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Transcatheter Self-Expandable Valve Implantation for Aortic Stenosis in Small Aortic Annuli

The TAVI-SMALL Registry

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate and compare the outcomes of transcatheter self-expandable prostheses in patients with small annuli.

BACKGROUND Transcatheter aortic heart valves appear to have better performance than surgical valves in terms of prosthesis-patient mismatch, especially in patients with aortic stenosis with small aortic annuli.

METHODS TAVI-SMALL (International Multicenter Registry to Evaluate the Performance of Self-Expandable Valves in Small Aortic Annuli) is a retrospective registry of patients with severe aortic stenosis and small annuli (annular perimeter <72 mm or area <400 mm^2 on computed tomography) treated with transcatheter self-expandable valves (n = 859; Evolut R, n = 397; Evolut PRO, n = 84; ACURATE, n = 201; Portico, n = 177). Primary endpoints were post-procedural mean aortic gradient, indexed effective orifice area, and rate of severe prosthesis-patient mismatch.

RESULTS Pre-discharge gradients were consistently low in every group, with a slight benefit with the Evolut R (8.1 mm Hg; 95% confidence interval [CI]: 7.7 to 8.5 mm Hg) and Evolut PRO (6.9 mm Hg; 95% CI: 6.3 to 7.6 mm Hg) compared with the ACURATE (9.6 mm Hg; 95% CI: 8.9 to 10.2 mm Hg) and Portico (8.9 mm Hg; 95% CI: 8.2 to 9.6 mm Hg) groups ($p < 0.001$). Mean indexed effective orifice area was 1.04 cm^2/m^2 (95% CI: 1.01 to 1.08 cm^2/m^2) with a trend toward lower values with the Portico. No significant differences were reported in terms of severe prosthesis-patient mismatch (overall rate 9.4%; $p = 0.134$), permanent pacemaker implantation (15.6%), and periprocedural and 1-year adverse events. Pre-discharge more than mild paravalvular leaks were significantly more common with the Portico (19.2%) and less common with the Evolut PRO (3.6%) compared with the Evolut R (11.8%) and ACURATE (9%) groups.

CONCLUSIONS Transcatheter self-expandable valves showed optimal clinical and echocardiographic results in patients with small aortic annuli, although supra-annular functioning transcatheter heart valves seemed to slightly outperform intra-annular functioning ones. The role of transcatheter aortic valve replacement with self-expandable valves for the treatment of aortic stenosis in patients with small annuli needs to be confirmed in larger trials.
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ABBREVIATIONS AND ACRONYMS

ACU = ACURATE

BEV = balloon-expandable valve

CI = confidence interval

EvPRO = CoreValve Evolut PRO

EvR = CoreValve Evolut R

iEOA = indexed effective orifice area

LV = left ventricular

OR = odds ratio

PM = pacemaker

POR = Portico

PPM = prosthesis-patient mismatch

PVL = paravalvular leak

SAVR = surgical aortic valve replacement

SEV = self-expandable valve

TA = transapical

TAVR = transcatheter aortic valve replacement

TF = transfemoral

Transcatheter aortic valve replacement (TAVR) in patients affected by aortic stenosis has been shown to have good clinical results in a wide range of patients, from inoperable subjects to those at high surgical risk (1–5), and furthermore in patients at moderate (6–8) and even low (9–11) predicted risk for surgical complications.

Nevertheless, some technical aspects may reduce the efficacy of percutaneous procedures, despite progressive technological improvements (newer generation valves and delivery systems, detailed pre-procedural imaging and planning) (12) and increasing operator expertise. One of the most relevant anatomic features that could influence hemodynamic and clinical outcomes after TAVR is aortic annular size, which may play a major role in determining post-procedural gradients, effective orifice area, and paravalvular leak (PVL) (13,14).

Previous studies suggested that surgical aortic valve replacement (SAVR) (15) is associated with a high risk for prosthesis-patient mismatch (PPM) in patients with small annuli, which in turn may result in worse prosthetic performance and eventually in worse mid-term clinical outcomes. A post hoc analysis of pivotal trials that compared TAVR with surgery showed that transcatheter bioprostheses offered better hemodynamic results and a reduced risk for developing PPM (16,17). In addition, a few studies compared outcomes after implantation of balloon-expandable valves (BEVs) and self-expandable valves (SEVs) in patients with small aortic annuli, suggesting improved hemodynamic performance with SEVs compared with BEVs (18,19).

However, no direct comparisons of the performance of SEVs in this subgroup of patients are available. Therefore, the aim of the present study was to assess hemodynamic and clinical outcomes of patients affected by severe aortic stenosis with small aortic annuli undergoing TAVR with SEVs.

METHODS

STUDY DESIGN AND DEFINITIONS. Between June 2011 and October 2018, consecutive patients with aortic stenosis and small aortic annuli treated with transcatheter implantation of current-generation SEVs at 9 high-volume, experienced European centers (Online Figure 1), were included in the TAVI-SMALL (International Multicenter Registry to Evaluate the Performance of Self-Expandable Valves in Small Aortic Annuli) registry.

Key inclusion criteria were the use of a current-generation SEV (CoreValve Evolut R [EvR] and Evolut PRO [EvPRO], Medtronic, Minneapolis, Minnesota; ACURATE [ACU], Boston Scientific, Marlborough, Massachusetts; and Portico [POR], Abbott Vascular, Santa Clara, California) in native aortic stenosis (both tricuspid and nontricuspid anatomies) in patients with small aortic annuli. A small aortic annulus was defined as annular area <400 mm^2 and/or annular perimeter <72 mm on computed tomography; these thresholds were selected on the basis of previous studies on this topic (17–20).

Main exclusion criteria were valve-in-valve procedures, TAVR for pure aortic regurgitation, and a lack of pre-procedural computed tomographic data. No limits were set with respect to age, comorbidities, risk class, and access site. The ACU TransApical transcatheter heart valve, which is no longer commercially available, was included because it was still marketed at the time of data collection.

Local multidisciplinary heart teams evaluated all patients and confirmed the indications for TAVR. All patients underwent pre-procedural screening by means of clinical assessment (patient demographic features, New York Heart Association functional class, history of angina and/or syncope, comorbidities, laboratory examinations, surgical risk, and frailty evaluation), echocardiography, and multidetector computed tomography.

Aortic annular, leaflet, and left ventricular (LV) outflow tract calcifications were classified and graded using a semiquantitative scoring system, as

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previously described (21). Prosthesis type and size selection, as well as implantation technique and subsequent antithrombotic therapy, were left to discretion of the treating physician at each center.

This study complied with the Declaration of Helsinki and was approved by local ethics committees. Each patient provided written informed consent for the procedure and subsequent data collection.

DATA COLLECTION AND FOLLOW-UP PROCEDURES. Dedicated databases were used for data collection. Active follow-up was performed by means of telephone interviews or follow-up visits.

ENDPOINTS. Coprimary endpoints were short-term mean aortic valve gradient, indexed effective orifice area (iEOA), and rate of severe PPM. PPM was defined as moderate in case of post-procedural iEOA <0.85 cm^2/m^2 and severe in case of post-procedural iEOA <0.65 cm^2/m^2 (22).

Secondary procedural endpoints were short-term rate of more than mild PVL, need for permanent pacemaker (PM) implantation, and major vascular complications. Secondary clinical endpoints included the 1-year rate of all-cause death, rehospitalization for heart failure, ischemic stroke, myocardial infarction, and major bleeding.

Echocardiographic and clinical endpoints were defined according to the Valve Academic Research Consortium-2 (23). Bleeding events were defined according to the Bleeding Academic Research Consortium. Major bleeding was defined as Bleeding Academic Research Consortium grade ≥3 bleeding events (24).

STATISTICAL ANALYSIS. Continuous variables are reported as mean ± SD and were compared using Student's *t*-test or the Mann-Whitney *U* or Wilcoxon test in case of 2-group comparisons on the basis of normality of data distribution, verified using the Kolmogorov-Smirnov goodness-of-fit test. In case of a skewed distribution, variables are reported as median (interquartile range). 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. For the primary endpoints of pre-discharge gradient and iEOA, 95% confidence intervals (CIs) are also reported. Categorical variables are reported as number (percentage) and were compared using the chi-square test without Yates' correction for continuity or the Fisher exact test as appropriate. A subgroup analysis was performed to assess eventual differences in terms of post-procedural mean gradient among patients with very small aortic annuli, defined as perimeter- or area-derived diameter <20 mm (25). Furthermore, linear regression was performed to assess the correlation between mean gradient and iEOA with annular perimeter. Last, we performed a multivariate binary logistic regression to assess if the implantation of any SEVs could be independently associated with moderate or severe PPM. All variables associated (with p values <0.1) with the outcome at univariate analysis were included in the model. 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. Two-sided p values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 24 (SPSS, Chicago, Illinois) and Stata version 13.1 (StataCorp, College Station, Texas).

RESULTS

STUDY POPULATION AND CLINICAL CHARACTERISTICS. A total of 859 patients with small aortic annuli treated with TAVR were included: EvR, n = 397; EvPRO, n = 84; ACU, n = 201; and POR, n = 177.

Baseline features of the study population stratified by SEV type are shown in Table 1. The mean age was 82.4 ± 0.23 years. The vast majority of patients were women (89.9%). Mean Society of Thoracic Surgeons Predicted Risk of Mortality score was 5.7 ± 0.15%. At baseline, 72.9% of patients were in New York Heart Association functional class III or IV. No significant differences were noted between groups in terms of clinical history, with the exception of chronic obstructive pulmonary disease (which was more common in the EvR and ACU compared with EvPRO and POR groups) and previous percutaneous coronary interventions (less frequent in patients treated with the EvPRO).

Baseline echocardiographic and computed tomographic features are shown in Table 2. There were no differences among groups in terms of echocardiographic variables, with the exception of slightly lower LV end-diastolic volume and pre-procedural mean and peak aortic gradients in the POR group compared with the other groups. Mean aortic annular area was 347.23 mm^2, while mean aortic annular perimeter was 67.3 mm.

PROCEDURAL OUTCOMES. Procedural outcomes are shown in Table 3. The majority of patients were treated by transfemoral (TF) access (87.3%), with a significantly lower percentage of patients reported in the ACU group (69.7%; p < 0.001) compared with the other groups because of the use of the transapical

TABLE 1 Baseline Clinical Characteristics

	Overall (N = 859)	EvR (n = 397)	EvPRO (n = 84)	ACU (n = 201)	POR (n = 177)	p Value
Age, yrs	82.4 ± 0.2	82.0 ± 0.4	83.5 ± 0.7	82.7 ± 0.4	82.7 ± 0.5	0.244
Male	87 (10.1)	43 (10.8)	9 (10.7)	21 (10.5)	14 (7.9)	0.747
BMI, kg/m^2	26.6 ± 0.2	26.8 ± 0.4	26.5 ± 0.9	26.6 ± 0.4	26.2 ± 0.4	0.763
BSA, m^2	1.7 ± 0.01	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	0.141
Weight, kg	65.1 ± 0.5	64.7 ± 0.7	63.7 ± 1.4	66.5 ± 1	65 ± 1	0.347
Height, cm	158.3 ± 0.2	158.7 ± 0.3	156.8 ± 0.8	158.7 ± 0.6	157.6 ± 0.5	**0.044**
Hypertension	719 (83.8)	339 (85.4)	68 (81.9)	162 (80.6)	150 (84.8)	0.459
Diabetes mellitus	234 (27.3)	104 (26.2)	20 (24.1)	55 (27.4)	55 (31.1)	0.584
Dyslipidemia	418 (48.8)	202 (51)	40 (48.1)	86 (42.8)	90 (51.1)	0.253
COPD	93 (10.9)	52 (13.1)	3 (3.6)	26 (12.9)	12 (6.8)	**0.015**
Peripheral artery disease or prior PTA	140 (16.3)	72 (18.1)	16 (19.1)	30 (14.9)	22 (12.6)	0.321
Cerebrovascular disease	76 (8.9)	34 (8.6)	8 (9.5)	15 (7.5)	19 (10.8)	0.708
Previous BAV	21 (2.5)	14 (3.5)	1 (1.2)	3 (1.5)	3 (1.7)	0.300
Previous CABG	56 (6.5)	27 (6.8)	4 (4.8)	15 (7.5)	10 (5.7)	0.089
Previous PCI	203 (23.7)	87 (21.9)	12 (14.5)	53 (26.4)	51 (29)	**0.043**
Previous MI	93 (11.3)	42 (11.1)	8 (9.6)	24 (12.9)	19 (10.8)	0.857
Coronary artery disease	318 (37.1)	152 (38.4)	24 (28.6)	80 (39.8)	62 (35.2)	0.285
PM or ICD	87 (10.2)	37 (9.4)	12 (14.5)	19 (9.5)	19 (10.9)	0.538
Atrial fibrillation	200 (23.3)	82 (20.6)	21 (25)	47 (23.4)	50 (28.3)	0.249
Angina	140 (19)	79 (20.1)	10 (12.1)	27 (19)	24 (19.8)	0.395
NYHA functional class III or IV	626 (72.9)	294 (74,1)	68 (81)	135 (67.2)	129 (72.9)	0.095
STS-PROM, %	5.7 ± 0.2	5.9 ± 0.3	5.5 ± 0.4	5.7 ± 0.3	5.3 ± 0.2	0.337
Hemoglobin, g/dl	11.6 ± 0.1	11.5 ± 0.1	11.4 ± 0.2	11.9 ± 0.1	11.8 ± 0.2	0.064
NT-proBNP, pg/ml	2,842.3 ± 393.6	2,746 ± 571	3,655 ± 1,331	4,035 ± 1,436	2,000 ± 384	0.406

Values are mean ± SD or n (%). The values in **bold** represent statistical significant differences between groups.

ACU = Acurate; BAV = balloon aortic valvuloplasty; BMI = body mass index; BSA = body surface area; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; EvPRO = Evolut PRO; EvR = Evolut R; 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; POR = Portico; PTA = percutaneous transluminal angioplasty; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

(TA) approach in 60 patients (29.9%). Mean nominal bioprosthesis diameter was 25.1 ± 1 mm (EvR, 25.8 ± 1 mm; EvPRO, 25.8 ± 0.4 mm; ACU, 23.6 ± 1 mm; POR, 24.7 ± 1 mm; $p < 0.001$). Pre-dilatation was significantly more common in the ACU and POR groups compared with the EvR and EvPRO groups ($p = 0.001$) because of manufacturers' recommendations to perform valvuloplasty prior to valve implantation, especially in the early phase of marketing. No differences were observed in terms of post-dilatation rate ($p = 0.711$). Procedural complications were rare, with no differences observed between groups in terms of the need for second valve implantation (2.3%), major vascular complications (5%), and major bleeding (5.2%). Three cases of annular rupture were reported (0.5%). In all 3 cases, post-dilation was performed and likely led to annular damage that was treated conservatively and did not result in major adverse clinical events.

ECHOCARDIOGRAPHIC AND CLINICAL OUTCOMES. Pre-discharge echocardiographic and 1-year follow-up data are shown in Table 4. Lower mean gradients were observed in the EvR (8.1 mm Hg; 95% CI: 7.7 to 8.5 mm Hg) and EvPRO (6.9 mm Hg; 95% CI: 6.3 to 7.6 mm Hg) groups compared with the ACU (9.6 mm Hg; 95% CI: 8.9 to 10.2 mm Hg) and POR (8.9 mm Hg; 95% CI: 8.2 to 9.6 mm Hg) groups ($p < 0.001$). Mean iEOA was 1.04 cm^2/m^2 (95% CI: 1.01 to 1.08 cm^2/m^2), with a trend toward lower values in the POR group (0.95 cm^2/m^2 [95% CI: 0.89 to 1.01 cm^2/m^2]; EvR, 1.07 cm^2/m^2 [95% CI: 1.01 to 1.13 cm^2/m^2]; EvPRO, 1.08 cm^2/m^2 [95% CI: 1.01 to 1.16 cm^2/m^2]; ACU, 1.04 cm^2/m^2 [95% CI: 0.98 to 1.11 cm^2/m^2]; $p = 0.06$) compared with the other groups (Figure 1), leading to a significantly higher rate of moderate PPM in the POR group (38.7%; EvR, 24.5%; EvPRO, 20.5%; ACU, 32.7%; $p = 0.037$). No significant differences were reported in terms of severe PPM (overall rate

TABLE 2 Echocardiographic and Procedural Characteristics

	Overall (N = 859)	EvR (n = 397)	EvPRO (n = 84)	ACU (n = 201)	POR (n = 177)	p Value
Baseline echocardiographic features						
Mean AV gradient, mm Hg	50.1 ± 0.6	50.6 ± 0.8	51.6 ± 1.9	51.5 ± 1.2	46.5 ± 1.2	**0.015**
Maximum AV gradient, mm Hg	80.3 ± 0.9	82.1 ± 1.3	83.9 ± 2.9	81.4 ± 1.8	73 ± 2	**0.001**
EOA, cm^2	0.64 ± 0.01	0.65 ± 0.01	0.61 ± 0.02	0.64 ± 0.01	0.65 ± 0.02	0.401
iEOA, cm^2/m^2	0.39 ± 0.004	0.39 ± 0.01	0.37 ± 0.12	0.38 ± 0.01	0.39 ± 0.01	0.415
sPAP, mm Hg	41.4 ± 0.5	41 ± 0.8	39.3 ± 1.5	42.4 ± 1	42.1 ± 1.3	0.416
RV dysfunction*	119 (13.9)	54 (13.6)	13 (15.5)	19 (9.5)	33 (18.6)	0.076
Bicuspid AV	27 (3.9)	16 (5.5)	0 (0)	5 (2.6)	6 (3.5)	0.177
Moderate or greater MR	90 (10.5)	45 (11.3)	13 (15.5)	16 (8.0)	16 (9.0)	0.231
Moderate or greater AR	58 (6.8)	31 (7.8)	8 (9.5)	11 (5.5)	8 (4.5)	0.302
Moderate or greater TR	50 (5.8)	29 (7.3)	2 (2.4)	8 (3.4)	11 (6.2)	0.195
LVEF <40%	71 (8.3)	38 (9.6)	9 (10.7)	16 (7.8)	8 (4.5)	0.183
LVEDV, ml	80.2 ± 1.6	82.4 ± 2.3	74.9 ± 6.9	85.0 ± 2.9	69.7 ± 3.1	**0.006**
LVESV, ml	34.8 ± 1.3	34.7 ± 1.8	35.6 ± 5.3	38.5 ± 3.1	31.8 ± 1.9	0.414
Baseline MDCT features						
Mean annular diameter, mm	21.3 ± 0.05	21.2 ± 0.1	21.4 ± 0.1	21.5 ± 0.1	21.2 ± 0.1	0.061
Maximum diameter, mm	23.6 ± 0.1	23.4 ± 0.1	23.7 ± 0.2	23.8 ± 0.1	23.9 ± 0.1	**0.039**
Minimum diameter, mm	18.9 ± 0.1	18.9 ± 0.1	19.0 ± 0.2	19.1 ± 0.1	18.4 ± 0.1	**0.003**
Mean aortic annular perimeter, mm	67.3 ± 0.2	67.1 ± 0.2	68.0 ± 0.4	67.3 ± 0.3	67.4 ± 0.4	0.335
Mean aortic annular area, mm^2	347.2 ± 1.4	346.1 ± 2.3	346.02 ± 4.6	351.5 ± 2.7	344.7 ± 2.6	0.307
Severe AV calcification	84 (9.8)	42 (10.6)	8 (9.5)	23 (11.4)	11 (6.2)	0.324
LMCA distance	11.9 ± 2.7	12 ± 0.2	12.4 ± 0.7	11.7 ± 0.2	11.8 ± 0.3	0.557
RCA distance	14.3 ± 2.8	14.4 ± 0.2	15.8 ± 0.6	13.9 ± 0.2	14.5 ± 0.2	**0.032**
Sinotubular junction diameter	26.1 ± 2.5	26 ± 0.2	25.7 ± 0.5	26.1 ± 0.3	26.2 ± 0.2	0.780
Sinus of Valsalva diameter	29.1 ± 2.5	29 ± 0.2	30.2 ± 0.4	29 ± 0.2	29 ± 0.2	0.077
Ascending aorta diameter	32.1 ± 4.1	31.5 ± 0.3	32.3 ± 0.7	32.3 ± 0.4	32.8 ± 0.4	**0.014**
Porcelain aorta	34 (4.1)	6 (1.5)	4 (5.7)	15 (7.8)	9 (5.3)	**0.002**

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

AV = aortic valve; AR = aortic regurgitation; EOA = effective orifice area; iEOA = indexed effective orifice area; LMCA = left main coronary artery; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end systolic volume; LVESV = left ventricular end systolic volume; MDCT = multidetector computed tomographic; MR = mitral regurgitation; sPAP = systolic pulmonary artery pressure; RCA = right coronary artery; RV = right ventricular; TR = tricuspid regurgitation; other abbreviations as in Table 1.

9.4%; p = 0.134) (Online Figure 2). Mean gradients, iEOA, and rate of PPM in patients treated via TF access are reported in Online Table 1. In the TF cohort, pre-discharge mean gradients were significantly higher in the POR group and slightly but significantly lower in the EvPRO group compared with the EvR and ACU groups. Considering only the ACU group, the rates of moderate and severe PPM were considerably lower in patients treated via TF access compared with the entire group (moderate PPM, 11.1% vs. 32.7%; severe PPM, 6.4% vs. 10.6%, respectively) (**Central Illustration**, Online Table 2).

POR and TA ACU implantation was found to be independently associated with moderate PPM (EvR, odds ratio [OR] 0.75 [95% CI: 0.33 to 1.68; p = 0.480]; EvPRO, OR: 0.54 [95% CI: 0.11 to 2.68; p = 0.448]; ACU TF, OR: 0.27 [95% CI: 0.07 to 1.07; p = 0.062]; ACU TA, OR: 3.05 [95% CI: 1.17 to 7.93; p = 0.022]; POR, OR: 3.00 [95% CI: 1.46 to 6.16; p = 0.003]), while no significance associations with severe PPM were found for any SEVs. When patients with very small annuli (n = 175) were analyzed, we found a significant inverse correlation between post-procedural gradients and annular perimeter (β = −0.07; p = 0.042) (Online Figure 3). Consistently, mean gradients in this subset were slightly but significantly higher compared with those in patients with annular diameters >20 mm (8.1 vs. 10 mm Hg, mean difference 1.9 mm Hg; 95% CI: 1.1 to 2.6 mm Hg). However, the difference may not be clinically relevant, and only 13.7% of patients with very small annulus had severe PPM, without differences among valve groups (p = 0.291).

Pre-discharge more than mild PVLs were significantly more common in the POR group (19.2%) and significantly less common in the EvPRO group (3.6%) compared with the EvR (11.8%) and ACU (9%) groups. Conversely, there were no differences between groups in terms of more than moderate PVL (overall rate 1.6%; p = 0.257). The permanent PM implantation

TABLE 3 Procedural Outcomes

	Overall (N = 859)	EvR (n = 397)	EvPRO (n = 84)	ACU (n = 201)	POR (n = 177)	p Value
Access						
Transaortic	7 (0.8)	4 (1.0)	1 (1.2)	0 (0)	2 (1.1)	0.532
Percutaneous axillary/subclavian	11 (1.3)	6 (1.5)	1 (1.2)	0 (0)	6 (3.4)	0.159
Surgical axillary/subclavian	29 (3.4)	20 (5.0)	4 (4.8)	1 (0.5)	4 (2.3)	**0.022**
Apical	62 (7.2)	0 (0)	0 (0)	60 (29.9)	0 (0)	**<0.001**
Femoral	749 (87.3)	367 (92.4)	77 (91.7)	140 (69.7)	165 (93.2)	**<0.001**
Valve size, mm	25.1 ± 0.06	25.8 ± 0.08	25.8 ± 0.14	23.6 ± 0.07	24.7 ± 0.09	**<0.001**
Pre-dilatation	422 (49.3)	123 (31.1)	27 (32.5)	151 (75.5)	121 (68.4)	**<0.001**
Post-dilatation	312 (36.6)	141 (35.7)	35 (42.2)	71 (35.5)	65 (37.1)	0.711
Contrast medium, ml	139.5 ± 2.8	147.5 ± 4.0	132.4 ± 6.8	119.6 ± 6.0	145.7 ± 6.9	**<0.001**
Annular rupture	3 (0.5)	2 (0.8)	0 (0)	0 (0)	1 (0.6)	0.830
Any vascular complication	124 (14.4)	52 (13.1)	8 (9.5)	35 (17.4)	29 (16.4)	0.244
Major vascular complication	43 (5.0)	20 (5.0)	2 (2.4)	10 (5.0)	11 (6.2)	0.652
Need for second valve implantation	19 (2.3)	11 (2.9)	1 (1.2)	1 (0.5)	6 (3.5)	0.143

Values are mean ± SD or n/N (%). The values in **bold** represent statistical significant differences between groups.
Abbreviations as in Table 1.

rate was 15.6%, with a numeric trend toward lower risk in the ACU group. Hemorrhagic events were rare, with a Bleeding Academic Research Consortium major bleeding rate of 5.23%, without significant differences among groups (p = 0.161).

Median follow-up duration was 342.5 days (interquartile range: 80 to 478 days). No differences were observed in terms of all-cause mortality, stroke or transient ischemic attack, myocardial infarction, hospitalization for heart failure, valve dysfunction, New York Heart Association functional class III or IV, and major bleeding.

DISCUSSION

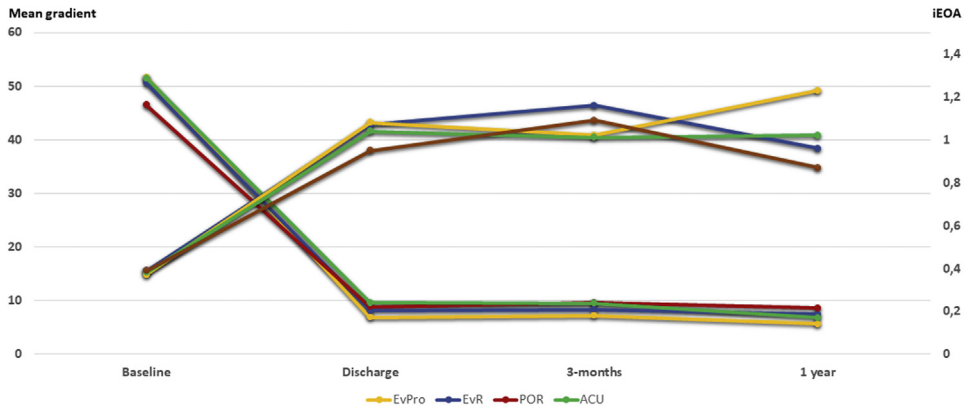
The aim of the present study was to provide a direct comparison, although not randomized, of SEVs in a real-world cohort of patients with aortic stenosis with

TABLE 4 Pre-Discharge Outcomes and 1-Year Follow-Up Data

	Overall (N = 859)	EvR (n = 397)	EvPRO (n = 84)	NEO (n = 201)	POR (n = 177)	p Value
Pre-discharge outcomes						
Mean AV gradient, mm Hg	8.5 ± 0.15 (8.2-8.8)	8.1 ± 0.2 (7.7-8.5)	6.9 ± 0.3 (6.3-7.6)	9.6 ± 0.3 (8.9-10.2)	8.9 ± 0.3 (8.2-9.6)	**<0.001**
Maximum AV gradient, mm Hg	15.1 ± 0.3	14.7 ± 0.4	14.1 ± 0.8	15.9 ± 0.7	16.0 ± 0.9	0.196
iEOA	1.04 ± 0.02	1.07 ± 0.03	1.08 ± 0.04	1.04 ± 0.05	0.95 ± 0.03	0.058
Moderate PPM	129 (29.0)	50 (24.5)	9 (20.5)	34 (32.7)	36 (38.7)	**0.039**
Severe PPM	42 (9.4)	17 (8.3)	1 (2.2)	11 (10.6)	13 (14.0)	0.134
New permanent PM	132 (15.6)	70 (18.1)	11 (13.3)	25 (12.6)	26 (14.7)	0.330
More than mild PVL	102 (11.9)	47 (11.8)	3 (3.6)	18 (9.0)	34 (19.2)	**0.001**
More than moderate PVL	14 (1.6)	5 (1.3)	0 (0)	6 (3.0)	3 (1.7)	0.285
BARC major bleeding	38 (5.2)	23 (7.4)	2 (4.1)	6 (3.1)	7 (4.0)	0.161
1-yr follow-up data						
Follow-up, days	343 (80-478)	283.5 (66-468)	104 (42-244)	364 (128-516)	372 (170-541)	**<0.001**
All-cause death	71 (11.1)	29 (10)	6 (9.5)	18 (11.7)	18 (13.6)	0.705
MI	5 (0.9)	2 (0.7)	0 (0)	1 (0.8)	2 (1.9)	0.659
TIA/stroke	21 (3.9)	15 (5.2)	3 (4.3)	2 (1.9)	1 (1.3)	0.342
Acute kidney injury	18 (4.8)	9 (4.1)	3 (7.1)	4 (7.3)	2 (3.3)	0.532
Hospitalization for HF	29 (5.5)	11 (3.8)	4 (6.2)	8 (7.7)	6 (7.9)	0.257
NYHA functional class III or IV	31 (3.6)	13 (3.3)	2 (2.4)	9 (4.5)	7 (4.0)	0.804

Values are mean ± SD, n/N (%), mean ± SD (95% confidence interval), or median (interquartile range). The values in **bold** represent statistical significant differences between groups.
BARC = Bleeding Academic Research Consortium; HF = heart failure; PPM = prosthesis patient mismatch; PVL = paravalvular leak; TIA = transient ischemic attack; other abbreviations as in Tables 1 and 2.

FIGURE 1 **Indexed Effective Orifice Area and Mean Gradient From Baseline to 1 Year**



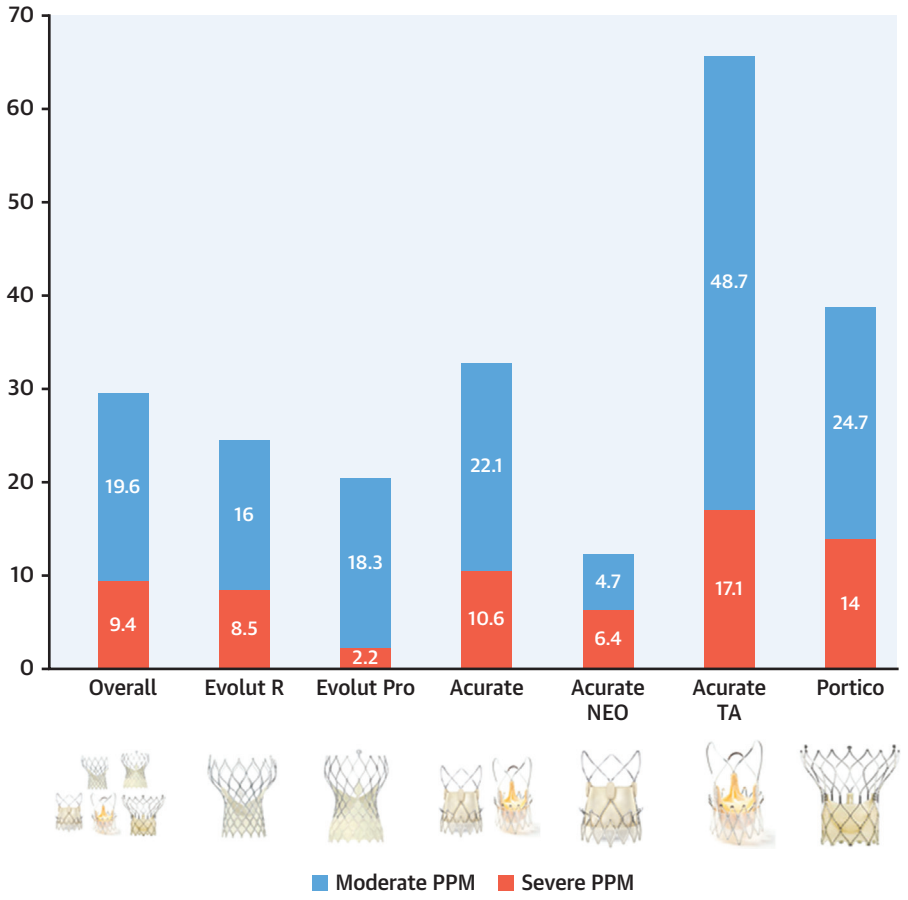
ACU = Acurate; EvPRO = Evolut PRO; EvR = Evolut R; iEOA = indexed effective orifice area; POR = Portico.

small aortic annuli. We decided to focus our attention on this specific subgroup, considering that patients with small aortic annuli showed the highest benefit in terms of valve forward hemodynamic and PPM in those studies comparing outcomes after TAVR and SAVR, especially in case of SEV implantation. The main findings can be summarized as follows: 1) Currently available SEVs showed excellent acute and mid-term clinical results, with a low incidence of adverse events and with no differences among groups. 2) The use of SEVs proved to be effective and showed good hemodynamic results in patients with small and very small annuli. An inverse correlation between annular perimeter and post-procedural gradients was found, but its clinical relevance is not clear, because the incidence of severe PPM was low in patients with both small (9.4%) and very small (13.7%) annuli. 3) The POR valve showed a significantly higher mean gradient, lower iEOA, and consequently higher rates of moderate (but not severe) PPM compared with the EvR and EvPRO valves, with intermediate valve performance shown by the ACU valve. 4) More than mild PVLs were rare with the EvPRO and significantly more common with the POR valve, with intermediate rates shown by the EvR and ACU valves. 5) No differences were noted in terms of need for PM implantation, despite a nonsignificant favorable trend in the ACU group.

This large retrospective registry of consecutive patients treated with SEVs showed low rates of in-hospital and 1-year adverse events in terms of procedural complications, death, and stroke or transient ischemic attack. These data, comparable with those observed in other contemporary TAVR studies (26), are consistent between groups, suggesting good procedural planning and implantation technique, irrespective of the selected device.

The main aim of the study was to evaluate the hemodynamic performance of currently available SEVs, with a focus on PPM. PPM was initially defined as an effective prosthesis area lower than that of the normal human valve (27). According to this definition, all patients undergoing aortic valve replacement should present some degree of PPM. In any case, no clinical implications may present until mismatch exceeds a critical threshold (28), especially in the absence of those factors (e.g., reduced LV ejection fraction, severe LV hypertrophy, significant mitral regurgitation, and low-flow, low-gradient aortic stenosis) that exacerbate the detrimental effect of PPM (29). Significant PPM is recognized as one of the most important predictors of valve dysfunction, persistence of LV hypertrophy, heart failure rehospitalization, and mortality among patients undergoing SAVR (15,30), and its impact on hemodynamic valve function and on clinical outcomes is progressively more recognized also among patients treated percutaneously (13,16,17,31). Post hoc analysis of the pivotal trials comparing surgical and transcatheter therapies (namely PARTNER [Placement of Aortic Transcatheter Valves] and the U.S. CoreValve High Risk Study) have shown a lower rate of PPM with TAVR than with SAVR (16,17). This is probably due to the thin struts and the lack of a sewing ring and because with TAVR larger valves are implanted compared with SAVR. Of note, the rate of PPM is higher after SAVR than after TAVR in cases of implantation of both stentless and stented surgical valves (32).

CENTRAL ILLUSTRATION **Moderate and Severe Prosthesis-Patient Mismatch in Patients With Aortic Stenosis and Small Aortic Annuli Treated With Self-Expandable Valves**



Regazzoli, D. et al. J Am Coll Cardiol Intv. 2019;■(■):■-■.

PPM = prosthesis-patient mismatch.

The improved hemodynamic performance of transcatheter prostheses, first noted with the SAPIEN XT BEV (Edwards Lifesciences, Irvine, California), seemed to be more pronounced in patients with small compared with large annuli (16). In contrast, the newer generation SAPIEN 3 was designed with an outer skirt that decreased the incidence of PVL but increased the occurrence of PPM (10). Indeed, the recent PARTNER 3 trial, which compared TAVR of the SAPIEN 3 valve and SAVR in patients at low surgical risk, was the first study comparing transcatheter and surgical valve replacement showing higher gradients and a higher rate of PPM in patients treated percutaneously (10).

Conversely, SEVs proved to consistently reduce PPM incidence (compared with SAVR) across all annular size dimensions (17), with a greater reduction among patients with small annuli.

Consistently, when directly compared with each other in the CHOICE trial and in the extended CHOICE registry, CoreValve and EvR SEVs showed lower post-procedural mean gradient and larger iEOA compared with SAPIEN 3 BEVs, with a consequent lower rate of PPM (18). Similarly, in a propensity score-matched analysis involving 246 patients with aortic stenosis and small aortic annuli, the ACU SEV showed lower gradients and a lower rate of PPM compared with the SAPIEN 3 BEV (19). The aforementioned SEVs share some important structural features that could explain the lower transvalvular gradient and higher iEOA compared with BEVs, such as the supra-annular leaflet position. Also, the supra-annular leaflet

position of these SEVs may avoid the additional constraints by native annulus combined to leaflets and stent, resulting in larger effective orifice area compared with intra-annular transcatheter valves.

Conversely, recently published data showed that the POR SEV had similar post-procedural gradients and PPM rate compared with the SAPIEN XT. Among currently available SEVs, the POR is the only one with intra-annular leaflets, which may explain this result and the findings in our study of slightly higher gradients and lower iEOA compared with the supra-annular SEVs (33).

The EvPRO was the most recent valve to be marketed, and there is still a paucity of data about its outcomes and hemodynamic performance (34,35), with no available data in patients with small annuli. This prosthesis is based on the EvR platform, with the implementation of an external porcine pericardial wrap for the reduction of PVL (35). This additional feature raised concerns regarding the risk for higher post-procedural gradients, which were not confirmed by preliminary studies (34).

The results of the present study are consistent with those in the published research, with good and comparable hemodynamic performance of the EvR, EvPRO, and ACU valves and slightly worse results achieved with the POR valve. As aforementioned, these findings could be at least partially explained by the POR's intra-annular leaflet design. This hypothesis is further corroborated by the post-procedural echocardiographic data observed in the ACU group in our study: we reported higher mean gradients, smaller iEOA, and consequently a higher rate of PPM in patients treated with the ACU TA device (which had intra-annular leaflets) compared with those treated with the ACU neo TF device (with a supra-annular design). Importantly, the ACU TA device is no longer available but was included in the present analysis because it was still available at the time of data collection.

Last, our findings regarding patients with very small annuli favorably compare with those observed after SAPIEN XT implantation in the OCEAN-TAVI registry; indeed, post-procedural mean gradients in patients with very small annuli ranged from 12.2 ± 4.8 mm Hg with the 23-mm SAPIEN XT to 15.4 ± 4.1 mm Hg with the 20-mm SAPIEN XT, compared with 10 ± 0.4 mm Hg observed in our studies, further suggesting the better forward hemodynamic function of SEVs compared with BEVs in patients with small annuli and at high risk for significant PPM (25).

With regard to PVL, the incidence of severe insufficiency was very low and consistent among groups. Conversely, the overall rate of more than mild regurgitation was significantly higher in the POR group than in the other SEV groups. This may be explained by the low radial force and absence of an external skirt of this device.

Of note, the prognostic role of residual PVL and of PPM is still debated; although both were identified as predictors of worse outcomes, the relative weight of each is unclear in patients with small annuli. However, the incidence of significant PVL seems to be lower in patients with small than in those with larger aortic annuli (18), which may provide a rationale to aggressively prevent PPM, thus making SEVs a good choice in this specific setting.

Finally, the permanent PM implantation rate seemed to be reasonable and with a nonsignificant trend in favor of the ACU. These findings are consistent with those reported in a large series assessing the rates of PM implantation after TAVR with new-generation valves (36).

The recently published PARTNER 3 and Evolut Low Risk trials showed that TAVR is noninferior to SAVR also in patients with low surgical risk (9,10). These results should lead to a reduction of the threshold for TAVR and further highlight the importance of the choice of the right device for each patient. Our results shed light on the different hemodynamic performance provided by commercially available SEVs in patients with small aortic annuli, showing slightly worse performance of the POR compared with the other SEVs. However, considering the small (although significant) differences, it remains uncertain if current results in terms of different hemodynamic valve performance could have an impact on long-term prognosis. Large-scale randomized trials are necessary to confirm our findings, and long-term follow-up is warranted to assess the impact of PPM and PVL on patients with aortic stenosis and small aortic annuli treated with SEV.

STUDY LIMITATIONS. The first limitation is the nonrandomized and retrospective design of our study. Therefore, we cannot exclude some source of selection bias that in turn could have influenced our results, although we did not observe important baseline differences among SEV groups.

Second, a certain level of underreporting or missing echocardiographic and follow-up data could exist, even if most of the relevant events were prospectively reported by the investigators in the course of the clinical follow-up or derived from an ad hoc database. Furthermore, in the present analysis we did not assess the impact on outcomes of oversizing, or computed tomographic and procedural data, such as those regarding implantation depth and calcification distribution. Additional analyses of the TAVI-SMALL registry focusing on these topics are foreseen.

Third, our study lacked dedicated core laboratory adjudication of echocardiographic outcomes. Moreover, Doppler velocity index was available only for a limited number of patients and therefore was not reported.

Fourth, although the ACU TA device is no longer commercially available and despite the aforementioned differences with the ACU neo TF valve, we included in the ACU cohort also those patients treated with the ACU TA valve, because it was still marketed at the time of data collection.

Fifth, the decision to focus our attention on patients with small aortic annuli, therefore not including all aortic annular sizes, could have reduced the power of our analysis and results interpretation. Hence, this study was not powered for clinical outcomes and does not allow any inferential speculation on important clinical events such as stroke and mortality.

Nevertheless, the present evaluation of commercially available SEVs in a real-world population of patients with aortic stenosis and small aortic annuli represents an important piece of evidence by confirming favorable outcomes of these devices in this setting.

CONCLUSIONS

In this multicenter retrospective registry, SEVs showed optimal clinical and echocardiographic results in patients with small aortic annuli, although supra-annular functioning devices (EvR, EvPRO, and ACU) seemed to slightly outperform the intra-annular functioning POR valve. The promising role of TAVR with SEVs for treatment of aortic stenosis in patients with small annuli and the impact of supra-annular versus intra-annular valve design must be confirmed in larger trials.

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PERSPECTIVES

WHAT IS KNOWN? Patients with small aortic annuli are common in clinical practice among patients with aortic stenosis. A post hoc analysis of pivotal trials that compared TAVR with surgery showed that transcatheter prostheses offered better hemodynamic results and a reduced risk for developing PPM, especially with SEV implantation.

WHAT IS NEW? This direct comparison among SEVs shows that these devices have good hemodynamic performance in patients with aortic stenosis and small annuli, with low post-procedural gradients, large orifice areas, and a low incidence of severe PPM. The EvR, EvPRO, and ACU seemed to slightly outperform the POR regarding hemodynamic function, while similar rates of severe PVL and need for PM implantation were reported.

WHAT IS NEXT? The possible role of SEVs as first-line therapy in patients with aortic stenosis and small annuli and the impact of supra-annular versus intra-annular valve design need to be confirmed in large-scale randomized trials.

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KEY WORDS self-expandable valves, small annuli, TAVR

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