 2 BAVs, valve-in-valve procedures, pure aortic regurgitation, and the non-transfemoral approach. All patients provided written

ABBREVIATIONS AND ACRONYMS

BAV = bicuspid aortic valve
BE = balloon expandable
LVOT = left ventricular outflow tract
MAE = major adverse event(s)
MSCT = multislice computed tomography
PVR = paravalvular regurgitation
RCT = randomized clinical trial
SE = self-expanding
STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality
TAVR = transcatheter aortic valve replacement
THV = transcatheter heart valve
VRR = virtual raphe ring

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informed consent for the procedure, and subsequent data collection was based on local practice and/or local Institutional Review Board approval. Local multidisciplinary heart teams evaluated all patients and confirmed the indications for TAVR. The choice of the THV (type and size) and all intraprocedural steps were left to the operators' discretion.

DATA COLLECTION AND CLINICAL ENDPOINTS. Baseline clinical, electrocardiographic, echocardiographic, MSCT, and procedural data were retrospectively collected in a dedicated data set. Echocardiographic and MSCT data were analyzed and reported by board-certified expert operators in each center according to current recommendations.[7,8] The registry did not include a core laboratory to independently analyze echocardiographic and MSCT scans. PVR was evaluated at predischarge after the index procedure and classified as none/trace, mild, moderate, and severe according to qualitative, semiquantitative, and quantitative parameters as recommended by the American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines.[9,10] The maximum length of the raphe was captured and analyzed at MSCT, together with the extent of its calcification, according to a previously proposed methodology.[11] The degree of calcification was also assessed at the level of aortic leaflets, annular/LVOT, and nonfused coronary cusps.[12] Lastly, the virtual raphe ring (VRR) measurements, along with the anteraphe space length, were assessed at the MSCT plane where the raphe shows its maximum length as reccomended.[13] The measurements on the aortic annulus were performed in the plane aligned with the most basal attachment points of the 3 aortic valve cusps as recommended.[8] A tapered configuration (in which supra-annular dimensions are smaller compared to annular ones) was retrospectively defined if at least 1 of the supra-annular sizing methods (bicuspid aortic valve anatomy and relationship with devices [BAVARD],[14] level of implantation at the raphe [LIRA],[15] calcium algorithm sizing for bicuspid evaluation with raphe [CASPER],[16] and CIRCLE[17] methods [Supplemental Table 2], calculated in all the enrolled patients with the latter applied only for balloon-expandable [BE] THVs) indicated narrower dimensions at the supra-annular level than the annulus level, which may require THV downsizing. THV positioning was classified as annular or supra-annular according to the identified intentional landing zone, with supra-annular positioning defined as a planned anchoring at the raphe plane and above the annulus plane (ground zero or above-annulus implantation) as previously described.[13] In-hospital outcome and post-TAVR echocardiographic evaluations were recorded at patient discharge. The last available clinical follow-up was collected by medical contact (outpatient visit or phone call). The endpoint of major adverse events (MAEs) was assessed at the last available follow-up and was defined as a composite of all-cause death, stroke, or hospitalization for heart failure.

STATISTICAL ANALYSIS. Categoric variables are reported as counts and percentages. Continuous variables are reported as mean ± SD or median (IQR) according to their distribution assessed by the Shapiro-Wilk test. Comparisons among groups (no/trace PVR, mild PVR, and moderate or severe PVR) for categoric variables were performed with the chi-square or Fisher exact test, whereas those for continuous variables were performed with 1-way analysis of variance or the Kruskal-Wallis test as appropriate. Cumulative rates of MAEs were calculated using Kaplan-Meier survival analysis, and survival curves were compared across prespecified groups (none/trace PVR, mild PVR, and moderate or severe PVR) with the log-rank test. Univariable and multivariable Cox regression models were performed to evaluate clinical, electrocardiographic, echocardiographic, MSCT, and procedural predictors of MAEs, including the following variables: age, sex, diabetes mellitus, coronary artery disease, peripheral arterial disease, atrial fibrillation, Society of Thoracic Surgeons-Predicted Risk of Mortality (STS-PROM) score, estimated glomerular filtration rate, right bundle branch block, left bundle branch block, left ventricular ejection fraction, severe aortic regurgitation, severe mitral regurgitation, severe annular/LVOT calcification, severe qualitative aortic valve calcification, severe raphe calcification, restricted nonfused cusp, tapered configuration, self-expanding (SE) THV, and PVR. The assumption of the proportional hazards model was evaluated with a 2-sided test of the scaled Schoenfeld residuals over time. Univariable and multivariable logistic regression models were performed to evaluate MSCT and procedural predictors of moderate or severe PVR. The main logistic regression model (model 1) included the following variables: VRR perimeter, severe annular/LVOT calcification, severe qualitative aortic valve calcification, severe raphe calcification, restricted nonfused cusp, tapered configuration, index raphe/anteraphe, SE THV, predilatation, postdilatation, and intentional supra-annular THV positioning. Moreover, we performed a second logistic regression model (model 2), including a single variable for THV models (Supplemental Table 3) and excluding SE THV as a covariate. As a sensitivity analysis, we

TABLE 1 Baseline Clinical, Electrocardiographic, and Echocardiographic Characteristics

	Total (N = 946)	No/Trace PVR (n = 523)	Mild PVR (n = 387)	Moderate or Severe PVR (n = 36)	*P* Value
Clinical characteristics					
Age, y	78 (73-83)	77 (72-82)	79 (75-84)	82 (75-84)	<0.001
BMI, kg/m^2	25.4 (23.0-28.4)	25.5 (23.2-28.9)	25.2 (22.5-28.2)	24.6 (22.9-27.0)	0.157
Male	592 (62.6)	330 (63.1)	237 (61.2)	25 (69.4)	0.583
Hypertension	684 (72.3)	372 (71.1)	284 (73.4)	28 (77.8)	0.570
Diabetes mellitus	168 (17.8)	102 (19.5)	61 (15.8)	5 (13.9)	0.284
Prior pacemaker	68 (7.2)	41 (7.8)	25 (6.5)	2 (5.6)	0.676
Coronary artery disease	324 (34.2)	182 (34.8)	128 (33.1)	14 (38.9)	0.722
Peripheral arterial disease	77 (8.1)	51 (9.8)	21 (5.4)	5 (13.9)	0.027
Carotid artery disease	46 (4.9)	25 (4.8)	18 (4.7)	3 (8.6)	0.586
History of atrial fibrillation	263 (27.8)	131 (25.0)	126 (32.6)	6 (16.7)	0.014
Prior cerebrovascular accident	83 (8.8)	44 (8.4)	33 (8.6)	6 (17.1)	0.207
COPD	155 (16.4)	92 (17.6)	58 (15.0)	5 (13.9)	0.530
eGFR, mL/min/1.73 m^2	67 (52-84)	70 (55-87)	64 (49-78)	57 (43-74)	<0.001
NYHA functional class					0.746
I	42 (4.5)	24 (4.6)	16 (4.1)	3 (8.3)	
II	371 (39.2)	203 (38.8)	152 (39.3)	16 (44.4)	
III	457 (48.3)	248 (47.4)	194 (50.1)	15 (41.7)	
IV	74 (7.8)	47 (9.0)	25 (6.5)	2 (5.6)	
EuroSCORE II	2.48 (1.64-3.85)	2.30 (1.51-3.48)	2.67 (1.80-4.11)	2.48 (1.65-4.84)	0.022
STS-PROM score	2.50 (1.55-3.81)	2.35 (1.45-3.50)	2.70 (1.70-4.00)	3.09 (1.79-4.85)	0.006
Electrocardiographic characteristics					
First-degree AVB	149 (16.0)	84 (16.4)	57 (14.9)	8 (22.9)	0.442
RBBB	67 (7.2)	34 (6.6)	30 (7.8)	3 (8.3)	0.746
LBBB	88 (9.4)	41 (7.9)	37 (9.6)	10 (27.8)	<0.001
Echocardiographic characteristics					
LVEF, %	60 (48-64)	60 (50-65)	58 (45-62)	60 (52-65)	0.021
Mean transvalvular gradient, mm Hg	48 (40-59)	47 (40-57)	49 (40-60)	52 (41-66)	0.054
Aortic valve area, cm^2	0.70 (0.56-0.80)	0.70 (0.60-0.80)	0.70 (0.50-0.80)	0.69 (0.60-0.90)	0.074
Severe aortic regurgitation	15 (1.6)	9 (1.7)	4 (1.0)	2 (5.6)	0.108
Severe mitral regurgitation	23 (2.4)	11 (2.1)	11 (2.8)	1 (2.8)	0.767

Values are median (Q1-Q3) or n (%).

AVB = atrioventricular block; BMI = body mass index; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; PVR = paravalvular regurgitation; RBBB = right bundle branch block; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

performed a logistic regression model to evaluate predictors of moderate or severe PVR according to a purposeful selection of variables for which all reported MSCT and procedural variables were tested using a univariable model, and only variables with *P* values <0.10 were included in the multivariable model. Moreover, we performed sensitivity analyses of the main models excluding patients receiving THVs not available on the market anymore (Acurate Neo [Boston Scientific] and Portico [Abbott]). To account for potential intercenter heterogeneity, we used random intercepts for each center in a mixed effects model for all logistic regression models. Statistical significance was defined as a *P* value < 0.05. Statistical analyses were performed using SPSS version 29 (IBM Corp) and Stata version 18 (StataCorp).

RESULTS

During the study period, 8 patients without predischarge echocardiographic assessment because of 7 in-hospital deaths (3 annular ruptures [2 with SAPIEN 3/3 Ultra (Edwards Lifesciences) THVs and 1 during postdilatation of a Portico THV], 3 major vascular complications, and 1 cardiac tamponade) and 1 case of missing data were also excluded. Finally, a total of 946 patients who underwent TAVR for Sievers type 1 BAV stenosis were included in the analysis.

INCIDENCE OF POSTPROCEDURAL PVR. At predischarge echocardiographic assessment, a total of 423 patients (44.7%) had post-TAVR PVR, 387 (40.9% of the total population, 91.5% of patients with PVR) of whom had mild PVR, 32 (3.4% of the total population, 7.6% of patients with PVR) had moderate PVR, and 4 (0.4% of the total population, 0.9% of patients with PVR) had severe PVR.

BASELINE CHARACTERISTICS OF THE POPULATION. The median age of the patients was 78 years (Q1-Q3: 73-83 years), 592 (62.6%) were men, and the median STS-PROM score was 2.50% (Q1-Q3: 1.55%-3.81%).

TABLE 2 Baseline Multislice Computed Tomography Features

	Total (N = 946)	No/Trace PVR (n = 523)	Mild PVR (n = 387)	Moderate or Severe PVR (n = 36)	*P* Value
Raphe localization					0.167
R-L	806 (85.2)	435 (83.2)	342 (88.4)	29 (80.6)	
R-NC	127 (13.4)	79 (15.1)	41 (10.6)	7 (19.4)	
L-NC	13 (1.4)	9 (1.7)	4 (1.0)	0 (0.0)	
Annulus perimeter, mm	81.9 ± 8.2	81.7 ± 7.9	82.0 ± 8.5	83.4 ± 9.4	
Annulus area, mm^2	513 (447-578)	512 (451-571)	512 (438-582)	550 (450-620)	0.259
Mean LVOT diameter, mm	25.3 ± 3.2	25.3 ± 3.2	25.4 ± 3.2	25.7 ± 3.4	0.806
Mean SOV diameter, mm	34.4 ± 4.0	34.3 ± 4.0	34.6 ± 4.1	34.8 ± 3.4	0.453
Mean STJ diameter, mm	30.7 (27.5-33.4)	30.7 (27.5-33.2)	30.2 (27.2-33.3)	32.2 (29.0-34.2)	0.127
Major ascending aorta diameter, mm	36.7 (33.5-40.2)	36.7 (33.9-40.1)	36.8 (33.3-41.0)	37.0 (34.0-40.0)	0.970
Aortic angle, °	53 (46-61)	53 (46-61)	53 (47-60)	52 (48-59)	0.797
Leaflet calcification					0.032
None	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	
Mild	180 (19.0)	120 (22.9)	56 (14.5)	4 (11.1)	
Moderate	401 (42.4)	213 (40.7)	169 (43.7)	19 (52.8)	
Severe	364 (38.5)	189 (36.1)	162 (41.9)	13 (36.1)	
Raphe calcification					0.265
None	161 (17.0)	95 (18.2)	62 (16.0)	4 (11.1)	
Mild	228 (24.1)	136 (26.0)	80 (20.7)	12 (33.3)	
Moderate	310 (32.8)	162 (31.0)	136 (35.1)	12 (33.3)	
Severe	247 (26.1)	130 (24.9)	109 (28.2)	8 (22.2)	
Annular/LVOT calcification					<0.001
None	615 (65.0)	374 (71.5)	229 (59.2)	12 (33.3)	
Mild	199 (21.0)	93 (17.8)	92 (23.8)	14 (38.9)	
Moderate	86 (9.1)	36 (6.9)	45 (11.6)	5 (13.9)	
Severe	46 (4.9)	20 (3.8)	21 (5.4)	5 (13.9)	
Nonfused cusp calcification					0.088
Restrictive	190 (20.1)	92 (17.6)	87 (22.5)	11 (30.6)	
Unrestrictive	463 (48.9)	273 (52.2)	177 (45.7)	13 (36.1)	
Intermediate	293 (31.0)	158 (30.2)	123 (31.8)	12 (33.3)	
Maximum raphe length, mm	10.1 (7.6-12.6)	9.9 (7.4-12.4)	10.6 (8.0-13.0)	10.9 (7.9-12.9)	0.081
Anteraphe space, mm	23.3 ± 4.3	23.3 ± 4.2	23.3 ± 4.4	23.7 ± 3.6	0.832
Index raphe/anteraphe	0.44 (0.31-0.59)	0.43 (0.30-0.57)	0.46 (0.32-0.61)	0.44 (0.34-0.56)	0.281
VRR height, mm	7.9 (6.4-9.4)	7.7 (6.2-9.4)	8.0 (6.6-9.4)	7.2 (6.0-8.9)	0.057
VRR perimeter, mm	73.3 (67.0-79.1)	73.3 (67.0-79.0)	73.0 (67.0-79.1)	75.8 (71.2-81.1)	0.084
ICD at 4 mm, mm	27.1 ± 3.1	27.0 ± 3.0	27.1 ± 3.1	27.8 ± 3.3	0.312
Tapered configuration	715 (75.6)	400 (76.5)	291 (75.2)	24 (66.7)	0.404

Values are n (%), median (Q1-Q3), or mean ± SD.

ICD = intercommissural distance; L-NC = left-noncoronary; LVOT = left ventricular outflow tract; PVR = paravalvular regurgitation; R-L = right-left; R-NC = right-noncoronary; SOV = sinus of Valsalva; STJ = sinotubular junction; VRR = virtual raphe ring.

Baseline clinical, electrocardiographic, and echocardiographic characteristics of the total population, further stratified according to the degree of PVR, are summarized in Table 1. Briefly, compared to patients with no/trace PVR, those experiencing PVR were older, had a higher STS-PROM score, and had a lower estimated glomerular filtration rate.

MSCT features are depicted in Table 2. Anatomical dimensions and the prevalence of tapered configuration were similar between patients with no/trace PVR, mild PVR, and moderate or severe PVR. The most frequent raphe localization occurred between the right and the left coronary cusp (806 [85.2%] patients). Severe calcification involving the leaflets, raphe, and annulus/LVOT was frequent, being observed in 364 (38.5%), 247 (26.1%), and 46 (4.9%) patients, respectively. A restrictive pattern of the nonfused cusp was detected in 190 (20.1%) patients. Patients with postprocedural moderate or severe PVR had a higher prevalence of severe annulus/LVOT calcification compared with patients experiencing postprocedural mild PVR or no/trace PVR (moderate or severe PVR vs mild PVR vs no/trace PVR: 13.9% vs 5.4% vs 3.8%; $P < 0.001$).

TABLE 3 Procedural Characteristics and In-Hospital Outcomes Data

	Total (N = 946)	No/Trace PVR (n = 523)	Mild PVR (n = 387)	Moderate or Severe PVR (n = 36)	*P* Value
Procedural characteristics					
General anesthesia	80 (8.5)	64 (12.2)	13 (3.4)	3 (8.3)	<0.001
Cerebral embolic protection	174 (18.4)	111 (21.3)	61 (15.8)	2 (5.6)	0.014
Type of THV					<0.001
BE THV	417 (44.1)	288 (55.1)	126 (32.6)	3 (8.3)	
SE THV	529 (55.9)	235 (44.9)	261 (67.4)	33 (91.7)	
Type of external skirt					<0.001
None[a]	209 (22.1)	93 (17.8)	101 (26.1)	15 (41.7)	
Short[b]	339 (35.8)	204 (39.0)	131 (33.9)	4 (11.1)	
Tall[c]	398 (42.1)	226 (43.2)	155 (40.1)	17 (47.2)	
Implanted THV size					0.491
Annular	757 (80.0)	420 (80.3)	311 (80.4)	26 (72.2)	
Supra-annular	189 (20.0)	103 (19.7)	76 (19.6)	10 (27.8)	
Intentional THV positioning (landing zone)					<0.001
Annular	881 (93.1)	487 (93.1)	366 (94.6)	28 (77.8)	
Supra-annular	65 (6.9)	36 (6.9)	21 (5.4)	8 (22.2)	
Valve predilatation	662 (70.0)	333 (63.7)	299 (77.3)	30 (83.3)	<0.001
Maximum predilatation balloon diameter, mm	22 (20-24)	22 (20-23)	23 (20-24)	23 (20-24)	0.543
Balloon sizing technique	93 (10.0)	55 (10.6)	32 (8.4)	6 (17.6)	0.174
THV size changed after balloon sizing	12 (7.0)	7 (8.1)	3 (4.3)	2 (11.8)	0.469
Valve postdilatation	335 (35.4)	135 (25.8)	179 (46.3)	21 (58.3)	<0.001
Maximum postdilatation balloon diameter, mm	24 (22-26)	24 (22-26)	24 (22-25)	25 (23-27)	0.407
In-hospital outcomes					
VARC-3 technical success[d]	905 (95.7)	502 (96.0)	369 (95.3)	34 (94.4)	0.839
Correct implant position	931 (98.4)	516 (98.7)	380 (98.2)	35 (97.2)	0.720
Conversion to surgery	5 (0.5)	3 (0.6)	1 (0.3)	1 (2.8)	0.134
Multiple valves	17 (1.8)	5 (1.0)	10 (2.6)	2 (5.6)	0.042
Major vascular complication	27 (2.9)	18 (3.4)	8 (2.1)	1 (2.8)	0.469
New pacemaker implantation	129 (14.5)	57 (11.7)	62 (16.9)	10 (28.6)	0.006
Postprocedural mean transvalvular gradient, mm Hg	9 (6-13)	9 (6-13)	9 (6-13)	9 (6-14)	0.606
Postprocedural effective orifice area, mm^2	1.97 (1.60-2.51)	1.90 (1.53-2.48)	2.0 (1.60-2.62)	2.20 (1.60-2.96)	0.058

Values are n (%) and median (Q1-Q3). [a]Evolut R, Portico, and Venus A Plus (Venus Medtech Inc, Hangzhou, China). [b]Acurate Neo, SAPIEN 3, Navitor, MyVal (Meril Life Sciences Pvt Ltd, Gujarat, India), Taurus Valve (Peijia Medical Technology Co Ltd, Suzhou, China), and Prizvalve (Shanghai NewMed Medical Co Ltd, Shangai, China). [c]Acurate Neo2, SAPIEN 3 Ultra, and Evolut Pro/Pro+. [d]Defined as freedom from mortality; successful access, delivery of the device, and retrieval of the delivery system; correct positioning of a single prosthetic heart valve into the proper anatomical location; freedom from surgery or intervention related to the device or to a major vascular or access related or cardiac structural complication.

BE = balloon expandable; PVR = paravalvular regurgitation; SE = self-expanding; THV = transcatheter heart valve; VARC-3 = Valve Academic Research Consortium 3.

PROCEDURAL DATA AND IN-HOSPITAL OUTCOMES. Procedural features and outcomes are shown in Table 3. BE THVs were implanted in 417 (44.1%) patients, whereas SE THVs were used in the remaining 529 (55.9%) patients; in 737 (77.9%) patients, a device equipped with an external skirt was implanted. In 189 (20.0%) patients, the implanted THV size was supra-annular. Valve predilatation and postdilatation was performed in 662 (70.0%) and 335 (35.4%) patients, respectively. Technical success according to the Valve Academic Research Consortium 3 criteria[18] was achieved in 905 (95.7%) patients. Compared with patients with mild PVR and those with no/trace PVR, those who developed moderate or severe PVR were more frequently treated with SE THVs (91.7% vs 67.4% vs 44.9%; $P < 0.001$), THVs without an external skirt (41.7% vs 26.1% vs 17.8%; $P = 0.001$), and multiple valves (5.6% vs 2.6% vs 1.0%; $P = 0.042$) and more frequently underwent predilatation (83.3% vs 77.3% vs 63.7%; $P < 0.001$) and postdilatation (58.3% vs 46.3% vs 25.8%; $P < 0.001$). No in-hospital deaths directly related to moderate or severe PVR occurrence were observed. Compared with patients with mild PVR and patients with no/trace PVR, patients with moderate or severe PVR had a higher rate of new permanent pacemaker implantation during the entire hospitalization (28.6% vs 16.9% vs 11.7%; $P = 0.006$) and a numerically higher postprocedural effective orifice area (2.20 mm^2 [Q1-Q3: 1.60-2.96 mm^2] vs 2.0 mm^2 [Q1-Q3: 1.60-2.62mm^2] vs 1.97 mm^2 [Q1-Q3: 1.60-2.51 mm^2]; $P = 0.058$).

PREDICTORS OF MODERATE OR SEVERE POST-PROCEDURAL PVR. In model 1 of the multivariable logistic regression analysis (Table 4), the VRR perimeter (per mm, adjusted OR: 1.07; 95% CI: 1.02-1.13; $P = 0.009$), severe annular/LVOT calcification

TABLE 4 Predictors of Moderate or Severe PVR at Univariate and Multivariate Analysis (Model 1)

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
VRR perimeter, per mm	1.04 (1.00-1.08)	0.046	1.07 (1.02-1.13)	0.009
Index raphe/anteraphe	0.90 (0.20-4.08)	0.890	0.19 (0.02-1.58)	0.124
Severe annular/LVOT calcification	3.42 (1.26-9.25)	0.015	5.21 (1.45-18.77)	0.012
Severe aortic valve calcification	0.90 (0.45-1.80)	0.766	0.94 (0.35-2.52)	0.900
Severe raphe calcification	0.80 (0.36-1.78)	0.589	0.78 (0.28-2.17)	0.629
Restricted nonfused cusp	1.80 (0.87-3.72)	0.114	1.69 (0.66-4.33)	0.272
Tapered configuration	0.63 (0.31-1.29)	0.208	0.80 (0.32-2.00)	0.630
SE THV	9.18 (2.80-30.15)	<0.001	9.01 (2.09-38.86)	0.003
Predilatation	2.20 (0.91-5.34)	0.082	1.19 (0.42-3.42)	0.745
Postdilatation	2.66 (1.35-5.23)	0.005	1.87 (0.84-4.19)	0.127
Intentional supra-annular THV positioning	3.76 (1.47-9.62)	0.006	3.31 (1.04-10.54)	0.043

Abbreviations as in Tables 1 and 3.

(adjusted OR: 5.21; 95% CI: 1.45-18.77; $P = 0.012$), the use of an SE THV (adjusted OR: 9.01; 95% CI: 2.09-38.86; $P = 0.003$), and intentional supra-annular THV positioning (adjusted OR: 3.31; 95% CI 1.04-10.54; $P = 0.043$) were independent predictors of moderate or severe PVR.

In model 2 of the multivariable logistic regression analysis including THV models and selecting SAPIEN 3/3 Ultra (Edwards Lifesciences) as the reference platform (Supplemental Table 4), the THVs that emerged as independent predictors of moderate or severe PVR were Evolut R (Medtronic), Evolut Pro/Pro+ (Medtronic), and Portico; conversely, Acurate Neo, Acurate Neo 2 (Boston Scientific), and Navitor (Abbott) exhibited a nonsignificant trend as predictors. The distribution of anatomical and procedural independent predictors of moderate or severe PVR were assessed post hoc across THV models (Supplemental Table 5). Notably, there was no significant difference in the distribution of various degrees of annular/LVOT calcification.

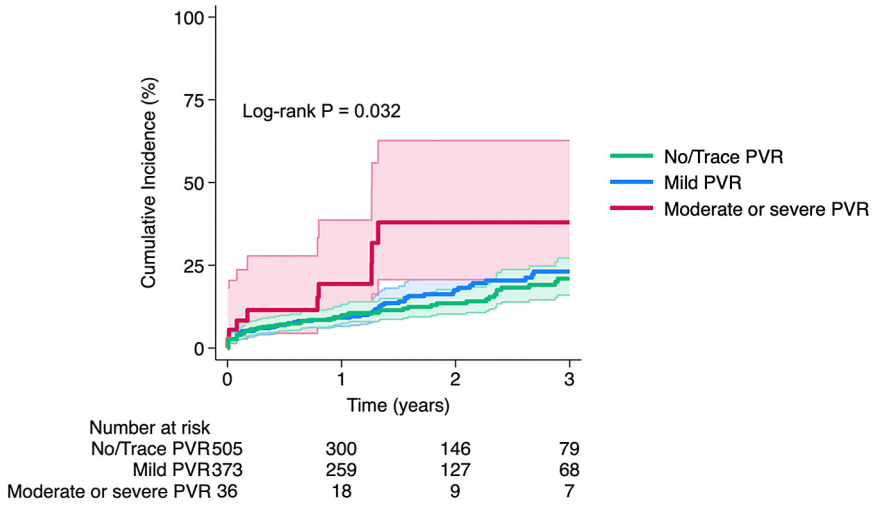
CLINICAL OUTCOMES ACCORDING TO PVR GRADE. A total of 914 patients (505 [55.3%] with no/trace PVR, 373 [40.8%] with mild PVR, 32 [3.5%] with moderate PVR, and 4 [0.4%] with severe PVR) had data on clinical follow-up. During a median follow-up of 1.3 years (Q1-Q3: 0.5-2.4 years), 149 (17.1%) patients experienced MAEs (72 [14.3%] patients in the no/trace PVR group, 66 [17.7%] patients in the mild PVR group, and 11 [30.6%] patients in the moderate or severe PVR group) (Figure 1). Three patients with moderate or severe PVR underwent corrective intervention during follow-up, including 2 THV postdilatation (at days 22 and 63 after the index procedure) and 1 plug closure implantation (at day 30 after the index procedure). In the multivariable Cox regression analysis (Supplemental Table 6), diabetes mellitus (adjusted HR: 1.63; 95% CI: 1.08-2.47; $P = 0.021$), a history of atrial fibrillation (adjusted HR: 1.58; 95% CI: 1.11-2.25; $P = 0.011$), right bundle branch block (adjusted HR: 2.00; 95% CI: 1.19-3.38; $P = 0.009$), and moderate or severe PVR (adjusted HR: 2.52; 95% CI: 1.24-5.09; $P = 0.010$) were independent predictors of MAEs. Of note, mild PVR was not found to be an independent predictor of MAEs (adjusted HR: 1.01; 95% CI: 0.71-1.44; $P = 0.950$) (Supplemental Table 6). The test of the Schoenfeld residuals over time was not significant ($P = 0.404$) (Supplemental Table 7), indicating that the assumption of the proportional hazards model had not been violated.

SENSITIVITY ANALYSES. The results of the logistic regression model with purposeful selection of variables to evaluate predictors of moderate or severe PVR (Supplemental Table 8) were consistent with those of the main model 1. Finally, sensitivity analyses excluding patients receiving Acurate Neo and Portico (Supplemental Tables 9 to 11) showed findings consistent with the primary analysis in terms of the incidence of PVR, predictors of moderate or severe PVR, and predictors of MAEs.

DISCUSSION

This large-scale multicenter study specifically addresses the incidence, predictors, and clinical outcomes of PVR after TAVR with contemporary-generation THVs in patients with Sievers type 1 BAV stenosis. The main findings can be summarized as follows (Central Illustration): 1) PVR after TAVR in Sievers type 1 BAV stenosis occurred in 44.7% of patients and was mild, moderate, and severe in 40.9%, 3.4%, and 0.4% of cases, respectively; 2) independent

FIGURE 1 Kaplan-Meier Estimates of Major Adverse Events According to PVR Grade



PVR = paravalvular regurgitation.

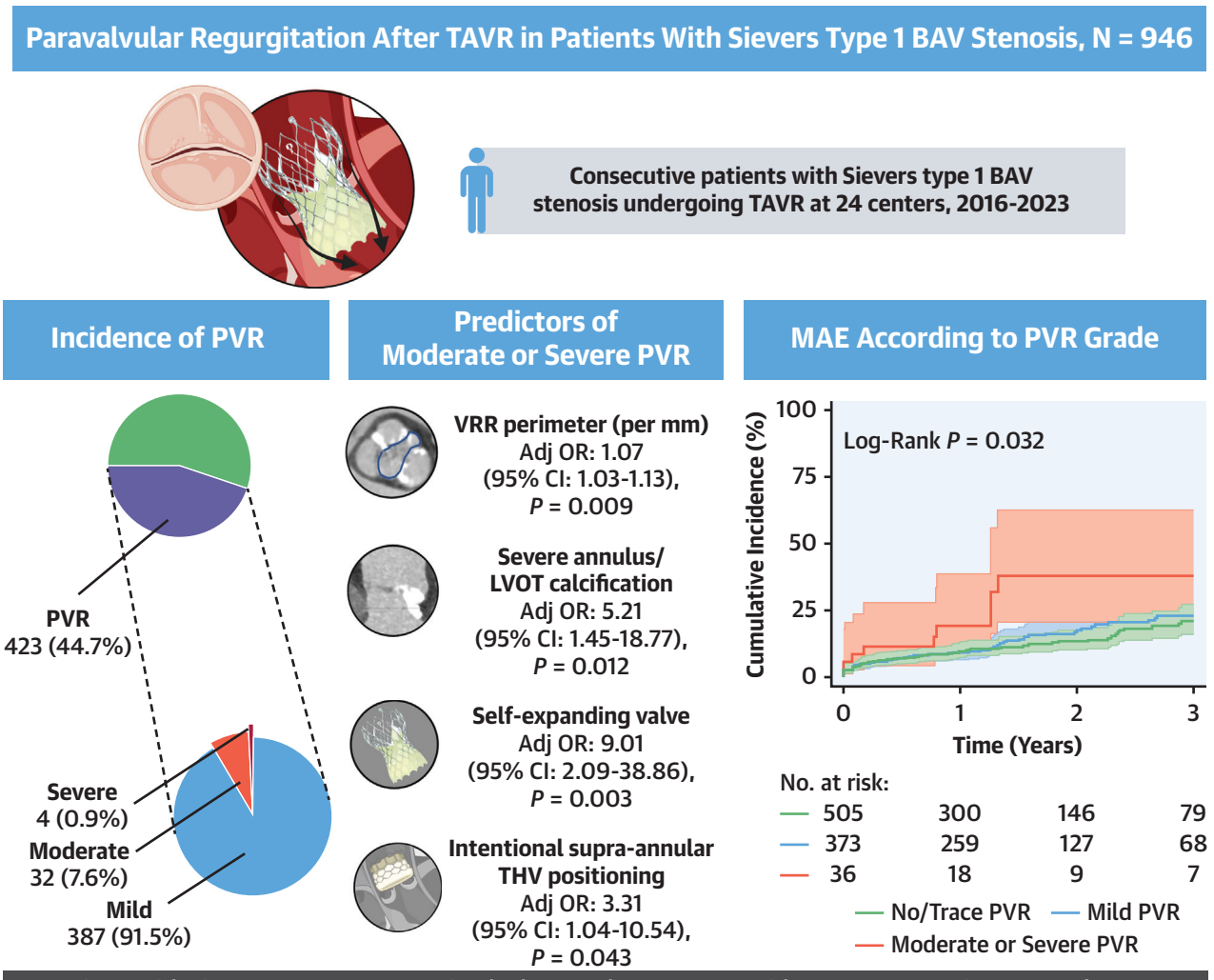
predictors of moderate or severe PVR encompass anatomical (larger VRR perimeter and the presence of severe annular or LVOT calcification) and procedural factors (SE THV and intentional supra-annular THV positioning); and 3) moderate or severe PVR was independently associated with an increased risk of MAEs at a median follow-up of 1.3 years.

BAV is a common congenital heart defect that represents a significant cause of severe aortic stenosis and presents several challenging anatomical features for TAVR, especially in cases with raphe phenotype.[1,5] Early attempts to perform TAVR with first-generation THVs in BAV patients yielded unsatisfactory results, primarily because of a high incidence of moderate or severe PVR (>20%).[3,19] In contrast, our findings demonstrate that TAVR with more contemporary THV generations in patients with Sievers type 1 BAV stenosis results in a reasonable incidence of PVR, with a rare occurrence of moderate or severe PVR. These findings are consistent with recent studies suggesting a similar incidence of at least moderate PVR (<5%) in BAV stenosis compared to the tricuspid counterpart when treated with new-generation THVs.[20] This finding can be attributed to advancements in TAVR techniques and THV technology, including the introduction of sealing skirts, cuffs, and partial repositionability, which have led to better outcomes and a reduced risk of PVR.

Nevertheless, PVR remains a significant cause of morbidity and mortality.[4] There is ongoing debate regarding the potential impact of varying degrees of regurgitation. Although a post hoc analysis of the PARTNER-IA (Placement of AoRTic TraNscathetER Valves) study also suggested an impact of mild PVR on clinical outcomes at a median follow-up of 2 years,[21] several large registries and subsequent post hoc analyses of RCTs have shown an impact of moderate or severe PVR but not mild PVR.[22-24] A recent retrospective single-center registry suggested a potential delayed detrimental effect of mild PVR on long-term clinical outcomes, mainly emerging during extended follow-up times (5-year follow-up).[25] In our study with a median follow-up of 1.3 years, moderate or severe PVR emerged as an independent predictor of MAE, whereas mild PVR, which was observed in around 40% of patients, was not associated with an increased risk of MAEs. This highlights an interplay between the hemodynamic consequences associated with moderate or severe PVR and clinical outcomes at midterm follow-up, whereas other factors, such as left ventricular tolerability and PVR worsening, may influence the impact of mild PVR at long-term follow-up.[26] Nonetheless, it is essential to accurately assess the presence and severity of PVR to promptly consider corrective interventions, including post-dilation, leak closure, or valve-in-valve procedure, potentially before left ventricular remodeling occurs. However, data on the potential clinical impact of corrective intervention at various time frames are not available still.

Our study identified specific independent predictors associated with the occurrence of moderate or

CENTRAL ILLUSTRATION **Incidence, Predictors, and Outcomes of Post-Transcatheter Aortic Valve Replacement Paravalvular Regurgitation in Sievers Type 1 Bicuspid Aortic Valve Stenosis**



- In patients with Sievers type 1 BAV stenosis who have undergone TAVR with current-generation transcatheter heart valves, PVR is common but mostly mild
- Moderate or severe PVR occurred in ~4% of cases and was associated with increased risk of MAE during follow-up (Adj HR: 2.52, 95% CI: 1.24-5.09, *P* = 0.009)

Zito A, et al. JACC Cardiovasc Interv. 2024;17(14):1652-1663.

Ad_j HR = adjusted HR; Ad_j OR = adjusted OR; BAV = bicuspid aortic valve; LVOT = left ventricular outflow tract; MAE = major adverse event(s); PVR = paravalvular regurgitation; TAVR = transcatheter aortic valve replacement; THV = transcatheter heart valve; VRR = virtual raphe ring.

severe PVR in patients with raphe-type 1 BAV stenosis undergoing TAVR. The VRR perimeter was identified as a novel predictor, indicating that a larger perimeter in this region may increase the risk of moderate or severe PVR. We can speculate that a larger VRR perimeter could reflect a more irregular shape of this virtual structure (mostly associated with the presence of marginal calcifications of the raphe or nonfused cusp), which could be largely different from that of the virtual basal ring and potentially lead to incomplete circumferential apposition of the prosthesis. However, post-TAVR MSCT studies are needed to investigate this intriguing link. Furthermore, severe annular or LVOT calcification emerged as a predictor

by impacting the shape and the correct apposition of the prosthesis. Conversely, severe calcification at the leaflet or raphe was not found to be an independent predictor, which is in line with previous analyses.[27] The use of SE THVs was found to be a strong predictor, likely because of their design characteristics and deployment techniques. In fact, compared with BE THVs, SE THVs may be more capable of conforming to the irregular BAV orifice but less capable of achieving a circular shape.[28,29] Moreover, some platforms of SE THVs still lack the external sealing skirt, whereas BE THVs do not. Despite the limited statistical power within certain THV platforms, model 2 of the multivariable regression analysis indicated a consistent trend across the main SE THV platforms as independent predictors of moderate or severe PVR compared to the Sapien THV. However, the statistical uncertainty reflected by the wide CIs hampers reliable conclusions to be drawn for each THV model. Nevertheless, it should be acknowledged that BAV stenosis is associated with a higher prevalence of severe annular/LVOT calcification than the tricuspid counterpart,[1] potentially leading some operators to prefer SE THV to BE THVs to mitigate the perceived risk of annulus rupture. Notably, the use of SE THVs has not demonstrated predictive value for MAEs in both uni- and multivariate analyses, which is consistent with previous analyses.[29] This could be because the occurrence of moderate or severe PVR is rare and is not the only procedural determinant affecting the prognosis of BAV patients undergoing TAVR, but other factors, such as post-TAVR residual gradients and patient-prosthesis mismatch, must be considered. Finally, the intentional supra-annular THV positioning emerged as a predictor of moderate or severe PVR, potentially related to frequent suboptimal supra-annular sealing when VRR is selected as the landing zone.[13] Importantly, these results were made possible by the comprehensive collection in our registry of preprocedural MSCT features. These predictors may provide valuable insights for risk stratification and patient selection in clinical practice and reinforce the importance of a detailed anatomical evaluation in TAVR planning of severe BAV stenosis.

STUDY LIMITATIONS. First, this is a retrospective observational study that may suffer selection and reporting biases. Second, the lack of a core laboratory for imaging analysis raises concerns about potential interobserver variability and inconsistency in MSCT and echocardiographic analyses. Third, the sample contribution from the various centers was dissimilar, thus limiting the generalizability of the results. Fourth, the raphe is a 3-dimensional structure, and some inherent MSCT measurements (eg, raphe length and VRR) should be intended as surrogates because of their 2-dimensional natures. Fifth, the relatively high age of the included population limits the generalizability of the results to a younger population with Sievers type 1 BAV stenosis. Sixth, the follow-up duration may not capture the long-term clinical implications of post-TAVR PVR. Lastly, a potential detrimental effect of mild predischarge PVR may have been missed at a longer follow-up. For these reasons, future prospective studies are needed to confirm our findings and explore the impact of mild PVR over extended time frames.

CONCLUSIONS

PVR after TAVR with contemporary-generation THVs in patients with Sievers type 1 BAV stenosis occurred in about 45% of patients and was mostly mild. Moderate or severe PVR occurred in about 4% of patients and was associated with an increased risk of MAEs at a median follow-up of 1.3 years. Larger VRR perimeter, severe annular or LVOT calcification, the use of SE THVs, and intentional supra-annular THV positioning were independent predictors of moderate or severe PVR.

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Dr Aurigemma has reported speaker fees from Abbott, Medtronic, Abiomed, and Terumo. Dr Trani has been involved in advisory board meetings or received speaker fees from Medtronic, Abbott, Terumo, Daiichi-Sankyo, and Abiomed. Dr Adamo has reported speaker honoraria from Abbott Vascular and Edwards Lifesciences. Dr Burzotta has been involved in advisory board meetings or has received speaker fees from Medtronic, Abbott, Terumo, Daiichi-Sankyo, and Abiomed. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? TAVR in patients with BAV stenosis is burdened by an increased risk of PVR.

WHAT IS NEW? In patients with Sievers type 1 BAV stenosis undergoing TAVR with contemporary-generation THVs, moderate or severe PVR occurred in about 4% of cases and was associated with an increased risk of MAEs during follow-up. A larger VRR perimeter, severe annular or LVOT calcification, the use of self-expanding THVs, and intentional supra-annular THV positioning were independent predictors of moderate or severe PVR.

WHAT IS NEXT? Future studies are needed to explore the impact of corrective intervention at various time frames and of mild PVR over an extended follow-up.

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KEY WORDS aortic stenosis, bicuspid aortic valve, paravalvular leak, paravalvular regurgitation, transcatheter aortic valve replacement

APPENDIX For supplemental tables, please see the online version of this paper.