

Implantation of contemporary transcatheter aortic valves in small aortic annuli: the international multicentre TAVI-SMALL 2 registry

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KEYWORDS

- aortic stenosis
- other

Abstract

Background: Treatment of aortic stenosis in patients with small annuli is challenging and can result in prosthesis-patient mismatch (PPM).

Aims: We aimed to compare the forward flow haemodynamics and clinical outcomes of contemporary transcatheter valves in patients with small annuli.

Methods: The TAVI-SMALL 2 international retrospective registry included 1,378 patients with severe aortic stenosis and small annuli (annular perimeter <72 mm or area <400 mm²) treated with transfemoral self-expanding (SEV; n=1,092) and balloon-expandable valves (BEV; n=286) in 16 high-volume centres between 2011 and 2020. Analyses comparing SEV versus BEV and supra-annular (SAV; n=920) versus intra-annular valves (IAV; n=458) included inverse probability of treatment weighting (IPTW). The primary endpoints were the pre-discharge mean aortic gradient and incidence of severe PPM. The secondary endpoint was the incidence of more than mild paravalvular leak (PVL).

Results: The pre-discharge mean aortic gradient was lower after SAV versus IAV (7.8±3.9 vs 12.0±5.1; p<0.001) and SEV versus BEV implantation (8.0±4.1 vs 13.6±4.7; p<0.001). Severe PPM was more common with IAV and BEV when compared to SAV and SEV implantation, respectively, (8.8% vs 3.6%; p=0.007 and 8.7% vs 4.6%; p=0.041). At multivariable logistic regression weighted by IPTW, SAV protected from severe PPM regardless of its definition. More than mild PVL occurred more often with SEV versus BEV (11.6% vs 2.6%; p<0.001).

Conclusions: In small aortic annuli, implantation of SAV and SEV was associated with a more favourable forward haemodynamic profile than after IAV and BEV implantation, respectively. More than mild PVL was more common after SEV than BEV implantation.

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Abbreviations

BEV	balloon-expandable valve
EOA	effective orifice area
IAV	intra-annular valve
PPI	permanent pacemaker implantation
PPM	prosthesis-patient mismatch
PVL	paravalvular leak
SAV	supra-annular valve
SAVR	surgical aortic valve replacement
SEV	self-expanding valve
TAVI	transcatheter aortic valve implantation

Introduction

Prosthesis-patient mismatch (PPM) is present when the effective area of a prosthetic valve inserted into a patient is inferior to that of a normal human valve; the haemodynamic consequence of a valve that is too small compared with the size of the patient's body is the generation of higher than expected transprosthetic gradients¹. The incidence of PPM in patients undergoing transcatheter aortic valve implantation (TAVI) tends to be lower than in patients undergoing surgical aortic valve replacement (SAVR) and is reported to be between 6 and 46% for moderate PPM and between 0 and 15% for severe PPM^{2,3}. In this setting, self-expanding valves (SEV) were shown to provide a more favourable forward haemodynamic profile compared to balloon-expandable valves (BEV), possibly thanks to the supra-annular leaflet position of most SEV^{4,5}. A specific focus on patients with small aortic annuli stems from the fact that these patients showed the greatest benefit in terms of haemodynamics when treated with TAVI as compared to SAVR⁶. Similarly to the overall population, the haemodynamic advantage of TAVI in this subgroup of patients is particularly evident after SEV implantation^{7,8}. Nonetheless, while evidence of the prognostic relevance of PPM after SAVR is well described, its clinical impact in patients undergoing TAVI remains debatable^{2,5,9,10}.

In this context, the relative performance of currently available transcatheter heart valves (THV) has not been investigated thoroughly. The aim of this study was to compare the haemodynamics and clinical outcomes of contemporary prostheses in patients with severe aortic stenosis and small annuli treated with TAVI.

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Methods

STUDY DESIGN AND DEFINITION

The observational, retrospective TAVI-SMALL 2 registry included a total of 1,378 patients with severe native aortic valve stenosis and small aortic annuli (defined as an annular area <400 mm² and/or annular perimeter <72 mm on computed tomography) treated with transfemoral implantation of current-generation SEV (Evolut R and Evolut PRO [Medtronic]; ACURATE *neo* [Boston Scientific]; Portico [Abbott Vascular]) and BEV (SAPIEN 3 [Edwards Lifesciences]) at 16 high-volume centres (**Supplementary Figure 1**) between June 2011 and April 2020. 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, based on local practice and/or local institutional review board approval.

Inclusion criteria were implantation via the transfemoral route of current-generation transcatheter heart valves in native aortic stenosis (both tricuspid and non-tricuspid anatomies) in patients with small aortic annuli. Exclusion criteria were valve-in-valve procedures, TAVI for pure aortic regurgitation and lack of preprocedural computed tomographic data.

Local multidisciplinary Heart Teams evaluated all patients and confirmed the indications for TAVI. All patients underwent preprocedural screening by means of clinical assessment (patient demographic features, New York Heart Association [NYHA] Functional Class, history of angina and/or syncope, comorbidities, laboratory examinations, surgical risk, and frailty evaluation), echocardiography and computed tomography. Aortic annular, leaflet, and left ventricular outflow tract calcifications were classified and graded using a semiquantitative scoring system, as previously described¹¹. Also, computed tomography-derived annular eccentricity (maximum/minimum annular diameter) and percentage of oversizing according to the perimeter ($[(SEV \text{ perimeter/annulus perimeter}-1]/100)$ and area ($[(BEV \text{ area/annulus area}-1]/100)$) were calculated. Prosthesis type and size selection, as well as implantation technique and subsequent antithrombotic therapy, were left to the discretion of the treating physician at each centre.

The rationale of the study was to evaluate the impact of different prosthesis designs on transvalvular haemodynamics and clinical outcomes. Analyses were thus performed according to the mechanism of valve implantation, i.e., SEV (n=1,092: in particular Evolut R/Pro, n=750; ACURATE *neo*, n=170; and Portico, n=172) versus BEV (SAPIEN 3, n=286), and according to leaflet position, i.e., supra-annular valve (SAV; including Evolut R/Pro and ACURATE *neo*, n=920) versus intra-annular valve (IAV; including SAPIEN 3 and Portico, n=458). Additional analyses per implanted prosthesis were also performed.

ENDPOINTS

Primary endpoints were the pre-discharge mean aortic gradient and incidence of severe PPM. PPM was defined as an indexed effective orifice area (EOA) <0.85 cm²/m² in patients with a body mass index (BMI) <30 kg/m²; those with PPM were further divided into moderate (indexed EOA 0.65-0.85 cm²/m²) or severe PPM (indexed EOA <0.65 cm²/m²) groups. Indexed EOA <0.70 cm²/m² and <0.55 cm²/m² were the adjusted thresholds used for moderate and severe PPM, respectively, in patients with a BMI ≥30 kg/m², as per Valve Academic Research Consortium 3 endpoint definitions¹². Additional analyses of PPM without BMI adjustment were also conducted. The EOA was calculated at pre-discharge transthoracic echocardiography with the continuity equation method; stroke volume was estimated via the 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 stent¹². The secondary endpoint was the incidence of pre-discharge more than mild paravalvular leak (PVL).

STATISTICAL ANALYSIS

Continuous variables are reported as mean±standard deviation or median±interquartile range, and were compared using the Student's t-test or the Mann-Whitney U test (or Wilcoxon rank-sum test) in case of 2-group comparisons on the basis of normality of data distribution and 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 the 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' correction for continuity, or Fisher's exact test, as appropriate. Unadjusted survival curves for all-cause mortality were constructed with the use of Kaplan-Meier estimates and compared with the log-rank test. To account for selection bias between SAV- and IAV-treated patients and between SEV- and BEV-treated patients, a propensity score methodology with inverse probability of treatment weighting (IPTW) was performed^{13,14}. Propensity scores predicting each patient's probability of undergoing TAVI with SAV or IAV and TAVI with SEV or BEV, respectively, were estimated with multivariable logistic regression including variables with a difference in their distribution between the treatment groups or deemed to be clinically relevant. The following covariates were included in the models used to estimate the propensity scores: age, BMI, sex, hypertension, chronic obstructive pulmonary disease (COPD), cerebrovascular disease, coronary artery disease, previous pacemaker (PM) or implantable cardioverter defibrillator (ICD) implant, NYHA Class III or IV, Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM), preprocedural mean aortic valve (AV) gradient, ejection fraction and AV annular perimeter. Stabilised weights were computed from propensity scores by means of IPTW. The weight for SAV treatment was the inverse of the respective propensity score, whereas the weight for IAV treatment was the inverse of 1-propensity score. The weights for SEV and BEV treatment were calculated in the same way, starting from the respective propensity score. Post-IPTW adjustment, the balance of covariates between the treatment groups was assessed by means of standardised mean differences (SMD), and variables were considered balanced if the SMD was ≤10%¹³. Logistic regression models evaluating the impact of SAV versus IAV and of SEV versus BEV on severe PPM, severe PPM (non-BMI-adjusted) and more than mild PVL were weighted by IPTW, and IPTW-adjusted odds ratios (OR) with 95% confidence intervals (CI) were reported. Cox regression models evaluating the impact of SAV versus IAV and of SEV versus BEV on all-cause mortality were weighted using IPTW. The proportionality assumption was verified using the Schoenfeld residuals method. Adjusted Kaplan-Meier survival curves were generated by weighting the survival function with the IPTW in the 2 comparisons. Doubly robust IPTW adjustment was also performed, augmenting the logistic regression models with covariates that either were unbalanced after the initial IPTW adjustment (SMD >10%) or were considered clinically relevant for the outcome of interest

(severe PPM)¹⁵. Considering the relatively low number of events, the variables of interest were added separately to the IPTW-adjusted models in order to avoid overfitting.

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 two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed using Stata version 16.0 (StataCorp).

Results

STUDY POPULATION AND CLINICAL FEATURES

Baseline characteristics of patients stratified according to both the mechanism of valve expansion and leaflet position are reported in **Table 1**. Treated patients were mostly female (89%), had a mean age of 83±6 years and were at moderate surgical risk (STS-PROM 5.7±4.0%). Weight and body surface area (BSA) were higher in patients with IAV and BEV versus SAV and SEV, respectively (p<0.001), as was BMI. Small, although statistically significant, differences were noted among groups with regard to clinical variables, such as hypertension, cerebrovascular disease, coronary artery disease, NYHA Functional Class at baseline, previous percutaneous coronary intervention, COPD, angina, atrial fibrillation and previous PM or ICD implantation. **Supplementary Table 1** includes baseline characteristics of the cohorts stratified according to the single prosthesis implanted.

ECHOCARDIOGRAPHIC AND COMPUTED TOMOGRAPHY FEATURES

Baseline echocardiographic and computed tomography features are shown in **Table 2**. Slightly higher preprocedural mean and peak aortic gradients and lower measured EOA were present in SAV versus IAV and SEV versus BEV cohorts, respectively, (p<0.001). The SAV and SEV groups also had lower ejection fractions (58±11% vs 61±10% and 58±11% vs 62±10%; both p<0.001) and a higher prevalence of baseline moderate or more aortic regurgitation, mitral regurgitation or tricuspid regurgitation when compared with IAV and BEV, respectively, while bicuspid valves were less common in the two former cohorts (3.4% vs 5.8%; p=0.053 and 3.5% vs 7.3%; p=0.007). Computed tomography-derived mean diameters and the area- and perimeter-derived diameters slightly differed between groups, with a trend to wider eccentricity in the IAV and BEV groups. Severe annular and LVOT calcifications were more frequent among patients with SAV and SEV, while severe leaflet calcifications differed only when comparing SEV and BEV. On the other hand, porcelain aorta was more common in IAV versus SAV and BEV versus SEV, respectively. Baseline echocardiographic and computed tomography features of single prosthesis cohorts are reported in **Supplementary Table 2**.

PROCEDURAL FEATURES

Procedural data are shown in **Table 3**. With respect to prosthesis selection, a higher proportion of THV with a nominal diameter of 25 mm or less were implanted among the IAV and BEV groups (30.8% vs 95.2% [SAV vs IAV] and 39.9% vs 98.9% [SEV vs

Table 1. Baseline demographic characteristics according to leaflet position and mechanism of valve expansion.

Characteristic	Overall (n=1,378)	Supra-annular valve (n=920)	Intra-annular valve (n=458)	p-value (supra-annular vs intra-annular)	Self-expanding valve (n=1,092)	Balloon-expandable valve (n=286)	p-value (self-expanding vs balloon-expandable)
Age, years	82.9±6.2	83.0±6.2	82.6±6.2	0.239	83.0±6.2	82.5±6.5	0.291
Female	89.5 (1,233)	89.3 (822)	89.7 (411)	0.824	89.6 (979)	88.8 (254)	0.680
Weight, kg	64.7±14.7	63.5±14.2	67.0±15.5	<0.001	63.9±14.2	67.5±16.4	<0.001
Height, cm	157.7±7.7	157.3±7.7	158.5±7.7	0.006	157.4±7.4	159.1±8.5	0.001
Body surface area, m ²	1.65±0.19	1.63±0.19	1.68±0.19	<0.001	1.64±0.18	1.69±0.21	<0.001
Body mass index, kg/m ²	25.9±5.4	25.6±5.3	26.6±5.6	<0.001	25.7±5.3	26.6±5.8	0.018
Hypertension	85.5 (1,177)	84.1 (773)	88.2 (404)	0.042	84.5 (922)	89.2 (255)	0.047
Diabetes mellitus	26.4 (364)	25.4 (234)	28.4 (130)	0.242	26.3 (287)	26.9 (77)	0.827
Dyslipidaemia	51.8 (712)	53.2 (488)	49.1 (224)	0.159	52.7 (574)	48.4 (138)	0.197
COPD	11.5 (158)	11.0 (101)	12.5 (57)	0.417	10.3 (112)	16.1 (46)	0.006
Peripheral artery disease or previous PTA	11.7 (156)	12.6 (113)	9.7 (43)	0.114	12.2 (130)	9.5 (26)	0.214
Cerebrovascular disease	10.4 (143)	8.7 (80)	13.8 (63)	0.004	9.3 (101)	14.7 (42)	0.007
Previous PCI	21.9 (301)	20.3 (186)	25.3 (115)	0.035	21.4 (233)	23.9 (68)	0.355
Previous CABG	6.0 (82)	5.6 (51)	6.8 (31)	0.365	5.6 (61)	7.3 (21)	0.268
Previous MI	9.5 (128)	9.1 (81)	10.3 (47)	0.464	9.3 (99)	10.2 (29)	0.656
Coronary artery disease	38.2 (525)	35.9 (329)	42.9 (196)	0.012	36.0 (391)	46.8 (134)	0.001
PM or ICD	11.4 (157)	10.4 (96)	13.3 (61)	0.112	10.6 (116)	14.3 (41)	0.079
Atrial fibrillation	29.4 (269)	31.3 (182)	26.2 (87)	0.106	31.6 (225)	21.9 (44)	0.008
Angina	20.2 (230)	19.2 (165)	23.4 (65)	0.134	19.0 (185)	27.8 (45)	0.010
NYHA Class III or IV	67.4 (929)	65.6 (604)	71.0 (325)	0.048	66.5 (726)	71.0 (203)	0.149
STS-PROM, %	5.7±4.0	5.9±4.3	5.5±3.3	0.097	5.7±4.1	5.7±3.6	0.951

Values are mean±standard deviation or % (n). The values in bold represent differences between groups with p<0.100. CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; ICD: implantable cardioverter-defibrillator; MI: myocardial infarction; NYHA: New York Heart Association; PTA: percutaneous transluminal angioplasty; PCI: percutaneous coronary intervention; PM: pacemaker; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality

BEV]; p<0.001). When compared with IAV and BEV, SAV and SEV, respectively, had higher proportions of oversizing ≥15% (64.2% vs 34.3% and 61.0% vs 28.7%; p<0.001). The proportion of predilation was higher in IAV versus SAV (46.9% vs 39.5%; p<0.001) and SEV versus BEV (44.3% vs 32.9%; p<0.001). On the other hand, post-dilation was more common in the SAV (31.9% vs 19.6% in IAV; p<0.001) and SEV (32.9% vs 8.2% in BEV; p<0.001) groups. As shown in **Supplementary Table 3**, the ACURATE *neo* and Portico cohorts presented the highest rates of predilation (65.7% and 70.0%) and post-dilation (36.5% and 38.2%). No difference in the incidence of annular rupture was observed.

PROCEDURAL AND CLINICAL OUTCOMES

Clinical and procedural outcomes are reported in **Table 4**. The mean aortic valve gradients were higher in the IAV and BEV cohorts (7.8 vs 12.0 mmHg [SAV vs IAV] and 8.0 vs 13.6 mmHg [SEV vs BEV]; p<0.001). This was accompanied by a higher incidence of severe PPM with IAV and BEV (3.6% vs 8.8%; p=0.007 and 4.6% vs 8.7%; p=0.041) (**Central illustration**), in turn paralleled by a higher proportion of severe PPM with no BMI adjustment, moderate PPM and any degree of PPM (p<0.001). The SMDs before and after covariate balancing with the IPTW method are illustrated in **Figure 1** and **Supplementary Table 4**. After IPTW adjustment, SAV implantation remained a stronger protective factor for the development of severe

PPM than SEV implantation (p=0.002 and p=0.029, respectively). On the other hand, SAV alone protected from severe PPM (non-BMI-adjusted) (**Table 5**), and doubly robust analyses were more consistent with SAV than with SEV (**Supplementary Table 5**). Among single THV patients, those with Portico and SAPIEN 3 had the highest mean aortic valve gradients (9.2±4.5 and 13.6±4.7 mmHg; overall p<0.001) and incidence of severe PPM (9.0% and 8.7%; overall p=0.058) (**Supplementary Table 6, Supplementary Figure 2**).

Acute complications were rare, with no differences between groups with regard to vascular complications or major bleeding events. More than mild PVL was more common after SEV versus BEV implantation (11.6% vs 2.6%; p<0.001) (**Central illustration**), while more than moderate PVL was more common after SAV versus IAV (p=0.043) and SEV versus BEV (p=0.052). SEV, but not SAV, implantation increased the risk of more than mild PVL after IPTW adjustment (**Table 5**). Of note, the highest incidence of more than mild PVL was observed with Portico (19.0% vs 9.9% Evolut R/Pro, 11.2% ACURATE *neo* and 2.6% SAPIEN 3; p<0.001). When compared with BEV, SEV recipients had a higher incidence of permanent pacemaker implantation (PPI) and second valve implantation (13.5% vs 8.1%; p=0.013 and 2.0% vs 0.3%; p=0.065, respectively). When comparing single prostheses, patients with the SAPIEN 3 had the lowest incidence of PPI (8.1%; p=0.039) (**Supplementary Table 6**).

Table 2. Baseline echocardiographic and computed tomography characteristics according to leaflet position and mechanism of valve expansion.

Characteristic	Overall (n=1,378)	Supra-annular valve (n=920)	Intra-annular valve (n=458)	p-value (supra-annular vs intra-annular)	Self-expanding valve (n=1,092)	Balloon-expandable valve (n=286)	p-value (self-expanding vs balloon-expandable)
Mean AV gradient, mmHg	47.7±16.0	49.0±16.1	45.3±15.5	<0.001	48.6±16.1	44.3±15.3	<0.001
Maximum AV gradient, mmHg	77.6±24.8	80.0±24.7	72.9±24.2	<0.001	79.0±24.7	72.3±24.4	<0.001
EOA, cm ²	0.64±0.21	0.63±0.18	0.66±0.25	0.023	0.64±0.19	0.67±0.27	0.034
sPAP, mmHg	40.3±13.7	39.6±13.0	41.9±15.1	0.012	40.1±13.3	41.5±15.2	0.189
TAPSE, mm	20.9±3.6	21.0±3.7	20.3±2.9	0.076	21.0±3.6	20.0±2.9	0.059
Bicuspid AV	4.3 (49)	3.4 (24)	5.8 (25)	0.053	3.5 (30)	7.3 (19)	0.007
Moderate or greater AR	6.7 (83)	8.3 (67)	3.8 (16)	0.003	7.6 (74)	3.4 (9)	0.017
Moderate or greater MR	8.8 (112)	10.4 (88)	5.6 (24)	0.004	10.4 (105)	2.6 (7)	<0.001
Moderate or greater TR	6.9 (74)	8.1 (54)	5.0 (20)	0.056	7.8 (65)	3.8 (9)	0.033
Ejection fraction, %	59.2±10.7	58.1±10.9	61.4±9.9	<0.001	58.4±10.6	62.2±10.2	<0.001
LVEF <40%	5.1 (71)	6.1 (56)	3.3 (15)	0.026	5.7 (62)	3.1 (9)	0.085
CT data							
Mean annular diameter, mm	21.2±1.3	21.2±1.4	21.3±1.1	0.084	21.2±1.3	21.4±1.0	0.005
Maximum diameter, mm	23.7±1.8	23.6±1.9	23.9±1.6	<0.001	23.6±1.9	24.0±1.4	0.005
Minimum diameter, mm	18.8±1.8	18.8±1.9	18.7±1.6	0.457	18.7±1.9	18.9±1.5	0.212
Annular eccentricity	1.27±0.17	1.27±0.17	1.29±0.17	0.029	1.27±0.17	1.28±0.18	0.553
Mean aortic annular perimeter, mm	66.9±4.3	67.3±3.6	66.0±5.3	<0.001	67.4±3.6	65.0±5.9	<0.001
Mean aortic annular area, mm ²	350.1±34.4	347.1±35.5	355.5±31.6	<0.001	346.5±35.1	362.3±28.7	<0.001
Area-derived diameter, mm	21.1±1.1	21.0±1.1	21.3±1.0	<0.001	21.0±1.1	21.5±0.9	<0.001
Perimeter-derived diameter, mm	21.3±1.5	21.4±1.2	21.0±1.7	<0.001	21.5±1.1	20.7±1.9	<0.001
Severe leaflet calcification	19.3 (185)	18.5 (107)	20.6 (78)	0.421	17.1 (115)	24.5 (70)	0.008
Severe annular calcification	4.4 (38)	6.2 (29)	2.2 (9)	0.005	5.6 (34)	1.5 (4)	0.008
Severe LVOT calcification	4.1 (40)	5.7 (34)	1.6 (6)	0.001	5.2 (36)	1.4 (4)	0.006
LMCA diameter, mm	12.5±2.6	12.4±2.5	12.6±2.7	0.184	12.3±2.5	12.8±2.6	0.003
RCA diameter, mm	14.4±2.8	14.2±3.0	14.6±2.5	0.034	14.3±2.9	14.7±2.5	0.042
Sinotubular junction diameter, mm	25.9±2.7	25.8±2.8	26.0±2.5	0.144	25.9±2.8	25.9±2.4	0.927
Sinus of Valsalva diameter, mm	28.7±2.5	28.8±2.5	28.6±2.5	0.180	28.9±2.5	28.4±2.5	0.013
Ascending aorta diameter, mm	31.9±3.9	31.6±3.9	32.3±3.9	0.016	31.9±4.0	32.0±3.8	0.657
Porcelain aorta	5.1 (61)	2.7 (21)	9.4 (40)	<0.001	3.2 (30)	11.9 (31)	<0.001

Values are mean±standard deviation or % (n). The values in bold represent differences between groups with p<0.100. AR: aortic regurgitation; AV: aortic valve; CT: computed tomography; EOA: effective orifice area; LMCA: left main coronary artery; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; MR: mitral regurgitation; RCA: right coronary artery; RV: right ventricular; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation

At a median follow-up of 377 days (interquartile range 168-700 days), no differences were observed between patients in the SAV versus IAV and SEV versus BEV cohorts in terms of all-cause mortality (9.4% vs 11.9%; p=0.172 and 9.8% vs 12.3%; p=0.218). When compared with SAV at Kaplan-Meier analysis, the use of IAV did not result in an increased risk of all-cause mortality (p=0.748). Similarly, no difference in all-cause mortality was observed between SEV and BEV (p=0.687) at the time-to-event analysis. Results were confirmed when comparing single-prosthesis cohorts (p=0.667) (**Supplementary Figure 3**). No significant differences in all-cause mortality were present when comparing SAV versus IAV and SEV versus BEV at Cox regression analysis, neither before nor after IPTW adjustment (**Table 5, Figure 2**). A trend towards decreased cardiovascular mortality was observed when comparing SAV and IAV (2.8% vs 4.5%; p=0.099), with the only significant difference at analysis

per single prosthesis present when comparing Evolut R/Pro with Portico (2.7% vs 5.4%; p=0.021) (**Supplementary Table 6**).

The incidence of myocardial infarction, stroke or transient ischaemic attack and hospitalisation for heart failure did not differ between groups. Acute kidney injury was more common after ACURATE *neo* and Portico implantations (p=0.020) (**Supplementary Table 6**) in the analysis per single prosthesis.

Discussion

The objective of the present study was to compare the forward flow haemodynamics and clinical outcomes of the currently available THV in patients with severe aortic stenosis and small annuli. The main findings are the following:

- IAV and BEV are associated with increased mean aortic valve (AV) gradients and the incidence of severe PPM when compared to SAV and SEV, respectively;

Table 3. Procedural characteristics according to leaflet position and mechanism of valve expansion.

Characteristic	Overall (n=1,378)	Supra-annular valve (n=920)	Intra-annular valve (n=458)	p-value (supra-annular vs intra-annular)	Self-expanding valve (n=1,092)	Balloon-expandable valve (n=286)	p-value (self-expanding vs balloon-expandable)
Valve size 25 mm or less	52.2 (719)	30.8 (283)	95.2 (436)	<0.001	39.9 (436)	98.9 (283)	<0.001
Oversizing by perimeter	15.0±8.7	17.5±7.2	11.2±9.9	<0.001	17.0±7.1	9.5±11.4	<0.001
Oversizing by perimeter ≥15%	54.1 (745)	64.2 (591)	33.6 (154)	<0.001	61.0 (666)	27.6 (69)	<0.001
Oversizing by area	36.9±21.2	45.5±18.4	22.0±17.3	<0.001	44.4±17.7	11.9±10.8	<0.001
Oversizing by area ≥15%	82.6 (1,138)	96.3 (886)	55.0 (252)	<0.001	96.7 (1,056)	28.7 (82)	<0.001
Oversizing ≥15%	54.3 (748)	64.2 (591)	34.3 (157)	<0.001	61.0 (666)	28.7 (82)	<0.001
Predilatation	41.9 (573)	39.5 (361)	46.9 (212)	0.009	44.3 (481)	32.9 (92)	0.001
Post-dilatation	27.8 (380)	31.9 (292)	19.6 (88)	<0.001	32.9 (357)	8.2 (23)	<0.001
Annular rupture	0.3 (4)	0.2 (2)	0.4 (2)	0.548	0.3 (3)	0.3 (1)	0.909

Values are mean±standard deviation or % (n). The values in bold represent differences between groups with p<0.100. Oversizing ≥15% refers to oversizing by perimeter ≥15% for self-expanding valves and oversizing by area ≥15% for balloon-expandable valves.

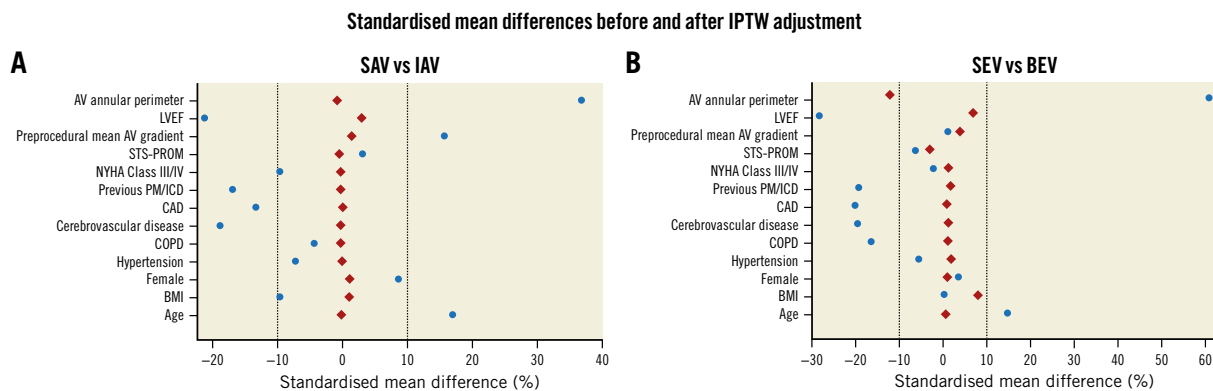


Figure 1. Standardised mean differences (SMDs) of the covariates used for propensity score modelling before and after inverse probability of treatment weighting (IPTW) adjustment for comparisons of SAV versus IAV (A) and SEV versus BEV (B). After adjustment, all covariates showed SMDs within the 10% cut-off (dashed vertical lines), except AV annular perimeter in the SEV versus BEV comparison (−11.2%). AV: aortic valve; BEV: balloon-expandable valve; BMI: body mass index; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; IAV: intra-annular valve; ICD: implantable cardioverter-defibrillator; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PM: pacemaker; SAV: supra-annular valve; SEV: self-expanding valve; STS-PROM: Society of Thoracic Surgery Predicted Risk of Mortality

- The incidence of more than mild PVL was higher after SEV versus BEV, but not SAV versus IAV implantation;
- IPTW-adjusted logistic regression analyses confirmed SAV as a protective factor from severe PPM, regardless of its definition, and BEV as protective factor from more than mild PVL.

Of patients treated with SAVR, up to one-half and one-quarter have PPM and severe PPM, respectively². A recent meta-analysis conducted on 745 patients described a relative risk reduction of 77% in the incidence of PPM in patients treated with TAVI as compared to surgery⁹. Nonetheless, not all THV are born equal. Indeed, not only did comparison of SAVR and TAVI with a SAPIEN 3 intra-annular BEV in the PARTNER 3 Trial show similar transvalvular gradients and incidence of severe PPM (4.6 vs 6.3%, respectively; p=0.30)¹⁶, but also SAPIEN 3 implantation was identified as an independent predictor of PPM in the OCEAN-TAVI registry¹⁷. Notwithstanding the slight, although significant, difference in BSA between groups, the lower mean AV gradients and incidence of severe PPM with SAV versus IAV implantation further clarify the role of leaflet

position in the development of PPM in patients with small annuli, in line with previous evidence from the TAVI-SMALL registry, which showed an increased risk of PPM in SEV with intra-annular leaflets^{8,10}. Similarly, in a recent subanalysis of propensity score-matched patients from the OCEAN-TAVI registry treated with a third-generation THV, Evolut R outperformed SAPIEN 3 in terms of the mean AV gradient¹⁸. Schofer et al reported data from 1,309 patients undergoing TAVI with different THV: the lowest rate of severe PPM was present with supra-annular SEV (4%), whereas the highest rate was detected in patients with self-expanding cusp-fixed prostheses (25%) and intra-annular BEV (24%)¹⁹. The importance of leaflet position in THV implanted in patients with small annuli has been recently reported in a retrospective registry of 1,069 patients, where a higher incidence of PPM was found after the implantation of intra-annular BEV or intra-annular mechanically expandable THV compared to intra- and supra-annular SEV; SEV implantation itself was linked to a lower incidence of PPM²⁰. The haemodynamic advantage of TAVI with supra-annular valves

Table 4. Post-procedural characteristics and follow-up according to leaflet position and mechanism of valve expansion.

Characteristic	Overall (n=1,378)	Supra-annular valve (n=920)	Intra-annular valve (n=458)	p-value (supra-annular vs intra-annular)	Self-expanding valve (n=1,092)	Balloon-expandable valve (n=286)	p-value (self-expanding vs balloon-expandable)
Predischarge							
Any vascular complication	14.0 (192)	13.6 (124)	14.8 (68)	0.545	14.2 (154)	13.3 (38)	0.678
Major vascular complication	4.7 (65)	4.4 (40)	5.5 (25)	0.386	4.5 (49)	5.6 (16)	0.453
Need for second valve implantation	1.7 (23)	1.7 (16)	1.5 (7)	0.770	2.0 (22)	0.3 (1)	0.065
Mean AV gradient, mmHg	9.3±4.8	7.8±3.9	12.0±5.1	<0.001	8.0±4.1	13.6±4.7	<0.001
Maximum AV gradient, mmHg	16.5±8.2	14.5±6.8	22.4±8.9	<0.001	14.8±7.1	24.8±7.7	<0.001
EOA, cm ²	1.61±0.45	1.74±0.50	1.47±0.34	<0.001	1.72±0.49	1.41±0.29	<0.001
Indexed EOA, cm ² /m ²	1.00±0.30	1.11±0.31	0.88±0.23	<0.001	1.08±0.31	0.84±0.19	<0.001
Any PPM (non-BMI-adjusted)	33.6 (211)	16.9 (56)	52.4 (155)	<0.001	20.5 (84)	58.3 (127)	<0.001
Any PPM	28.0 (176)	13.5 (45)	44.3 (131)	<0.001	16.6 (68)	49.5 (108)	<0.001
Moderate PPM (non-BMI-adjusted)	25.0 (157)	12.6 (42)	38.8 (115)	<0.001	14.9 (61)	44.0 (96)	<0.001
Moderate PPM	22.0 (138)	9.9 (33)	35.5 (105)	<0.001	11.9 (49)	40.8 (89)	<0.001
Severe PPM (non-BMI-adjusted)	8.6 (54)	4.2 (14)	13.5 (40)	<0.001	5.6 (23)	14.2 (31)	<0.001
Severe PPM	6.0 (38)	3.6 (12)	8.8 (26)	0.007	4.6 (19)	8.7 (19)	0.041
More than mild PVL	9.4 (107)	10.1 (73)	8.3 (34)	0.315	11.6 (100)	2.6 (7)	<0.001
More than moderate PVL	1.1 (12)	1.5 (11)	0.2 (1)	0.043	1.4 (12)	0	0.052
PPI	12.4 (169)	13.2 (120)	10.7 (49)	0.187	13.5 (146)	8.1 (23)	0.013
BARC major bleeding	5.9 (81)	6.4 (59)	4.8 (22)	0.231	5.9 (64)	5.9 (17)	0.958
Follow-up							
All-cause mortality	10.3 (129)	9.4 (76)	11.9 (53)	0.172	9.8 (95)	12.3 (34)	0.218
Cardiovascular mortality	3.4 (42)	2.8 (22)	4.5 (20)	0.099	3.2 (31)	4.0 (11)	0.537
Myocardial infarction	1.1 (12)	1.0 (7)	1.3 (5)	0.763	1.2 (10)	0.7 (2)	0.741
TIA/stroke	3.3 (36)	3.9 (28)	2.3 (8)	0.182	3.6 (29)	2.6 (7)	0.404
Acute kidney injury	2.9 (27)	3.2 (19)	2.4 (8)	0.497	3.4 (22)	1.9 (5)	0.284
Hospitalisation for HF	6.2 (65)	5.9 (42)	6.8 (23)	0.598	6.1 (48)	6.6 (17)	0.770
Values are mean±standard deviation or % (n). The values in bold represent differences between groups with p<0.100. AV: aortic valve; BARC: Bleeding Academic Research Consortium; BMI: body mass index; EOA: effective orifice area; HF: heart failure; PPI: permanent pacemaker implantation; PPM: prosthesis-patient mismatch; PVL: paravalvular leak; TIA: transient ischaemic attack							

in patients with small annuli has been addressed in other studies. Indeed, in the CHOICE-Extend registry, the supra-annular SEV (Evolut R) also had higher indexed EOA and lower post-procedural mean gradients and PPM than the intra-annular BEV (SAPIEN 3)⁷. Another supra-annular SEV, the ACURATE *neo*, was comparable to the Evolut R, in terms of the incidence of severe PPM, in a recent randomised trial²¹, which similarly resulted in lower gradients and lower rate of severe PPM when compared with the SAPIEN 3 among 246 propensity score-matched patients with small aortic annuli²². These findings were also confirmed in Japanese patients with very small annuli²³. In addition, both oversizing and post-dilation, previously shown to protect from the incidence of PPM¹⁰, were more common in SAV and SEV versus IAV and BEV, respectively. Of note, the method used for measuring PPM appears to be important. Indeed, not only did reclassification of PPM using a predicted EOA reveal a lower incidence with respect to a measured EOA-based method in a large cohort treated mainly with BEV, but also a stronger association with high residual gradient was appreciated with predicted versus measured PPM. Further studies will need to be undertaken to adequately address the definition of PPM²⁴.

The lower incidence of more than mild PVL after BEV implantation parallels available randomised evidence^{25,26} and supports the relevance

of an external skirt or seal at the inflow portion of the THV, also in patients with small annuli. We expect new prosthesis iterations, namely Navitor (Abbott) (Sondergaard L. 30-day outcomes from a next generation TAVI device with an active sealing cuff. EuroPCR 2021. Paris, France) and the ACURATE *neo2* (Boston Scientific),²⁷ to mitigate the rates of PVL. Of note, the observed increased risk of acute kidney injury with the Portico and ACURATE *neo* might also be related to the increased use of contrast agent and the performance of predilation and post-dilation, undertaken in order to mitigate the rates of PVL²⁸.

The increased risk of PPI after SEV versus BEV is similar to results from direct randomised comparisons in the SOLVE-TAVI, CHOICE and PORTICO-IDE trials^{25,26}. Also, the significant difference in the incidence of PPI after implantation of SAPIEN 3 versus Evolut R/Pro or Portico, but not ACURATE *neo*, confirms the favourable profile of the latter prosthesis among SEV in terms of impact on persistent conduction disturbances after TAVI^{21,29}.

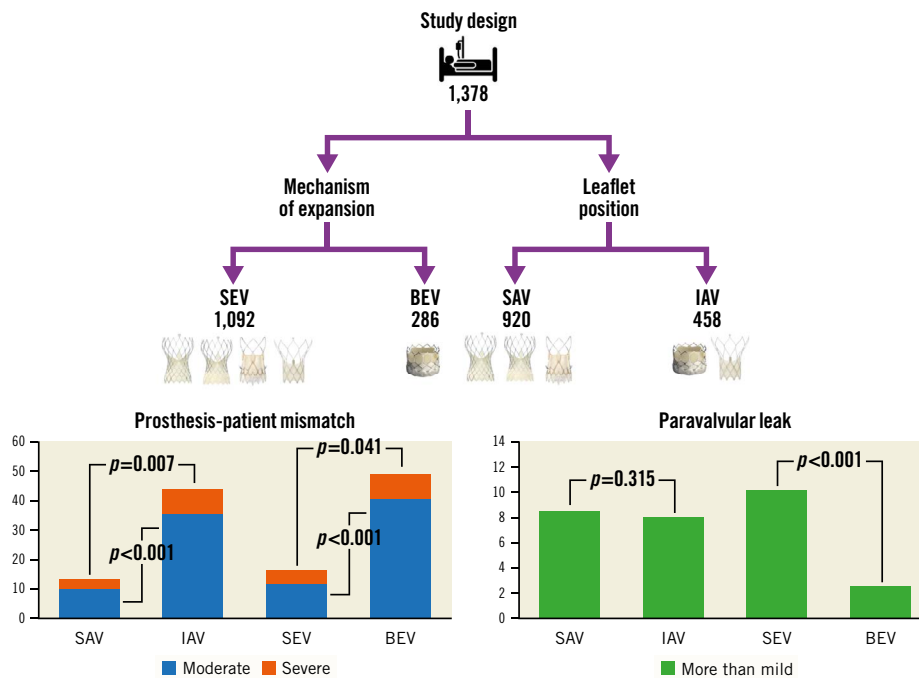
The absence of significant differences in all-cause mortality between groups, confirmed at IPTW-adjusted analyses, needs to be acknowledged in light of the non-uniform distribution of patients among groups and the related lack of power in assessing this outcome. These results parallel those from the TAVI-SMALL registry⁸ and those recently reported in a multicentre analysis of patients with

Table 5. Unadjusted and adjusted risk of clinical outcomes.

Characteristic	Overall (n=1,378)	Supra-annular valve (n=920)	Intra-annular valve (n=458)	Unadjusted OR/HR (95% CI)*	p-value	IPTW-adjusted HR/OR (95% CI)†	p-value
Severe PPM	6.0 (38)	3.6 (12)	8.8 (26)	0.22 (0.11-0.44)	<0.001	0.25 (0.10-0.60)	0.002
Severe PPM (non-BMI-adjusted)	8.6 (54)	4.2 (14)	13.5 (40)	0.28 (0.15-0.53)	<0.001	0.36 (0.16-0.82)	0.015
More than mild PVL	9.4 (107)	10.1 (73)	8.3 (34)	1.24 (0.81-1.90)	0.319	0.98 (0.60-1.60)	0.944
All-cause mortality	10.3 (129)	9.4 (76)	11.9 (53)	1.10 (0.77-1.56)^	0.604	1.34 (0.81-2.23)^	0.255
Characteristic	Overall (n=1,378)	Self-expanding valve (n=1,092)	Balloon-expandable valve (n=286)	Unadjusted OR/HR (95% CI)*	p-value	IPTW-adjusted HR/OR (95% CI)†	p-value
Severe PPM	6.0 (38)	4.6 (19)	8.6 (19)	0.25 (0.13-0.48)	<0.001	0.40 (0.18-0.91)	0.029
Severe PPM (non-BMI-adjusted)	8.6 (54)	5.6 (23)	14.2 (31)	0.36 (0.20-0.63)	<0.001	0.66 (0.33-1.33)	0.246
More than mild PVL	9.4 (107)	11.6 (100)	2.6 (7)	4.87 (2.24-10.6)	<0.001	4.85 (1.70-13.9)	0.003
All-cause mortality	10.3 (129)	9.8 (95)	12.3 (34)	1.26 (0.85-1.87)^	0.258	1.59 (0.90-2.81)^	0.109

Results reported as % (number of events), HR, OR, and 95% CI. Comparisons are SAV versus IAV and SEV versus BEV. *Generated with univariable logistic/Cox regression analysis. †Generated with logistic/Cox regression modelling after IPTW adjustment. ^HR was analysed via Cox regression analysis for the outcome all-cause mortality (at a median follow-up of 377 days). All other outcomes had OR assessed via logistic regression analysis. The values in bold represent differences between groups with p<0.100. AV: aortic valve; BEV: balloon-expandable valve; BMI: body mass index; CI: confidence interval; HR: hazard ratio; IAV: intra-annular valve; IPTW: inverse probability of treatment weighting; OR: odds ratio; PPM: prosthesis-patient mismatch; PVL: paravalvular leak; SAV: supra-annular valve; SEV: self-expanding valve

EuroIntervention

CENTRAL ILLUSTRATION Incidence of PPM and more than mild PVL according to leaflet position and mechanism of valve expansion.

BEV: balloon-expandable valve; IAV: intra-annular valve; PPM: prosthesis-patient mismatch; PVL: paravalvular leak; SAV: supra-annular valve; SEV: self-expanding valve

small annuli, where 30-day and 12-month mortality rates were similar between patients treated with the SAPIEN 3, Evolut, ACURATE neo, Portico and Lotus THV²⁰. Of note, numerical differences favouring SAV versus IAV and SEV versus BEV were present, as were differences in cardiovascular mortality when comparing SAV and IAV (2.8% vs 4.5%; p=0.099) and Evolut R/Pro with Portico (2.7% vs 5.4%; p=0.021), although the observational, retrospective nature of the current study represents an additional relevant

limitation. Previous 30-day results from head-to-head randomised comparisons of SAV and IAV revealed either no difference in the valve-related efficacy endpoint between groups²⁵ or a higher incidence of the safety and efficacy endpoint in SAV versus IAV²⁹. The possibility that the favourable forward haemodynamic profile linked to SAV implantation might be of prognostic significance in patients with small annuli will need to be further addressed at long-term follow-up analysis and in randomised studies. In this setting, results

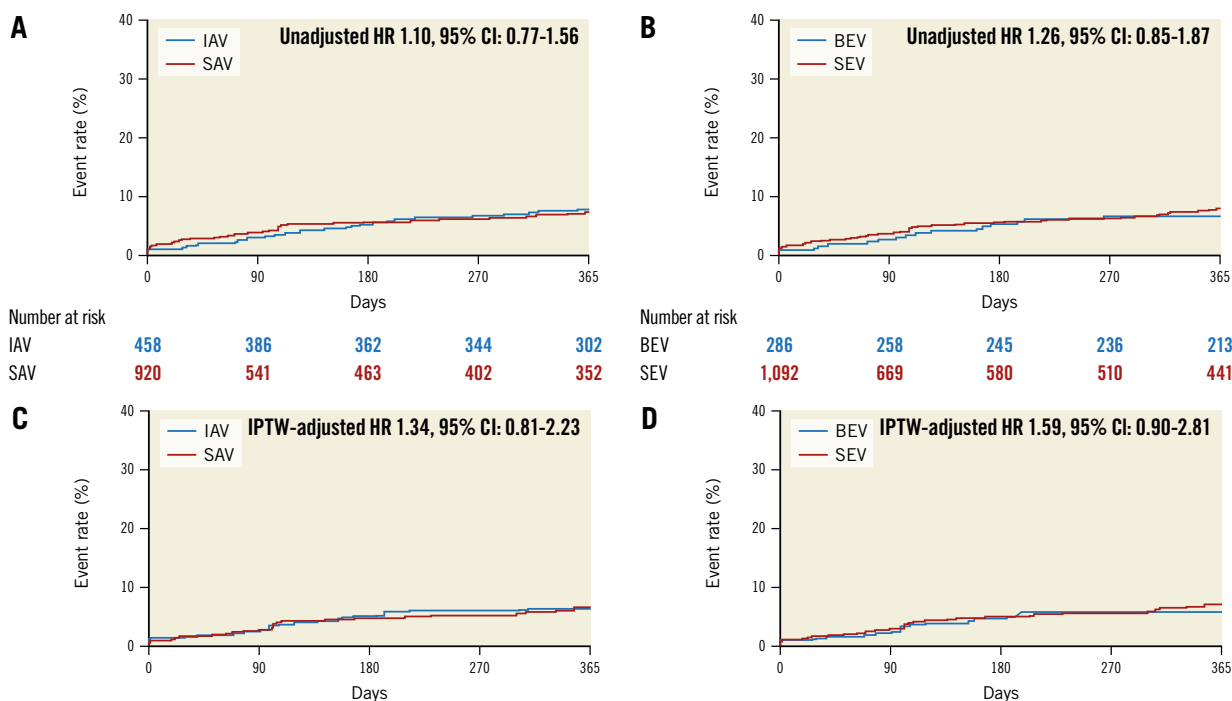


Figure 2. Non-adjusted and IPTW-adjusted Kaplan-Meier curves of all-cause mortality in patients treated with SAV versus IAV and SEV versus BEV. At a median follow-up of 377 (interquartile range 168-700) days, no significant difference in the risk of all-cause mortality was evident in either the non-adjusted comparison of SAV versus IAV (A) and SEV versus BEV (B) the adjusted comparison of SAV versus IAV (C) and SEV versus BEV (D). The number of patients at risk during follow-up is not applicable in the adjusted inverse probability of treatment weight analysis. BEV: balloon-expandable valve; CI: confidence interval; HR: hazard ratio; IAV: intra-annular valve; IPTW: inverse probability of treatment weighting. SAV: supra-annular valve; SEV: self-expanding valve

from the ongoing Small Annuli Randomized to Evolut or SAPIEN Trial (SMART) will be of paramount importance (ClinicalTrials.gov: NCT04722250). No differences between groups were observed at 12 months, in terms of transient ischaemic attack or stroke, myocardial infarction or hospitalisation for heart failure.

Limitations

First, selection and confounding bias cannot be excluded because of the observational nature of our study. Second, underreporting or missing echocardiographic and follow-up data need to be acknowledged. Third, the absence of core laboratory echocardiographic and computed tomography evaluation could have impacted the assessment of baseline and procedural results. Fourth, implantation depth was not assessed in the current study. Fifth, data on simultaneous haemodynamic measurements were not available. Also, the incidence of predicted PPM was not assessed in this study. Finally, we need to acknowledge the lack of power in assessing differences in all-cause mortality deriving from the non-uniform distribution of patients among groups, although it should be recognised that our retrospective cohort study provides a relevant real-world picture of the practice at 16 high-volume valve centres.

Conclusions

The TAVI-SMALL 2 multicentre observational retrospective registry, including patients with aortic stenosis and small aortic annuli

undergoing transfemoral TAVI, suggests that the implantation of SAV and SEV yields lower mean aortic valve gradients and protects from the development of severe PPM when compared to IAV and BEV, respectively, at the expense of higher rates of PVL. Also, PPI was more common after SEV than BEV implantation. Randomised trials assessing the long-term prognostic relevance of the type of THV implanted in small aortic annuli are eagerly awaited.

Impact on daily practice

The TAVI-SMALL 2 international multicentre registry is the largest to date to compare the performance of contemporary transcatheter valves in patients with aortic stenosis and small annuli undergoing TAVI. SAV and SEV yielded lower mean aortic valve gradients and incidence of severe PPM when compared to IAV and BEV, respectively, at the expense of higher rates of paravalvular leak. Permanent pacemaker implantation was more common after SEV than BEV implantation. This study supports the implantation of SAV for superior forward flow haemodynamics in patients with small annuli. The long-term relevance of PPM after TAVI will need to be addressed in larger randomised studies.

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Guest editor

This paper was guest edited by Franz-Josef Neumann, MD; Department of Cardiology and Angiology II, University Heart Center Freiburg - Bad Krozingen, Bad Krozingen, Germany.

Conflict of interest statement

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Supplementary data

Supplementary Table 1. Baseline demographic characteristics according to prosthesis implanted.

Supplementary Table 2. Baseline echocardiographic and computed tomography characteristics according to prosthesis implanted.

Supplementary Table 3. Procedural characteristics according to prosthesis implanted.

Supplementary Table 4. Standardised mean differences (SMDs) of the covariates used for propensity score modelling before and after inverse probability of treatment weight (IPTW) adjustment.

Supplementary Table 5. Prediction of severe prosthesis-patient mismatch using doubly-robust inverse probability of treatment weight (IPTW)-adjusted logistic regression analysis.

Supplementary Table 6. Post-procedural characteristics and follow-up according to prosthesis implanted.

Supplementary Figure 1. Map of centres involved in the study.

Supplementary Figure 2. Incidence of severe and moderate PPM according to prosthesis type.

Supplementary Figure 3. Kaplan-Meier analysis assessing all-cause mortality according to prosthesis type.

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