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Predictors and Clinical Impact of Prosthesis-Patient Mismatch After Self-Expandable TAVR in Small Annuli

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ABSTRACT

OBJECTIVES The aim of this study was to define predictors of prosthesis-patient mismatch (PPM) and its impact on mortality after transcatheter aortic valve replacement (TAVR) with self-expandable valves (SEVs) in patients with small annuli.

BACKGROUND TAVR seems to reduce the risk for PPM compared with surgical aortic valve replacement, especially in patients with small aortic annuli. Nevertheless, predictors and impact of PPM in this population have not been clarified yet.

METHODS Predictors of PPM and all-cause mortality were investigated using multivariable logistic regression analysis from the cohort of the TAVI-SMALL (International Multicenter Registry to Evaluate the Performance of Self-Expandable Valves in Small Aortic Annuli) registry, which included patients with severe aortic stenosis and small annuli (annular perimeter $<$72 mm or area $<$400 mm^2 on computed tomography) treated with transcatheter SEVs: 445 patients with (n = 129) and without (n = 316) PPM were enrolled.

RESULTS Intra-annular valves conferred increased risk for PPM (odds ratio [OR]: 2.36; 95% confidence interval [CI]: 1.16 to 4.81), while post-dilation (OR: 0.46; 95% CI: 0.25–0.84) and valve oversizing (OR: 0.53; 95% CI: 0.28–1.00) seemed to protect against PPM occurrence. At a median follow-up of 354 days, patients with severe PPM, but not those with moderate PPM, had a higher all-cause mortality rate compared with those without PPM (log-rank p = 0.008). Multivariable Cox regression confirmed severe PPM as an independent predictor of all-cause mortality (hazard ratio: 4.27; 95% CI: 1.34 to 13.6).

CONCLUSIONS Among patients with aortic stenosis and small aortic annuli undergoing transcatheter SEV implantation, use of intra-annular valves yielded higher risk for PPM; conversely, post-dilation and valve oversizing protected against PPM occurrence. Severe PPM was independently associated with all-cause mortality.
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First described by Rahimtoola (1) in 1978, prosthesis-patient mismatch (PPM) is currently defined as a nonstructural valvular dysfunction relatively occurring when the effective area of an implanted prosthetic valve is too small relative to the patient's body size (2). PPM is associated with higher than expected gradients for a properly functioning bioprosthetic valve and seems fairly common with surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR) (3).

The evidence of increased risk for short- and long-term mortality in patients with PPM after SAVR is well described (4–6), while its clinical impact in patients subject to TAVR is unclear (7). Recently, PPM has been associated with blunted left ventricular mass regression (8), increased risk for rehospitalization (9), and reduction in overall survival (10) and may vary according to the transcatheter heart valve platform (11).

Transcatheter bioprostheses seem to offer better hemodynamic status and a reduced risk for PPM compared with surgical valves (12–14). This applies particularly to the subset of patients with small aortic annuli (9,10), when using self-expandable valves (SEVs) (15,16). Data from the TAVI-SMALL (International Multicenter Registry to Evaluate the Performance of Self-Expandable Valves in Small Aortic Annuli) registry, which focused on this subgroup of patients, suggested that supra-annular SEVs seemed to slightly outperform intra-annular SEV in terms of transvalvular gradients (17). However, predictors of PPM and clinical outcomes in this context have not been investigated yet. Accordingly, the aim of this study was to evaluate predictors and clinical impact of PPM in patients with severe aortic stenosis and small annuli treated with self-expandable TAVR.

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METHODS

STUDY DESIGN AND DEFINITION. The study design of the observational, retrospective TAVI-SMALL registry has been previously described (17). Briefly, the registry included a total of 859 patients with severe native aortic valve stenosis and small aortic annuli (defined as annular area <400 mm^2 and/or annular perimeter <72 mm on computed tomography) treated with transcatheter implantation of current-generation supra-annular (Evolut R and Evolut PRO, Medtronic, Minneapolis, Minnesota; Acurate NEO, Boston Scientific, Marlborough, Massachusetts) and intra-annular (Acurate TransApical, Boston Scientific; Portico, Abbott Vascular, Santa Clara, California) SEVs between June 2011 and October 2018, at 9 high-volume European centers. This study complied with the Declaration of Helsinki and was approved by local ethics committees. All patients provided written informed consent for the procedure and subsequent data collection.

The present substudy was intended to focus on PPM; therefore, only patients with complete data (baseline computed tomographic measurements, baseline and follow-up echocardiographic parameters, and adequate clinical follow-up) were included, for a total of 445 cases.

Patients were then divided into groups according to the absence or presence of post-procedural PPM, defined as indexed effective orifice area (EOA) <0.85 cm^2/m^2; those with PPM were further divided into moderate (indexed EOA 0.65 to 0.85 cm^2/m^2) and severe PPM (indexed EOA <0.65 cm^2/m^2) groups (18). Additional analyses were conducted in groups divided according to body mass index (BMI)-adjusted PPM thresholds, that is, indexed EOA <0.70 and <0.60 cm^2/m^2 for moderate and severe PPM, respectively, in patients with BMI ≥30 kg/m^2 (19). EOA was calculated on pre-discharge echocardiography using the continuity equation method; stroke volume was estimated via left ventricular outflow tract (LVOT) diameter (outer to outer border of the valve stent) and velocity-time integral measured just underneath the ventricular margin of the valve stent (19).

ENDPOINTS. The primary objective of the study was to identify independent predictors of PPM. Secondary endpoints included 1-year all-cause mortality and ischemic stroke or transient ischemic attack; in addition, independent predictors of 1-year all-cause mortality were evaluated.

Clinical and technical endpoint definitions coincide with those of the original study (17); in addition, computed tomography-derived annular eccentricity (maximum/minimum annular diameter) and percentage of oversizing according to perimeter

ABBREVIATIONS AND ACRONYMS

BARC = Bleeding Academic Research Consortium

BEV = balloon-expandable valve

BMI = body mass index

CI = confidence interval

EOA = effective orifice area

HR = hazard ratio

LVOT = left ventricular outflow tract

OR = odds ratio

PPM = prosthesis-patient mismatch

SEV = self-expandable valve

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Baseline Demographic Characteristics According to Presence and Degree of PPM

			p Value		p Value		p Value		
	No PPM (n = 316)	PPM (n = 129)	No PPM vs. PPM	Moderate PPM (n = 87)	No vs. Moderate PPM	Severe PPM (n = 42)	No vs. Severe PPM	Moderate vs. Severe PPM	No vs. Moderate vs. Severe PPM
Age, yrs	82.5 ± 6.3	81.5 ± 7.7	**0.077**	82.5 ± 6.1	1.00	79.5 ± 10.0	**0.017**	**0.048**	**0.02**
Female	89.9 (284)	90.7 (117)	0.792	90.8 (79)	1.00	90.5 (38)	1.00	1.00	0.964
Weight, kg	63.1 ± 13.0	70.4 ± 13.9	**<0.001**	70.1 ± 13.1	**<0.001**	71.2 ± 15.5	**0.001**	1.00	**<0.001**
Height, cm	158.3 ± 6.9	159.5 ± 7.5	**0.052**	159.1 ± 7.6	1.00	160.3 ± 7.3	0.242	1.00	0.174
Body surface area, m^2	1.66 ± 0.18	1.78 ± 0.21	**<0.001**	1.78 ± 0.19	**0.001**	1.79 ± 0.25	**0.011**	1.00	**<0.001**
Body mass index, kg/m^2	25.9 ± 4.6	28.1 ± 5.5	**<0.001**	28.2 ± 5.2	**0.007**	28.0 ± 6.0	0.101	1.00	**0.003**
Hypertension	84.2 (266)	86.0 (111)	0.619	87.4 (76)	0.612	83.3 (35)	0.825	0.591	0.751
Diabetes mellitus	25.3 (80)	36.4 (47)	**0.062**	39.1 (34)	**0.024**	30.9 (13)	0.172	**0.060**	**0.018**
Dyslipidemia	44.1 (139)	45.0 (58)	0.872	48.3 (42)	0.543	38.1 (16)	0.510	0.346	0.568
COPD	11.1 (35)	7.8 (10)	0.302	9.2 (8)	0.844	4.8 (2)	0.284	0.496	0.427
Peripheral artery disease or previous PTA	16.8 (53)	16.3 (21)	0.888	16.1 (14)	0.871	16.7 (7)	0.979	0.934	0.987
Cerebrovascular disease	8,6 (27)	9.3 (12)	0.805	9.2 (8)	0.855	9.5 (4)	0.773	1.00	0.968
Previous BAV	3.2 (10)	3.9 (5)	0.695	4.6 (4)	0.510	2.4 (1)	1.00	1.00	0.741
Previous PCI	25.0 (79)	25.6 (33)	0.898	27.6 (24)	0.624	21.4 (9)	0.614	0.453	0.746
Previous CABG	6.6 (21)	11.6 (15)	**0.080**	11.5 (10)	0.133	11.9 (5)	0.217	0.946	0.216
Previous MI	10.7 (33)	13.2 (17)	0.467	14.9 (13)	0.282	9.5 (4)	1.00	0.580	0.510
Coronary artery disease	38.1 (120)	45.0 (58)	0.180	52.9 (46)	**0.013**	28.6 (12)	0.230	**0.009**	**0.013**
PM or ICD	9.2 (29)	13.2 (17)	0.208	11.5 (10)	0.517	16.7 (7)	0.129	0.416	0.301
Atrial fibrillation	22.8 (64)	28.1 (32)	0.266	27.6 (24)	0.147	19.0 (8)	0.941	0.345	0.331
Angina	20.7 (55)	15.5 (13)	0.294	6.9 (6)	0.114	16.7 (7)	0.805	0.169	0.261
NYHA functional class III or IV	73.2 (229)	89.8 (115)	**<0.001**	88.5 (77)	**0.001**	90.4 (38)	**0.015**	0.869	**0.001**
STS-PROM, %	5.87 ± 4.27	5.62 ± 2.97	0.559	5.77 ± 3.0	1.00	5.31 ± 2.9	1.00	1.00	0.704
NT-proBNP, pg/ml	2,638.8 ± 4,387.9	1,281.2 ± 2,209.0	0.100	1,449.2 ± 2,458.1	1.00	609.5 ± 702.1	1.00	1.00	0.617
Hemoglobin, g/dl	11.4 ± 2.10	11.5 ± 2.05	0.374	11.4 ± 2.03	1.00	11.8 ± 2.09	0.848	0.966	0.541

Values are mean ± SD or % (n). The p values in **bold** represent differences between groups with p values < 0.10.

BAV = balloon aortic valvuloplasty; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PM = pacemaker; PPM = prosthesis-patient mismatch; PTA = percutaneous transluminal angioplasty; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

([SEV perimeter/annular perimeter − 1]/100) were calculated.

STATISTICAL ANALYSIS. Continuous variables are reported as mean ± SD or median (interquartile range) and were compared using Student's *t*-test or the Mann-Whitney *U* test or Wilcoxon test in case of 2-group comparisons on the basis of normality of data distribution, verified using the Shapiro-Wilk test. In case of continuous variable comparisons between more than 2 groups, analysis of variance was performed; Bartlett's test for equal variances was performed to assess if the variances were comparable between groups, and Bonferroni correction was applied to adjust for multiple comparisons. Categorical variables are reported as percentage (number) and were compared using the chi-square test without Yates's correction for continuity or the Fisher exact test, as appropriate. Univariable and multivariable logistic regression modeling for severe PPM included the following variables: severe annular calcification, oversizing ≥15% by perimeter, intra-annular valve, pre-dilation, and post-dilation. Results of the logistic regression analysis are presented as odds ratios (ORs) with 95% confidence intervals (CIs). The accuracy of logistic regression model was tested using C statistics; Hosmer-Lemeshow goodness-of-fit tests were performed to assess the fit of the model. Survival curves for all-cause mortality were constructed with the use of Kaplan-Meier estimates and compared using the log-rank test. Unadjusted and adjusted Cox proportional hazards models were generated for all-cause mortality. Hazard ratios (HRs) and 95% CIs are reported. The adjusted model includes characteristics we considered relevant: age, sex, BMI, diabetes mellitus, coronary artery disease, New York Heart Association functional class III or IV, moderate or more mitral regurgitation,

TABLE 2 Baseline Echocardiographic and CT Characteristics According to Presence and Degree of PPM

			p Value		p Value		p Value		
	No PPM (n = 316)	PPM (n = 129)	No PPM vs. PPM	Moderate PPM (n = 87)	No vs. Moderate PPM	Severe PPM (n = 42)	No vs. Severe PPM	Moderate vs. Severe PPM	No vs. Moderate vs. Severe PPM
Echocardiographic data									
Mean AV gradient, mm Hg	51.7 ± 16.8	47.6 ± 17.1	**0.011**	47.4 ± 15.9	0.122	48.0 ± 19.5	0.553	1.00	**0.073**
Maximum AV gradient, mm Hg	82.8 ± 24.9	75.6 ± 26.5	**0.004**	74.7 ± 25.0	**0.035**	77.3 ± 29.4	0.606	1.00	**0.028**
EOA, cm^2	0,63 ± 0,19	0,64 ± 0,20	0.351	0.65 ± 0.19	1.00	0.62 ± 0.17	1.00	1.00	0.630
Indexed EOA, cm^2/m^2	0.38 ± 0.13	0.36 ± 0.11	0.565	0.36 ± 0.11	1.00	0.36 ± 0.10	1.00	1.00	0.689
sPAP, mm Hg	41.6 ± 14.3	43.3 ± 15.1	0.389	43.8 ± 14.9	0.726	42.1 ± 15.6	1.00	1.00	0.504
RV dysfunction*	12.3 (39)	13.2 (17)	0.809	9.2 (8)	0.418	21.4 (9)	0.104	**0.054**	0.141
Bicuspid AV	6.8 (16)	3.2 (3)	0.195	1.1 (1)	0.135	4.8 (2)	1.00	0.262	0.282
Moderate or greater AR	8.7 (27)	6.6 (8)	0.474	6.2 (5)	0.649	7.5 (3)	1.00	1.00	0.843
Moderate or greater MR	11.9 (36)	11.6 (14)	0.929	13.7 (11)	0.650	7.3 (3)	0.598	0.378	0.645
Moderate or greater TR	7.5 (18)	7.9 (7)	0.891	6.8 (4)	1.00	10.3 (3)	0.482	0.680	0.735
Ejection fraction, %	57.9 ± 9.9	58.1 ± 12.0	0.412	58.3 ± 11.8	1.00	57.8 ± 12.6	1.00	1.00	0.953
LVEF <40%	5.4 (17)	7.0 (9)	0.515	6.9 (6)	0.589	7.1 (3)	0.717	1.00	0.715
LVEDV, ml	85.8 ± 33.7	80.7 ± 31.8	0.178	77.8 ± 22.4	0.701	85.4 ± 43.3	1.00	1.00	0.489
LVESV, ml	36.3 ± 20.5	36.2 ± 30.0	0.487	35.4 ± 20.5	1.00	37.4 ± 40.0	1.00	1.00	0.962
CT data									
Mean annular diameter, mm	21.2 ± 1.3	21.1 ± 1.4	0.155	21.3 ± 1.4	1.00	20.7 ± 1.2	**0.057**	**0.083**	**0.053**
Maximum diameter, mm	23.4 ± 1.9	23.7 ± 2.0	**0.077**	23.9 ± 2.1	0.458	23.4 ± 1.7	1.00	0.461	0.131
Minimum diameter, mm	19.1 ± 1.9	18.5 ± 1.6	**0.001**	18.7 ± 1.7	0.250	18.1 ± 1.5	**0.004**	0.264	**0.003**
Annular eccentricity	1.24 ± 0.17	1.29 ± 0.14	**0.002**	1.29 ± 0.15	**0.058**	1.30 ± 0.13	**0.096**	1.00	**0.013**
Mean aortic annular perimeter, mm	67.4 ± 3.7	67.1 ± 3.5	0.182	67.4 ± 3.4	1.00	66.4 ± 3.6	0.324	0.546	0.272
Mean aortic annular area, mm^2	349.9 ± 38.0	338.8 ± 35.5	**0.007**	343.1 ± 34.8	0.583	330.4 ± 35.9	**0.015**	0.332	**0.013**
Area-derived diameter, mm	21.1 ± 1.1	20.7 ± 1.1	**0.007**	20.9 ± 1.09	1.00	20.5 ± 1.12	0.324	0.546	**0.014**
Perimeter-derived diameter, mm	21.5 ± 1.2	21.3 ± 1.1	0.182	21.4 ± 1.07	0.616	21.1 ± 1.17	**0.015**	0.320	0.272
Severe leaflet calcification	26.3 (31)	11.8 (4)	**0.077**	15.8 (3)	0.403	6.7 (1)	0.117	0.613	0.171
Severe annular calcification	12.0 (16)	4.8 (4)	**0.079**	3.8 (2)	0.106	6.4 (2)	0.531	0.624	0.219
Severe LVOT calcification	1.9 (6)	1.3 (1)	0.230	4.2 (1)	1.00	0.0 (0)	0.596	1.00	0.839
LMCA distance, mm	11.5 ± 2.6	11.4 ± 2.3	0.441	11.3 ± 2.1	1.00	11.8 ± 2.8	1.00	1.00	0.736
RCA distance, mm	14.1 ± 3.0	14.5 ± 2.1	0.153	14.4 ± 2.0	1.00	14.6 ± 2.3	1.00	1.00	0.579
Sinotubular junction diameter, mm	26.2 ± 2.4	26.0 ± 2.3	0.291	25.7 ± 1.9	0.501	26.8 ± 2.9	0.894	0.211	0.166
Sinus of Valsalva diameter, mm	29.5 ± 2.7	28.3 ± 2.2	**<0.001**	28.4 ± 1.9	**0.016**	28.3 ± 2.7	**0.066**	1.00	**0.004**
Ascending aorta diameter, mm	32.3 ± 4.1	31.8 ± 4.4	0.207	31.1 ± 3.9	0.120	33.7 ± 5.2	0.264	**0.015**	**0.014**
Porcelain aorta	3.8 (12)	7.7 (10)	**0.081**	10.3 (9)	**0.015**	2.4 (1)	1.00	0.165	**0.045**

Values are mean ± SD or % (n). The p values in **bold** represent differences between groups with p values < 0.10. *Defined as tricuspid annular plane systolic excursion <17 mm.

AR = aortic regurgitation; AV = aortic valve; CT = computed tomographic; EOA = effective orifice area; LMCA = left main coronary artery; LVEDV = left ventricular end systolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; LVOT = left ventricular outflow tract; MR = mitral regurgitation; PPM = prosthesis-patient mismatch; RCA = right coronary artery; RV = right ventricular; sPAP = systolic pulmonary artery pressure; TR = tricuspid regurgitation.

ejection fraction, transfemoral access, moderate PPM, and severe PPM. The interaction between severe PPM and BMI was assessed in the original cohort. Clinical follow-up was censored at the date of death or latest available follow-up. Data for patients lost to follow-up were censored at the time of the last contact. A 2-sided p value < 0.05 was considered to indicate statistical significance. Statistical analyses were performed using Stata version 13.0 (StataCorp).

RESULTS

STUDY POPULATION AND CLINICAL FEATURES. A total of 445 patients with aortic stenosis and small aortic annuli treated with transcatheter implantation of self-expandable bioprostheses were included in the analysis; of these, 316 patients did not develop PPM, while 87 (19.6%) and 42 (9.4%) patients had moderate and severe PPM, respectively, yielding a total of 129 patients with PPM (29.0%). When PPM thresholds were adjusted for BMI, 109 patients had PPM (24.5%); in particular, 71 (15.9%) had moderate and 38 (8.6%) severe PPM.

Table 1 reports baseline characteristics of patients according to presence and degree of PPM. Treated patients were mostly women (90%) and were at moderate surgical risk (mean Society of Thoracic Surgeons Predicted Risk of Mortality scores were

TABLE 3 Procedural Characteristics

			p Value		p Value		p Value		
	No PPM (n = 316)	PPM (n = 129)	No PPM vs. PPM	Moderate PPM (n = 87)	No vs. Moderate PPM	Severe PPM (n = 42)	No vs. Severe PPM	Moderate vs. Severe PPM	No vs. Moderate vs. Severe PPM
Access			**<0.001**		**<0.001**		**0.009**	0.632	**<0.001**
Femoral	90.2 (285)	69.8 (90)	**<0.001**	67.8 (59)	**<0.001**	73.8 (31)	**0.002**	0.487	**<0.001**
Apical	4.7 (15)	20.9 (27)	**<0.001**	23.0 (20)	**<0.001**	16.7 (7)	**0.003**	0.408	**<0.001**
Surgical axillary/subclavian	3.2 (10)	5.4 (7)	0.259	5.7 (5)	0.333	4.8 (2)	0.640	1.00	0.434
Percutaneous axillary/subclavian	0.3 (1)	3.1 (4)	**0.011**	3.4 (3)	**0.033**	2.4 (1)	0.221	1.00	**0.030**
Transaortic	1.6 (5)	0.8 (1)	0.503	0	0.590	2.4 (1)	0.530	0.326	0.372
Valve size			**<0.001**		0.135		**0.022**	0.706	**0.039**
≤25 mm	45.6 (144)	62.0 (80)	**0.002**	59.8 (52)	**0.020**	66.7 (28)	**0.011**	0.449	**0.006**
≥26 mm	54.4 (172)	38.0 (49)	**0.002**	40.2 (35)	**0.020**	33.3 (14)	**0.011**	0.449	**0.006**
Oversizing by perimeter	17.7 ± 7.7	16.0 ± 7.7	**0.019**	16.0 ± 7.7	0.176	16.2 ± 7.8	0.751	1.00	0.116
Oversizing by perimeter ≥15%	65.2 (206)	56.6 (73)	**0.089**	55.2 (48)	**0.087**	59.5 (25)	0.471	0.640	0.209
Valve type			**0.037**		0.179		**0.079**	0.602	0.110
Intra-annular valve	22.5 (71)	48.8 (63)	**<0.001**	49.4 (43)	**<0.001**	47.6 (20)	**<0.001**	0.847	**<0.001**
Evolut R	48.7 (154)	38.8 (50)	**0.055**	37.9 (33)	**0.074**	40.1 (17)	0.314	0.781	0.154
Evolut PRO	11.1 (35)	7.0 (9)	0.189	9.2 (8)	0.615	2.4 (1)	0.100	0.270	0.198
Acurate NEO	17.7 (56)	5.4 (7)	**0.001**	3.4 (3)	**<0.001**	9.5 (4)	0.270	0.214	**0.001**
Acurate TransApical	4.4 (14)	20.9 (27)	**<0.001**	23.0 (20)	**<0.001**	16.7 (7)	**0.002**	0.408	**<0.001**
Portico	18.0 (57)	27.9 (36)	**0.020**	26.4 (23)	**0.082**	30.9 (13)	**0.047**	0.592	**0.057**
Pre-dilation	48.6 (153)	50.4 (65)	0.728	47.1 (41)	0.477	54.8 (23)	0.685	0.416	0.677
Post-dilation	43.6 (137)	28.7 (37)	**0.003**	25.3 (22)	**0.002**	35.7 (15)	0.330	0.220	**0.007**
Contrast medium	135.6 ± 63.7	118.6 ± 57.7	**0.008**	115.0 ± 60.0	**0.037**	125.5 ± 52.9	1.00	1.00	**0.038**
Annular rupture	0.9 (2)	0.0 (0)	0.371	0.0 (0)	1.00	0.0 (0)	1.00	–	1.00

Values are % (n), mean ± SD, or % (n). The p values in **bold** represent differences between groups with p values < 0.10.
PPM = prosthesis-patient mismatch.

5.87 ± 4.27% and 5.62 ± 2.97% in patients without and with PPM, respectively). Mean age was lower in patients with severe PPM (79.5 ± 10.0 years) compared with those with no PPM (82.5 ± 6.3 years; p = 0.017) and moderate PPM (82.5 years; p = 0.048). As expected, weight and body surface area were higher in patients with any degree of PPM compared with those without PPM (70.4 ± 13.9 kg vs. 63.1 ± 13.0 kg [p < 0.001] and 1.78 ± 0.21 m^2 vs. 1.66 ± 0.18 m^2 [p < 0.001]); similarly, BMI was significantly higher in patients with moderate PPM. No significant differences were noted among groups with regard to traditional prognostic risk factors (such as diabetes, peripheral artery disease, and atrial fibrillation), with the exception of higher New York Heart Association functional class at baseline in patients who developed PPM (88.5% and 90.4% in class III or IV in patients with moderate and severe PPM compared with 73.2% in those with no PPM). Supplemental Table 1 includes baseline characteristics of cohorts derived from BMI-adjusted PPM thresholds.

ECHOCARDIOGRAPHIC AND COMPUTED TOMOGRAPHY FEATURES. Baseline echocardiographic and computed tomographic features are shown in **Table 2**. There were no relevant differences among groups in echocardiographic variables, except for slightly lower mean pre-procedural mean and peak aortic gradients in patients with PPM.

As expected, computed tomography-derived aortic annular area was lower in the PPM group (349.9 mm^2 vs. 338.8 mm^2; p = 0.007), especially in the severe PPM group (330.4 mm^2); similar differences were present in minimum annular diameter (19.1, 18.7, and 18.1 mm in the groups with no, moderate, and severe PPM, respectively; p = 0.003), annular eccentricity (p = 0.013), and sinus of Valsalva diameter (p = 0.004). Aortic annular perimeter did not significantly differ among groups (p = 0.272).

No significant differences were present in proportions of severe annular, leaflet, or LVOT calcifications, even though the former two tended to be more represented in patients without compared with those with PPM (12.0% vs. 4.8% [p = 0.079] and 26.3% vs. 11.8% [p = 0.077]). Baseline echocardiographic and computed tomographic features of BMI-adjusted PPM threshold cohorts are reported in Supplemental Table 2.

PROCEDURAL FEATURES. Procedural data are shown in **Table 3**. Most patients were treated by transfemoral access, but a significant difference in access-site

TABLE 4 Post-Procedural Characteristics and Follow-Up

			p Value		p Value		p Value		
	No PPM (n = 316)	PPM (n = 129)	No PPM vs. PPM	Moderate PPM (n = 87)	No vs. Moderate PPM	Severe PPM (n = 42)	No vs. Severe PPM	Moderate vs. Severe PPM	No vs. Moderate vs. Severe PPM
Pre-discharge									
Any vascular complication	15.9 (50)	7.1 (9)	**0.014**	7.0 (6)	**0.034**	7.3 (3)	0.169	1.00	**0.052**
Major vascular complication	4.8 (15)	3.1 (4)	0.446	2.3 (2)	0.545	4.9 (2)	1.00	0.594	0.680
Need for second valve implantation	2.6 (8)	3.1 (4)	0.757	3.5 (3)	0.710	2.4 (1)	1.00	1.00	0.889
Mean AV gradient, mm Hg	8.4 ± 4.0	10.9 ± 4.7	**<0.001**	10.2 ± 3.8	**0.003**	12.3 ± 6.0	**<0.001**	**0.042**	**<0.001**
Maximum AV gradient, mm Hg	14.9 ± 7.0	17.7 ± 7.0	**0.002**	16.7 ± 7.1	0.354	19.2 ± 6.6	**0.006**	0.381	**0.005**
Indexed EOA, cm^2/m^2	1.18 ± 0.36	0.69 ± 0.12	**<0.001**	0.75 ± 0.06	**<0.001**	0.55 ± 0.09	**<0.001**	**0.001**	**<0.001**
More than mild PVL	9.3 (21)	10.6 (10)	0.711	13.6 (8)	0.334	5.7 (2)	0.749	0.312	0.431
More than moderate PVL	1.3 (3)	3.2 (3)	0.263	5.1 (3)	0.105	0	1.00	0.291	0.116
New permanent PM	15.6 (49)	18.1 (23)	0.528	19.8 (17)	0.363	14.6 (6)	0.865	0.482	0.627
BARC major bleeding	5.9 (15)	1.0 (1)	**0.043**	1.5 (1)	0.142	0	0.138	0.464	0.121
BARC bleeding			**0.095**		**0.092**		0.656	0.405	0.259
Type 1	10.3 (26)	20.0 (20)	**0.017**	22.7 (15)	**0.007**	14.3 (5)	0.478	0.311	**0.028**
Type 2	2.0 (5)	2.0 (2)	0.998	3.0 (2)	0.606	0	0.401	0.298	0.583
Type 3	5.9 (15)	1.0 (1)	**0.043**	1.5 (1)	0.142	0	0.138	0.464	0.121
Type 5	0	0	–	0	–	0	–	–	–
Follow-up									
All-cause mortality	6.6 (20)	10.5 (13)	0.176	8.4 (7)	0.567	14.6 (6)	**0.069**	0.289	0.191
Cardiovascular mortality	2.4 (7)	3.4 (4)	0.573	2.4 (2)	1.00	5.0 (2)	0.285	0.595	0.456
Myocardial infarction	0.7 (2)	0	0.365	0	1.00	0	1.00	–	1.00
TIA/stroke	1.8 (5)	3.5 (4)	0.298	3.9 (3)	0.376	2.6 (1)	0.533	1.00	0.441
Acute kidney injury	5.2 (9)	5.1 (2)	0.991	7.4 (2)	0.645	0	1.00	1.00	0.816
Hospitalization for HF	6.3 (13)	4.1 (2)	0.547	5.9 (2)	1.00	0	0.607	1.00	0.882
NYHA functional class III or IV	8.9 (12)	13.0 (3)	0.530	2.0 (3)	0.176	0	1.00	0.526	0.304

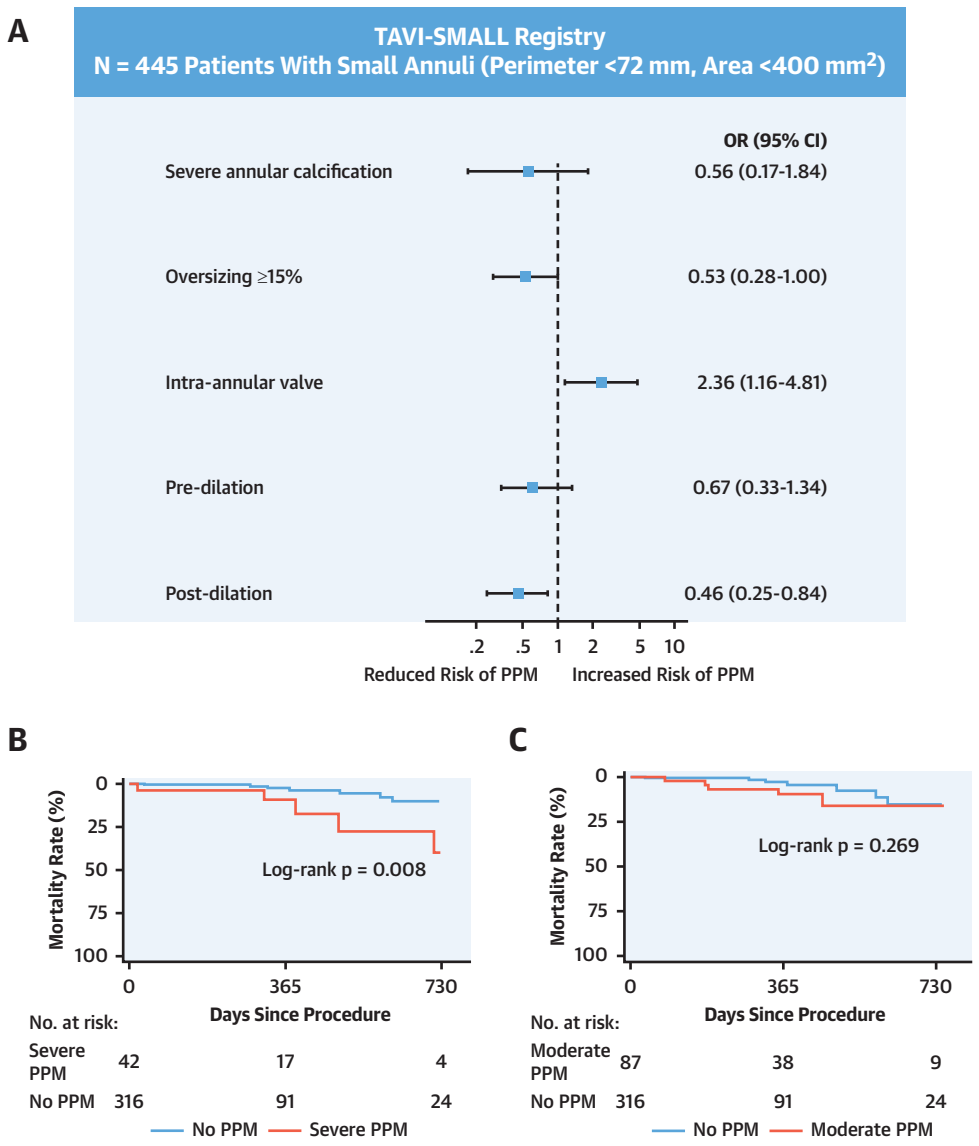
Values are % (n) or mean ± SD. The p values in **bold** represent differences between groups with p values < 0.10.

BARC = Bleeding Academic Research Consortium; HF = heart failure; PVL = paravalvular leak; TIA = transient ischemic attack; other abbreviations as in Tables 1 and 2.

selection was present, with a lower proportion of transfemoral procedures in the PPM group (90.2% vs. 69.8%; p < 0.001), a difference that was driven mainly by patients treated with the Acurate TransApical device and by those treated via axillary or subclavian access. With respect to prosthesis selection, a higher proportion of SEVs with nominal diameter of 25 mm or less were implanted in patients with PPM than those without (62.0% vs. 45.7%; p = 0.002). A trend toward increased oversizing according to perimeter in the no PPM group was present (17.7% vs. 16.0% [p = 0.057], no PPM vs. PPM group, respectively; oversizing >15% in 65.2% vs. 56.6% [p = 0.089], no PPM vs. PPM group, respectively). Although the rate of pre-dilation was similar between groups, more patients in the no PPM group underwent post-dilation (43.6% vs. 28.7%; p = 0.003). A higher proportion of patients with PPM underwent implantation of an intra-annular SEV (48.8% vs. 22.5%; p < 0.001), driven by a higher use of Portico (27.9% vs. 18.0%; p = 0.012) and Acurate TransApical (20.9% vs. 4.4%; p < 0.001) devices. Similar results are reported in Supplemental Table 3.

PROCEDURAL AND CLINICAL OUTCOMES. Clinical and procedural outcomes in patient cohorts without and with BMI-adjusted PPM thresholds are reported in Table 4 and Supplemental Table 4, respectively. Acute complications were rare, with no differences observed between groups in need of second valve implantation, new permanent pacemaker implantation, and more than mild or more than moderate paravalvular leak; similarly, no significant difference regarding the incidence of annular rupture was observed; the only 2 events occurred in patients belonging to the no PPM group who had undergone post-dilation and were treated conservatively, with no resulting major adverse events. Although the incidence of major vascular complications did not differ between groups (4.8% vs. 3.1%; p = 0.446), vascular complications of any degree were more common in the no PPM group than the PPM group (15.9% vs. 7.1%; p = 0.014), and this was paralleled by higher Bleeding Academic Research Consortium type 3 bleeding in the former group (5.9% vs. 1.0%; p = 0.043). As expected, mean and maximum gradients were higher in patients with PPM than in those without (8.4 mm Hg vs. 10.9 mm Hg [p < 0.001] and 14.9 mm Hg vs. 17.7 mm Hg [p < 0.001]).

CENTRAL ILLUSTRATION **Predictors and Impact on Mortality of Prosthesis-Patient Mismatch After Transcatheter Aortic Valve Replacement With Self-Expandable Valves in Small Annuli**



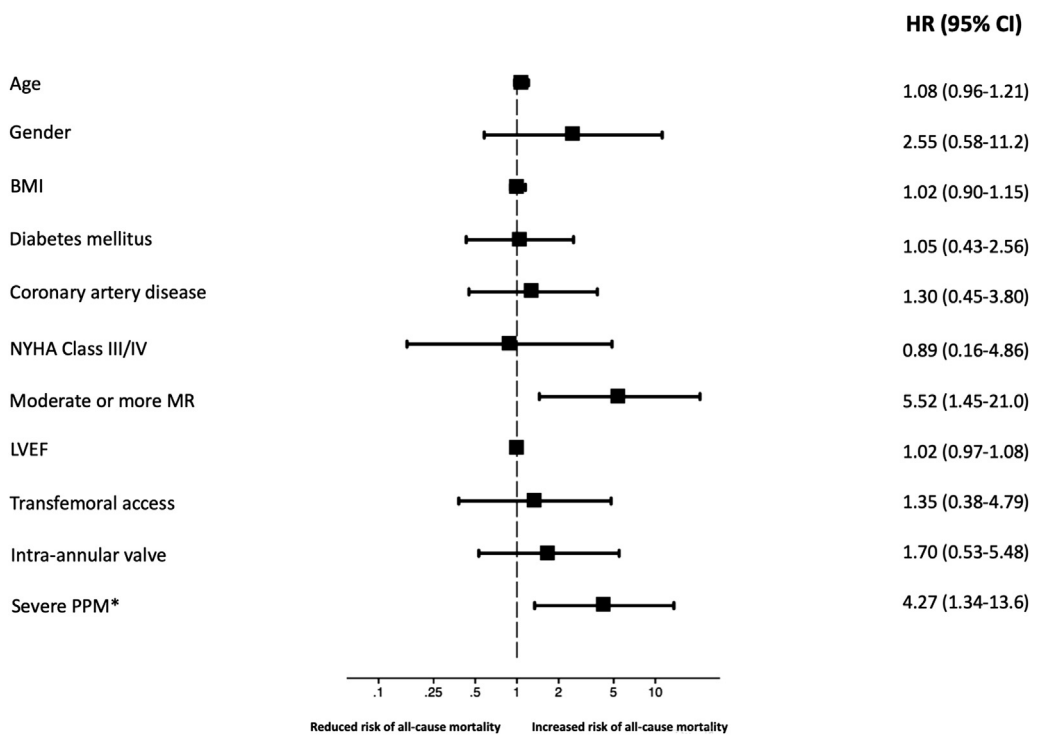
Leone, P.P. et al. J Am Coll Cardiol Intv. 2021;14(11):1218–28.

Forest plot illustrating predictive and protective factors toward the development of prosthesis-patient mismatch (PPM) after transcatheter aortic valve replacement with self-expanding valves in small annuli **(A)** and Kaplan-Meier analysis and log-rank test assessing all-cause mortality according to the presence of severe PPM **(B)** and moderate PPM **(C)**.

At a median follow-up of 354 days (interquartile range: 73 days-478 days), no differences were observed between patients with and those without PPM in terms of all-cause mortality, cardiovascular mortality, stroke or transient ischemic attack, myocardial infarction, hospitalization for heart failure, or New York Heart Association functional class III or IV.

Compared with no PPM on Kaplan-Meier analysis, moderate PPM did not result in increased risk for all-cause mortality ($p = 0.269$), while there was a significantly higher risk for all-cause mortality in the severe PPM group ($p = 0.008$), as shown in the **Central Illustration**. A higher risk for all-cause mortality was similarly present in patients with severe PPM compared with no or moderate PPM ($p = 0.008$), and

FIGURE 1 Forest Plot Illustrating Predictors of 1-Year All-Cause Mortality After Transcatheter Aortic Valve Replacement With Self-Expanding Valves in Small Annuli



*Severe prosthesis-patient mismatch (PPM) versus no or moderate PPM. BMI = body mass index; CI = confidence interval; HR = hazard ratio; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NYHA = New York Heart Association; OR = odds ratio; PPM = prosthesis-patient mismatch.

results were confirmed when comparing BMI-adjusted PPM threshold cohorts (Supplemental Figure 1).

Univariable and multivariable logistic regression results for PPM are shown in the **Central Illustration** and Supplemental Table 5. After multivariable adjustment, the risk for developing PPM was higher in patients implanted with intra-annular valves (adjusted OR: 2.36; 95% CI: 1.16-4.81). Conversely, post-dilation (HR: 0.46; 95% CI: 0.25-0.84) and relevant oversizing (>15%) according to perimeter (HR: 0.53; 95% CI: 0.28-1.00) were protective factors. Intra-annular valve implantation was a predictor of PPM development independently of its definition (Supplemental Table 6, Supplemental Figure 2).

After multivariable adjustment for clinically relevant baseline and procedural characteristics, severe PPM was independently associated with 1-year all-cause mortality (HR: 4.27; 95% CI: 1.34-13.6), as was moderate or more mitral regurgitation (HR: 5.52; 95% CI: 1.45-21.0), as seen in Supplemental Table 7 and **Figure 1**. Severe PPM predicted all-cause mortality independently of the PPM threshold accounted for (Supplemental Tables 7 and 8, Supplemental Figure 3), and no significant interaction with BMI was observed (p for interaction = 0.829).

DISCUSSION

The objective of the present study was to define predictors and clinical impact of PPM after TAVR with SEVs in patients with small aortic annuli. The main findings are the following: 1) intra-annular valves are associated with an increased risk for PPM, while post-dilation and valve oversizing reduced PPM occurrence; and 2) severe PPM, but not moderate PPM, conferred a higher risk for 1-year all-cause mortality.

To better understand PPM after TAVR, TAVI-SMALL focused on a population that is, by definition, at higher risk for developing this complication. Indeed, a small aortic annulus and body size were previously identified as the strongest clinical predictors of PPM (20). Notwithstanding the higher risk for developing PPM, patients with small annuli also appeared to benefit the most with respect to forward

hemodynamic status in studies comparing TAVR with SAVR (9–11,16).

Overall, PPM after TAVR is not rare, but not as common as after SAVR; a recent meta-analysis revealed incidence rates of overall and severe PPM following TAVR of 32.0% and 10.0%, respectively, both lower compared with rates after SAVR (OR: 0.31 [95% CI: 0.20 to 0.50] and 0.38 [95% CI: 0.28 to 0.52], respectively) (14). It was hypothesized that this difference may derive from the intrinsic need for oversizing the annular dimensions with TAVR compared with SAVR (in which often the valve is true-sized or slightly undersized), from the thinner struts, and from the absence of a sewing ring. Nevertheless, this advantage seems to be preserved also when TAVR is compared with stentless surgical valves (21), which were originally developed to mitigate this issue (22).

Of note, commercially available transcatheter valves did not seem to perform equally in terms of risk for PPM. Indeed, although forward hemodynamic status after balloon-expandable valve (BEV) implantation seems to be extremely sensitive to minimal structural modifications made between different iterations of the same valve (12,23), not only have SEVs shown a consistent reduction in PPM incidence in both large and small annuli compared with SAVR (13), but also they have been associated with larger prosthetic valve EOA and lower transprosthetic gradient compared with BEVs (16,24). This was confirmed by 2 recently published studies comparing SEVs and BEVs (19,25), which suggested that supra-annular leaflets may be a key structural feature to produce a favorable hemodynamic profile. The larger EOA may be related to the fact that prosthetic leaflets lie in a different plane than bulky native annulus and native cusps. Preliminary data from the TAVI-SMALL registry supported this evidence (17), and the present subanalysis showed that an intra-annular design was independently associated with PPM. Supra-annular prostheses may therefore represent the first choice when treating patients with aortic stenosis and small aortic annuli, and the randomized SMART (Small Annuli Randomized to Evolut or SAPIEN Trial) trial (NCT04722250) is planned to further clarify this issue.

In addition, our data suggest that 2 procedural aspects may play a protective role in PPM reduction. First, larger oversizing seemed to be related to lower gradients and risk for PPM. Although oversizing (between 9% and 15%) was previously reported to have a favorable effect in SEV implantation (26), our results suggest that a perimeter ratio >15% protects against PPM development when patients with small annuli are treated. Moreover, post-dilation seemed to have a protective role against PPM too, confirming previous findings (27–29). Interestingly, data from the present registry confirmed that such degree of oversizing did not result in a higher risk for pacemaker implantation, coronary occlusion, or annular rupture (Supplemental Table 9).

We observed significantly higher 1-year all-cause mortality in patients with severe PPM compared with patients without PPM. Furthermore, severe PPM was an independent predictor of all-cause mortality, together with more than moderate mitral regurgitation. Whenever the aortic valve is replaced, in the absence of root reconstruction, the resulting EOA is necessarily smaller than the native EOA, as the prosthesis is inserted within the aorta with its own structural support. Thus, by definition in these cases, some degree of post-operative PPM is always present, but an impact on mortality seems to arise only when it exceeds a critical threshold (6,30–32). Recent studies showed an association between PPM after TAVR and reduced post-procedural functional class improvement, left ventricular mass, and diastolic dysfunction regression (8,33) and increased risk for rehospitalization for heart failure (9). Of note, although several studies have shown PPM to reduce overall survival, in particular when severe (10,24,34), others have confirmed such findings only in specific subsets of patients, namely, those without post-procedural aortic regurgitation (11) and those with left ventricular ejection fractions <40% (35). Also, although the analysis from the Society of Thoracic Surgeons/American College of Cardiology TVT (Transcatheter Valve Therapy) Registry demonstrated that severe PPM is common after TAVR and is associated with greater 1-year mortality (HR: 1.19) (34), this may differ according to the type of transcatheter valve implanted (11,36,37). In line with the latter registry, our study did not find BMI to be a predictor of mortality on multivariable analysis, and no significant interaction with severe PPM was observed. It is in light of such evidence, in contrast to earlier reports of a more important impact of PPM on mortality in patients with smaller BMI (5), that PPM cutoff adjustment according to BMI might emerge apparently controversial (38).

In contrast, a meta-analysis revealed no statistically significant differences in late mortality between patients undergoing TAVR with at least moderate PPM and those without PPM (7), even though the investigators argued that concomitant paravalvular leak might represent a confounding bias. Whether this conflicting evidence stems from methodological differences, enrolled populations, or intrinsic limitations in the measurement of parameters needed to

estimate EOA after implantation (including neo-LVOT diameter and pulsed-wave Doppler velocity-time integral estimation) (39) is a matter of debate.

Overall, we believe that the risk for developing PPM should be kept in consideration when evaluating patients for TAVR (40), particularly influencing transcatheter valve type and size choice and procedural planning.

STUDY LIMITATIONS. Selection bias cannot be excluded, because of the observational nature of our study; also, although the majority of relevant data were either prospectively reported during the course of clinical follow-up or derived from an ad hoc database, underreporting or missing echocardiographic and follow-up data need to be acknowledged. Furthermore, the semiquantitative scoring system used for aortic valve and LVOT calcification was derived from a study using a centralized computed tomographic data assessment (17), so reproducibility in the absence of core laboratory analysis might not have been optimal. Similarly, the lack of a centralized echocardiographic evaluation could have affected the assessment of procedural results. Finally, event rates did not allow us to conduct additional analyses according to valve type and design, which will need to be addressed in future studies.

CONCLUSIONS

The present multicenter observational retrospective registry of patients with aortic stenosis and small aortic annuli undergoing TAVR with SEVs suggests that the use of intra-annular functioning transcatheter valves is a risk factor for PPM, while valve post-dilation and oversizing play a protective role. In addition, severe PPM is associated with higher 1-year all-cause mortality. Randomized trials assessing long-term prognostic relevance of PPM and impact of strategies to prevent it are needed to confirm our hypothesis-generating data.

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PERSPECTIVES

WHAT IS KNOWN? The clinical impact of PPM after TAVR is not clear yet. Transcatheter valves have been shown to offer better hemodynamic status compared with surgical prostheses, especially in patients with small annuli. Findings from the TAVI-SMALL registry suggested that supra-annular SEVs slightly outperform intra-annular SEVs in this setting.

WHAT IS NEW? In this additional analysis of the registry, intra-annular valves were found to confer an augmented risk for PPM, while post-dilation and valve oversizing protect against PPM occurrence. Patients with severe PPM had higher 1-year all-cause mortality compared with those without PPM, and severe PPM was an independent predictor of all-cause mortality.

WHAT IS NEXT? As severe PPM seems to play a major role in mid- and possibly long-term survival after TAVR, larger trials assessing the impact of possible strategies to prevent it are awaited.

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KEY WORDS prosthesis-patient mismatch, self-expandable valves, small annuli, TAVR

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