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STRUCTURAL

5-Year Outcomes With Self-Expanding vs Balloon-Expandable Transcatheter Aortic Valve Replacement in Patients With Small Annuli

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ABSTRACT

BACKGROUND Self-expanding transcatheter heart valves (THVs) are associated with better echocardiographic hemodynamic performance than balloon-expandable THVs and are considered preferable in patients with small annuli.

OBJECTIVES This study sought to compare 5-year outcomes between self-expanding vs balloon-expandable THVs in severe aortic stenosis (AS) patients with small annuli.

METHODS Consecutive severe AS patients with an aortic valve annulus area <430 mm^2 who underwent transcatheter aortic valve replacement (TAVR) with either the CoreValve Evolut (Medtronic) or SAPIEN (Edwards Lifesciences) THV between 2012 and 2021 were enrolled from the Bern TAVI registry. A 1:1 propensity-matched analysis was performed to account for baseline differences between groups.

RESULTS A total of 723 patients were included, and propensity score matching resulted in 171 pairs. Technical success was achieved in over 85% of both groups with no significant difference. Self-expanding THVs were associated with a lower transvalvular gradient (8.0 ± 4.8 mm Hg vs 12.5 ± 4.5 mm Hg; $P < 0.001$), a larger effective orifice area (1.81 ± 0.46 cm^2 vs 1.49 ± 0.42 cm^2; $P < 0.001$), and a lower incidence of prosthesis-patient mismatch (19.7% vs 51.8%; $P < 0.001$) than balloon-expandable THVs. At 5 years, there were no significant differences in mortality (50.4% vs 39.6%; $P = 0.269$) between groups. Disabling stroke occurred more frequently in patients with a self-expanding THV than those with a balloon-expandable THV (6.6% vs 0.6%; $P = 0.030$). Similar results were obtained using inverse probability of treatment weighting in the Bern TAVI registry and the nationwide Swiss TAVI registry.

CONCLUSIONS The echocardiographic hemodynamic advantage of self-expanding THVs was not associated with better clinical outcomes compared with balloon-expandable THVs up to 5 years in patients with small annuli. (Swiss TAVI Registry; NCT01368250) (J Am Coll Cardiol Intv 2023;16:429–440) © 2023 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

ASD = absolute standardized difference

AVC = aortic valvular complex

CT = computed tomography

EOA = effective orifice area

IPTW = inverse probability treatment weighting

LVOT = left ventricular outflow tract

NYHA = New York Heart Association

PCI = percutaneous coronary intervention

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

THV = transcatheter heart valve

VARC-3 = Valve Academic Research Consortium-3

Transcatheter aortic valve replacement (TAVR) is the standard of care in elderly patients with severe aortic valve stenosis (AS).[1] A variety of devices are now available for this treatment; the self-expanding CoreValve Evolut (Medtronic) and balloon-expandable SAPIEN (Edwards Lifesciences) transcatheter heart valves (THV) are the most widely used, with proven safety and efficacy in a series of randomized clinical trials.[2] Of note, both devices have their own strengths and limitations. A notable advantage of self-expanding THVs is the better systolic hemodynamic performance compared with balloon-expandable THVs because of the supra-annular position of the leaflets. Previous studies have consistently shown better echocardiographic hemodynamic performance in terms of lower transvalvular gradients and larger effective orifice areas (EOAs) of self-expanding THVs compared with balloon-expandable THVs.[3-7] Because the hemodynamic differences between the devices are most pronounced in patients with small annuli, self-expanding THVs are considered beneficial, particularly for patients with small annuli.[8,9] To evaluate the concept, the SMART (Small Annuli Randomized To Evolut or SAPIEN; NCT04722250) trial is currently ongoing and enrolling patients across Europe and North America.[10] The 5-year follow-up is expected to be completed in early 2028. Given the rapid expansion of TAVR to a younger and low-risk population and the continued evolution of TAVR devices, the potential for differences in long-term outcomes between devices in current clinical practice needs to be reported at this time.

In the present study, we used data from a prospective TAVR registry and compared 5-year outcomes between self-expanding THVs vs balloon-expandable THVs in severe AS patients with small annuli using propensity score-matched analysis.

METHODS

STUDY DESIGN AND POPULATION. The Bern TAVI registry, part of the nationwide Swiss TAVI registry, is a prospective registry enrolling all patients undergoing TAVR at Bern University Hospital, which is mandated by the Swiss health authorities (NCT01368250). The registry is approved by the Swiss national ethics committee, and patients provided written informed consent to participate. The present analysis included consecutive patients with an aortic valve annulus area <430 mm^2 who underwent transfemoral TAVR with either a Medtronic self-expanding (supra-annular) THV or an Edwards balloon-expandable (intra-annular) THV between January 2012 and June 2021. For the purpose of the present study, patients who underwent TAVR for a degenerated surgical or transcatheter aortic bioprosthesis and patients who underwent TAVR for pure native aortic valve regurgitation were excluded. The study was conducted in compliance with the Declaration of Helsinki.

DATA COLLECTION AND CLINICAL ENDPOINTS. All baseline clinical, procedural, and follow-up data were prospectively recorded in a web-based database. Standardized case report forms were used to collect the data. Clinical follow-up data were obtained through standardized interviews, documentation from referring physicians, and hospital discharge summaries. All adverse events were systematically collected and adjudicated by a dedicated clinical event committee based on the standardized Valve Academic Research Consortium-2 criteria.[11] Recently proposed Valve Academic Research Consortium-3 (VARC-3) technical success and device success were retrospectively adjudicated based on detailed documentation of adjudicated endpoints that form the individual components of the composite endpoints.[12,13] An independent clinical trials unit is responsible for central data monitoring to verify the completeness and accuracy of data and independent statistical analysis.

Standardized transthoracic echocardiography was performed by a board-certified cardiologist and an echocardiography specialist with the Phillip iE33 machine (Phillips Healthcare) at day 2 or 3 after TAVR and before hospital discharge at the latest. In accordance with the updated VARC-3 definitions,[12] prosthesis-patient mismatch was categorized based on prosthesis EOA indexed to body surface area as severe (≤0.65 cm^2/m^2) or moderate (>0.65-0.85 cm^2/m^2) in the nonobese population and as severe (≤0.55 cm^2/m^2) or moderate (>0.55-0.70 cm^2/m^2) in the obese population (body mass index ≥30 kg/m^2). For prosthesis-patient mismatch, an EOA measured at discharge by echocardiography using the continuity equation was used. "Predicted" prosthesis-patient mismatch was also evaluated using an EOA derived from a published normal reference value for each model and size of THV used.[5,14]

ANATOMY OF THE AORTIC VALVAR COMPLEX. Preprocedural computed tomography (CT) imaging was performed using a dual-source 128-row multislice CT system (Somaton Definition Flash, Siemens Healthcare) as previously described.[15] Acquired

images were transferred to a dedicated workstation (3mensio Structural Heart, 3mensio Medical Imaging BV) and independently re-evaluated by imaging specialists blinded to clinical outcomes in the Bern Imaging Core Lab. The systolic phase of CT imaging with the least motion artifact was selected for the analysis, and aortic valvular complex (AVC) dimensions were measured in accordance with an expert consensus document of the Society of Cardiovascular Computed Tomography.[16] AVC and left ventricular outflow tract (LVOT) calcium volume was quantified in contrast-enhanced images using a predefined Hounsfield unit threshold of 850 as previously described.[17,18]

STATISTICAL ANALYSIS. Categorical variables are presented as frequencies and percentages, and the differences are evaluated with the chi-square test or the 2-tailed Fisher exact test. Continuous variables are expressed as mean values ± SD and compared between groups using the 2-sample Student's *t*-test. Time-to-event curves were depicted using the Kaplan-Meier method. The Cox proportional hazards survival model was used to calculate HRs and 95% CIs for clinical outcomes. For the time-to-event analyses, adjudicated events up to 5 years of follow-up were considered. However, to avoid potential bias caused by earlier reporting of deaths without the correct denominator for pending reports of being alive, adjudicated events up to 3 years and 1 year were considered in patients undergoing TAVR between July 2018 and June 2020 and between July 2020 and June 2021, respectively. The median follow-up time available for alive patients was 590 days (IQR: 176-1,125 days), and the median time to death was 409 days (IQR: 365-1,822 days), considering only the information within 5 years.

Because the valve type was selected based on both patient-related and anatomy-related factors, propensity score matching was used to control for confounding caused by these factors. The propensity score was calculated using a multivariable logistic regression model based on 33 relevant variables that may affect valve-type selection as well as study outcomes. The variables included clinical variables (ie, the year of TAVR, age, sex, body mass index, Society of Thoracic Surgeons Predicted Risk of Mortality, New York Heart Association (NYHA) functional class III/IV, hypertension, diabetes, dyslipidemia, chronic kidney disease, atrial fibrillation, coronary artery disease, history of myocardial infarction, history of percutaneous coronary intervention, history of coronary artery bypass graft, history of a cerebrovascular event, peripheral artery disease, previous permanent pacemaker, aortic valve area, aortic valve mean gradient, left ventricular ejection fraction, moderate or severe aortic regurgitation, moderate or severe mitral regurgitation, and moderate or severe tricuspid regurgitation) and CT-measured variables (ie, bicuspid aortic valve morphology, annulus area [mm^2], annulus ellipticity [minimum/maximum diameter of the annulus], Sinus of Valsalva diameter [mm], left coronary height [mm], right coronary height [mm], AVC calcium volume [mm^3], LVOT calcium volume [mm^3], and aortic angulation). Given the potential difference in outcome because of device generation, 83 patients treated with old generation THVs (Edwards SAPIEN XT and Medtronic CoreValve) were matched independently from the overall cohort. A 1:1 greedy nearest neighbor matching protocol with a caliper of 0.2 was used for matching. Absolute standardized differences (ASDs) were estimated for all the baseline variables in the prematching and matched cohorts to assess the balance in baseline demographics. An ASD <0.10 was considered as an indicator of good balance.

Given the limited statistical power because of the modest number of patients after propensity score matching, an inverse probability treatment weighting (IPTW) approach was used as a sensitivity analysis. Furthermore, we extended the study cohort to the whole Swiss TAVI registry and performed IPTW analysis using propensity scores based on 23 previously mentioned clinical variables (excluding moderate or severe tricuspid regurgitation because of unavailability) and the CT annulus area (mm^2) (the other CT-measured variables were not systematically captured in the Swiss TAVI registry). IPTW of 5 and higher was truncated to 5 (n = 13 in the Bern TAVI registry and n = 8 in the Swiss TAVI registry). All *P* values were 2-sided, and $P < 0.05$ was considered significant for all tests. All statistical analyses were performed with the use of Stata 15.1 (StataCorp).

RESULTS

STUDY POPULATION AND BASELINE CHARACTERISTICS. Among 2,769 consecutive patients who underwent TAVR between January 2012 and June 2021, 723 patients met the inclusion criteria and were analyzed for the present study. Among them, 389 patients were treated with a self-expanding (supra-annular) THV and 334 with a balloon-expandable (intra-annular) THV. Baseline clinical, echocardiographic, and CT data of the unmatched and matched cohorts are detailed in **Table 1**. Before propensity score matching, patients treated with a self-expanding THV were older (83.1 ± 6.1 vs 81.7 ± 6.3; $P = 0.003$), less likely to be male (10.8% vs 28.4%; $P < 0.001$), had a lower

TABLE 1 Baseline Characteristics of the Unmatched and Matched Population

		Prematching Cohort				Matched Cohort			
	All Patients (N = 723)	SEV (n = 389)	BEV (n = 334)	*P* Value	ASD	SEV (n = 171)	BEV (n = 171)	*P* Value	ASD
Age, y	82.5 ± 6.2	83.1 ± 6.1	81.7 ± 6.3	0.003	0.222	82.2 ± 6.2	82.7 ± 6.4	0.484	0.076
Male	137 (18.9)	42 (10.8)	95 (28.4)	<0.001	0.455	27 (15.8)	25 (14.6)	0.880	0.032
Body mass index, kg/cm^2	26.4 ± 5.8	25.9 ± 6.0	26.9 ± 5.4	0.026	0.168	26.9 ± 6.1	26.5 ± 5.6	0.513	0.071
STS PROM	4.94 ± 3.43	5.13 ± 3.43	4.71 ± 3.42	0.101	0.123	5.15 ± 3.81	5.34 ± 3.64	0.633	0.052
NYHA functional class III or IV	472 (65.3)	270 (69.4)	202 (60.5)	0.012	0.188	112 (65.5)	119 (69.6)	0.488	0.087
Concomitant diseases									
Hypertension	634 (87.7)	340 (87.4)	294 (88.0)	0.821	0.019	149 (87.1)	154 (90.1)	0.497	0.092
Diabetes mellitus	171 (23.7)	95 (24.4)	76 (22.8)	0.661	0.039	45 (26.3)	43 (25.1)	0.902	0.027
Dyslipidemia	450 (62.2)	232 (59.6)	218 (65.3)	0.124	0.116	110 (64.3)	103 (60.2)	0.503	0.084
Chronic kidney disease, eGFR <60 mL/min/1.73 m^2	519 (71.9)	297 (76.5)	222 (66.5)	0.003	0.224	120 (70.2)	130 (76.0)	0.272	0.132
COPD	57 (7.9)	32 (8.2)	25 (7.5)	0.782	0.028	17 (9.9)	13 (7.6)	0.567	0.083
Atrial fibrillation	201 (27.8)	119 (30.6)	82 (24.6)	0.080	0.135	49 (28.7)	52 (30.4)	0.813	0.038
Previous history									
Coronary artery disease	357 (49.4)	177 (45.5)	180 (53.9)	0.025	0.168	92 (53.8)	91 (53.2)	>0.999	0.012
History of PCI	156 (21.6)	78 (20.1)	78 (23.4)	0.319	0.080	39 (22.8)	39 (22.8)	>0.999	0.000
History of CABG	29 (4.0)	13 (3.3)	16 (4.8)	0.347	0.073	7 (4.1)	6 (3.5)	>0.999	0.030
History of MI	74 (10.2)	32 (8.2)	42 (12.6)	0.065	0.143	21 (12.3)	22 (12.9)	>0.999	0.018
History of cerebrovascular accident	90 (12.4)	46 (11.8)	44 (13.2)	0.652	0.041	20 (11.7)	24 (14.0)	0.628	0.070
Peripheral artery disease	65 (9.0)	45 (11.6)	20 (6.0)	0.009	0.198	10 (5.8)	15 (8.8)	0.407	0.112
Previous pacemaker	38 (5.3)	26 (6.7)	12 (3.6)	0.068	0.140	8 (4.7)	7 (4.1)	>0.999	0.028
Echocardiographic data									
Aortic valve area, cm^2	0.60 ± 0.23	0.58 ± 0.22	0.63 ± 0.23	0.002	0.230	0.61 ± 0.21	0.61 ± 0.24	0.964	0.005
Aortic valve mean gradient, mm Hg	41.2 ± 17.5	41.5 ± 18.2	40.7 ± 16.5	0.542	0.046	40.1 ± 18.1	39.5 ± 17.8	0.761	0.033
LVEF, %	59.5 ± 11.9	59.5 ± 11.8	59.6 ± 12.1	0.935	0.006	59.5 ± 11.9	58.7 ± 12.8	0.564	0.063
Aortic regurgitation, ≥ moderate	51 (7.1)	27 (6.9)	24 (7.2)	1.000	0.010	13 (7.6)	13 (7.6)	>0.999	0.000
Mitral regurgitation, ≥ moderate	115 (18.2)	77 (22.1)	38 (13.3)	0.005	0.231	19 (11.1)	26 (15.2)	0.337	0.121
Tricuspid regurgitation, ≥ moderate	71 (11.7)	47 (14.1)	24 (8.8)	0.056	0.167	16 (9.9)	18 (11.0)	0.857	0.034
CT imaging data									
Bicuspid aortic valve, %	23 (3.2)	11 (2.8)	12 (3.6)	0.672	0.043	3 (1.8)	4 (2.3)	>0.999	0.041
Annulus area, mm^2	369.6 ± 42.8	360.5 ± 45.6	380.3 ± 36.6	<0.001	0.478	376.0 ± 35.7	372.5 ± 36.9	0.366	0.098
Sinus of Valsalva, mm	29.4 ± 2.7	28.8 ± 2.6	30.0 ± 2.6	<0.001	0.435	29.4 ± 2.6	29.3 ± 2.3	0.765	0.032
Left coronary height, mm	13.9 ± 3.1	13.6 ± 3.2	14.3 ± 3.0	0.002	0.236	13.8 ± 3.2	13.8 ± 2.8	0.911	0.012
Right coronary height, mm	16.6 ± 3.1	16.2 ± 3.0	17.0 ± 3.1	0.001	0.253	16.4 ± 3.1	16.6 ± 3.0	0.498	0.073
AVC calcium, mm^3	240.0 ± 239.9	233.0 ± 241.1	248.2 ± 238.6	0.399	0.063	212.9 ± 227.9	225.6 ± 221.9	0.602	0.056
LVOT calcium, mm^3	12.3 ± 39.4	16.5 ± 48.1	7.5 ± 24.9	0.002	0.234	8.0 ± 20.6	7.1 ± 25.8	0.708	0.041
Aortic angulation, °	49.1 ± 9.4	47.9 ± 8.5	50.6 ± 10.1	<0.001	0.291	49.3 ± 8.2	49.2 ± 10.4	0.871	0.018
Eccentricity of annulus, (min/max annulus diameter)	0.76 ± 0.07	0.76 ± 0.07	0.75 ± 0.07	0.432	0.059	0.76 ± 0.07	0.76 ± 0.07	0.538	0.067

Values are mean ± SD or n (%). *P* values from Fisher test (2 × 2 comparison), chi-square test (n × 2 comparisons), or Student's *t*-tests (continuous parameters).

ASD = absolute standardized difference; AVC = aortic valvular complex; BEV = balloon-expandable transaortic valve replacement; CABG = coronary artery bypass graft; CT = computed tomography; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SEV = self-expandable transaortic valve replacement; STS PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

body mass index (25.9 ± 6.0 vs 26.9 ± 5.4; $P = 0.026$), and had more advanced heart failure symptoms (NYHA functional class III/IV: 69.4% vs 60.5%; $P = 0.012$). Although coronary artery disease (45.5% vs 53.9%; $P = 0.025$) was less frequent, chronic kidney disease (76.5% vs 66.5%; $P = 0.003$) and peripheral artery disease (11.6% vs 6.0%; $P = 0.009$) were more frequent in patients with a self-expanding THV than those with a balloon-expandable THV.

In echocardiographic assessment, patients with a self-expanding THV had a smaller aortic valve area (0.58 ± 0.22 cm^2 vs 0.63 ± 0.23 cm^2; $P = 0.002$) and moderate or severe mitral regurgitation more frequently than those with a balloon-expandable THV

(22.1% vs 13.3%; $P = 0.005$). Aortic root dimensions as assessed by CT imaging were smaller in patients with a self-expanding THV than in those with a balloon-expandable THV. Although there was no significant difference in aortic valvular complex calcium volume (233.0 ± 241.1 mm^3 vs 248.2 ± 238.6 mm^3; $P = 0.399$), LVOT calcium volume was significantly greater (16.5 ± 48.1 mm^3 vs 7.5 ± 24.9 mm^3; $P = 0.002$) in patients with a self-expanding THV than in those with a balloon-expandable THV. Aortic angulation was less steep in patients with a self-expanding THV than in those with a balloon-expandable THV (47.9 ± 8.5 vs 50.6 ± 10.1; $P < 0.001$).

PROPENSITY SCORE MATCHING. Propensity score matching resulted in 171 matched pairs. After matching, patients with a self-expanding THV and those with a balloon-expandable THV were well balanced with ASD <0.10 across all measured baseline characteristics, except for lower rates of chronic kidney disease (70.2% vs 76.0%; $P = 0.272$; ASD = 0.132), peripheral artery disease (5.8% vs 8.8%; $P = 0.407$; ASD = 0.112), and moderate or severe mitral regurgitation (11.0% vs 15.2%; $P = 0.337$; ASD = 0.121) in patients with a self-expanding THV compared with a balloon-expandable THV (Table 1).

PROCEDURAL CHARACTERISTICS AND OUTCOMES. Procedural characteristics and outcomes in the matched cohort are shown in Table 2. Although there was no difference in the rate of predilatation, postdilatation was more frequently performed in patients with a self-expanding THV than those with a balloon-expandable THV. Overall, procedural complications were rare, and there were no differences between groups. VARC-3 technical success was achieved in more than 85% of patients without a difference between groups (87.1% vs 87.7%; $P > 0.999$).

Echocardiographic data at discharge are shown in Table 2 and Figure 1. Self-expanding THVs were associated with a lower mean transvalvular gradient (8.0 ± 4.8 mm Hg vs 12.5 ± 4.5 mm Hg; $P < 0.001$), a larger EOA (1.81 ± 0.46 cm^2 vs 1.49 ± 0.42 cm^2; $P < 0.001$), and a lower incidence of prosthesis-patient mismatch ($P < 0.001$) compared with balloon-expandable THVs. Although moderate or greater paravalvular regurgitation was rare in both groups (4.1% vs 1.2%), any paravalvular regurgitation, including mild and moderate, occurred more frequently in patients with a self-expanding THV than in those with a balloon-expandable THV ($P = 0.015$). Despite these differences, there was no difference in the rate of VARC-3 device success between groups (79.5% vs 79.5%; $P > 0.999$). "Predicted" prosthesis-patient mismatch was less frequent in patients with a self-expanding THV than in those with a balloon-expandable THV (5.8% vs 35.3%; $P < 0.001$); however, severe "predicted" prosthesis-patient mismatch was not observed in either group.

TABLE 2 Procedural Characteristics and Complications in the Matched Population

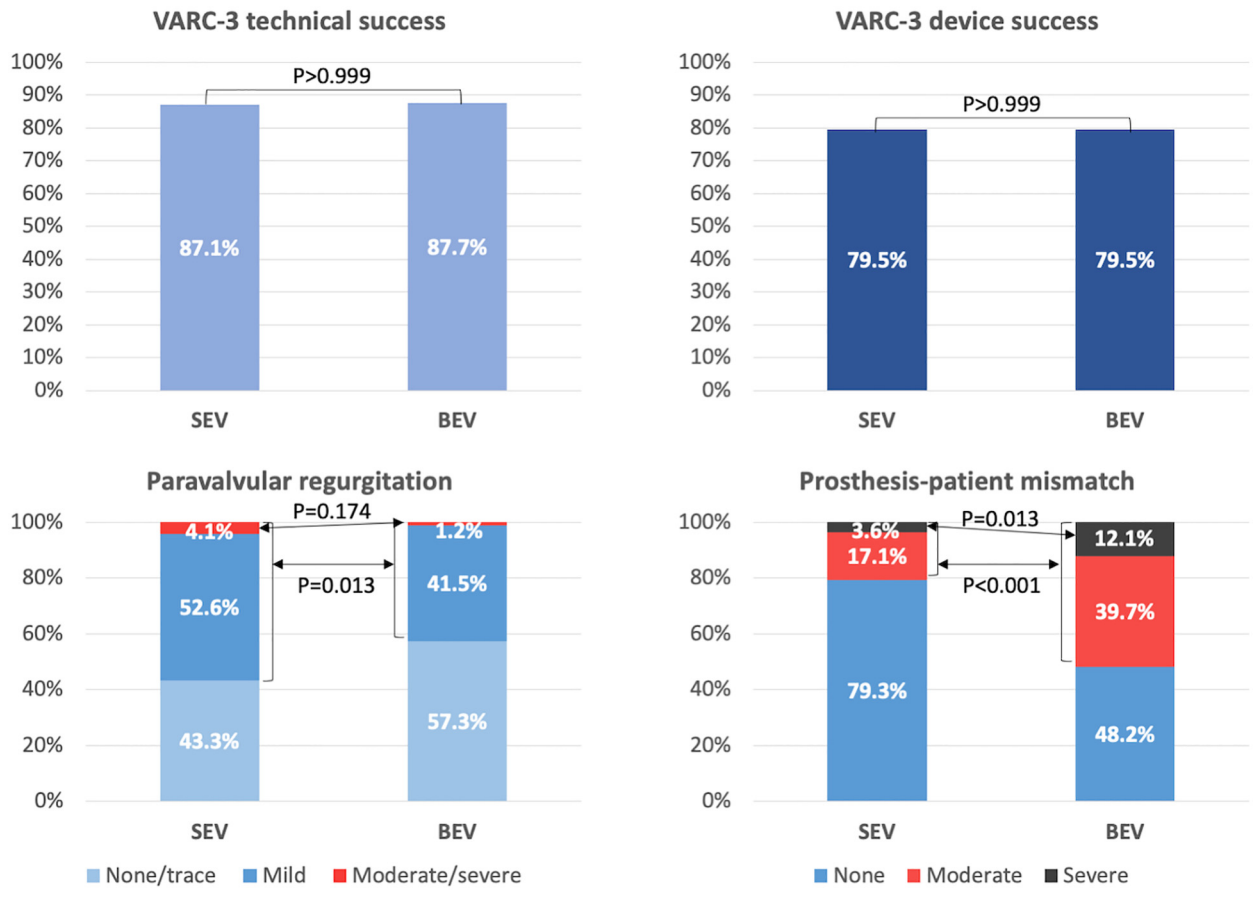
Matched Cohort	SEV (n = 171)	BEV (n = 171)	*P* Value
Type of valve			Exact matching
Old generation (SAPIEN XT, CoreValve)	11 (6.4)	11 (6.4)	
Newer generation (SAPIEN 3/3Ultra, Evolut R/PRO/PRO+)	160 (93.6)	160 (93.6)	
Predilation	80 (46.8)	84 (49.1)	0.745
Postdilation	55 (32.2)	34 (19.9)	0.013
Procedural complications			
Valve in series	1 (0.6)	4 (2.3)	0.371
Valve dislocation/embolization	2 (1.2)	4 (2.3)	0.685
Conversion to SAVR	0 (0.0)	2 (1.2)	0.499
Annulus rupture/aortic dissection	0 (0.0)	2 (1.2)	0.499
Coronary artery occlusion	1 (0.6)	1 (0.6)	>0.999
Major vascular complication[a]	18 (10.5)	14 (8.2)	0.578
Technical success[b]	149 (87.1)	150 (87.7)	>0.999
Echocardiographic assessment (discharge)			
Aortic valve area, mm	1.81 ± 0.46	1.49 ± 0.42	<0.001
Transvalvular mean gradient, mm Hg[c]	8.0 ± 4.8	12.5 ± 4.5	<0.001
Transvalvular mean gradient ≥20, mm Hg[c]	5 (2.9)	12 (7.1)	0.087
Paravalvular regurgitation[c]	(n = 171)	(n = 171)	0.015
None/trace	74 (43.3)	98 (57.3)	
Mild	90 (52.6)	71 (41.5)	
Moderate	7 (4.1)	2 (1.2)	
Prosthesis-patient mismatch[c]	(n = 140)	(n = 141)	<0.001
Insignificant	111 (79.3)	68 (48.2)	
Moderate	24 (17.1)	56 (39.7)	
Severe	5 (3.6)	17 (12.1)	
"Predicted" prosthesis-patient mismatch[d]	(n = 171)	(n = 170)	<0.001
Insignificant	161 (94.2)	110 (64.7)	
Moderate	10 (5.8)	60 (35.3)	
Severe	0 (0.0)	0 (0.0)	

Values are n (%) or mean ± SD. [a]Only in-hospital event included. [b]Valve Academic Research Consortium-3 definition: no death on the day of the procedure, no valve-in-series, no valve dislocation/embolization, no conversion to SAVR, no valve retrieval, no repositioning with snare, no complication with stent placement, and no vascular surgery required. [c]At discharge. If missing, postprocedure imaging used. No severe paravalvular regurgitation detected in this cohort. [d]Normal reference values of SAPIEN 3 were used for 3Ultra. Normal reference values of Evolut R were used for Evolut PRO/PRO+. *P* values from Fisher test (2 × 2 comparison), chi-square test (n × 2 comparisons), or Student's *t*-tests (continuous parameters).

SAVR = surgical aortic valve replacement; other abbreviations as in Table 1.

CLINICAL OUTCOMES. Clinical outcomes at 30 days, 1 year, and 5 years in the matched cohort are summarized in Table 3. At 30 days, there were no significant differences in mortality, stroke, major or life-threatening bleeding, major vascular complication, and heart failure symptoms (NYHA functional class). New permanent pacemaker implantation was more frequently required in patients with a self-expanding THV than in those with a

FIGURE 1 Procedural and Echocardiographic Outcomes Between Self-Expanding Transcatheter Heart Valves vs Balloon-Expandable Transcatheter Heart Valves



BEV = balloon-expandable valve; SEV = self-expanding valve; VARC-3 = Valve Academic Research Consortium-3.

balloon-expandable THV (20.6% vs 8.3%; HR: 2.68; 95% CI: 1.46-4.93; $P = 0.002$).

Kaplan-Meier curves of major clinical outcomes of interest according to the THV type are depicted in the **Central Illustration**. At 5 years, all-cause and cardiovascular mortality occurred in 50.4% and 39.0% of patients with a self-expanding THV, respectively, and 39.6% and 35.0% of patients with a balloon-expandable THV, respectively (all-cause mortality: HR: 1.26; 95% CI: 0.84-1.90; $P = 0.269$; cardiovascular mortality: HR: 1.00; 95% CI: 0.62-1.60; $P = 0.996$). Although there was no significant difference in the rate of any stroke (12.3% vs 7.2%; HR: 1.78; 95% CI: 0.87-3.65; $P = 0.114$), disabling stroke was more frequent in patients with a self-expanding THV than in those with a balloon-expandable THV (6.6% vs 0.6%; HR: 10.01; 95% CI: 1.25-80.01; $P = 0.030$). Repeat aortic valve intervention (valve-in-valve TAVR, balloon dilatation, paravalvular leak closure, and surgical revision) was performed in 2.1% of patients with a self-expanding THV and 1.2% of patients with a balloon-expandable THV (HR: 1.44; 95% CI: 0.24-8.56; $P = 0.689$). Structural valve deterioration was reported in 1.6% of patients with a self-expanding THV and 3.2% of patients with a balloon-expandable THV (HR: 0.46; 95% CI: 0.08-2.51; $P = 0.367$). There were no significant differences in the occurrence of myocardial infarction and major or life-threatening bleeding. The rate of residual heart failure symptoms (NYHA functional class III/IV) was comparable between groups at 1 and 5 years, respectively. A sensitivity analysis using IPTW generated qualitatively similar results with no differences in clinical outcomes, except for a higher rate of disabling stroke in patients with a self-expanding THV compared with a balloon-expandable THV at 1 and 5 years (Supplemental Table 1).

TABLE 3 Clinical Outcomes in the Matched Population

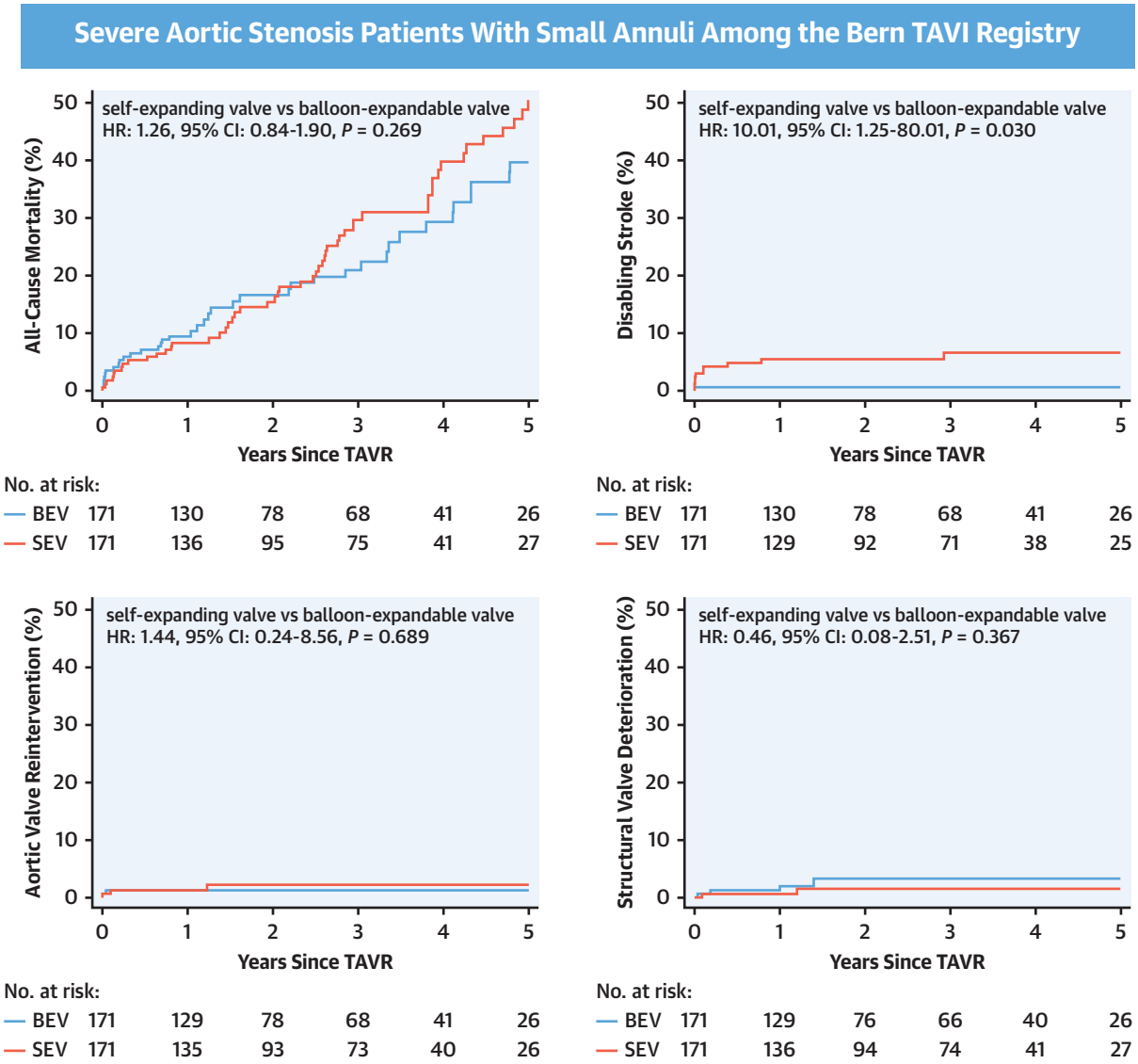
	Matched Cohort		SEV vs BEV	
	SEV (n = 171)	BEV (n = 171)	HR or RR (95% CI)	*P* Value
At 30 days				
All-cause mortality	3 (1.8)	6 (3.5)	0.50 (0.12-2.02)	0.327
Cardiovascular mortality	2 (1.2)	5 (2.9)	0.40 (0.08-2.08)	0.275
Any stroke (disabling and nondisabling)	10 (5.9)	6 (3.5)	1.67 (0.59-4.68)	0.333
Disabling stroke	5 (2.9)	1 (0.6)	5.02 (0.57-43.83)	0.144
Life-threatening or major bleeding	27 (15.9)	17 (9.9)	1.61 (0.86-2.99)	0.133
Major vascular complication	19 (11.1)	14 (8.2)	1.36 (0.67-2.77)	0.397
New permanent pacemaker implantation	35 (20.6)	14 (8.3)	2.68 (1.46-4.93)	0.002
VARC-3 device success[a]	136/171 (79.5)	136/171 (79.5)	1.00 (0.64-1.57)	>0.999
NYHA functional class III or IV	16/162 (9.9)	8/154 (5.2)	1.90 (0.81-4.45)	0.138
At 1 year				
All-cause mortality	14 (8.3)	16 (9.5)	0.86 (0.42-1.78)	0.688
Cardiovascular mortality	6 (3.6)	13 (7.8)	0.46 (0.17-1.23)	0.121
Any stroke (disabling and nondisabling)	15 (8.9)	8 (4.9)	1.89 (0.78-4.58)	0.159
Disabling stroke	9 (5.4)	1 (0.6)	9.07 (1.12-73.23)	0.038
Myocardial infarction	1 (0.6)	4 (2.4)	0.25 (0.03-2.26)	0.215
Life-threatening or major bleeding	31 (18.3)	21 (12.5)	1.50 (0.87-2.59)	0.141
Structural valve deterioration	1 (0.6)	3 (2.0)	0.32 (0.03-3.19)	0.335
Repeat aortic valve intervention[b]	2 (1.2)	2 (1.2)	0.99 (0.14-7.14)	0.994
NYHA functional class III or IV	24/151 (15.9)	17/148 (11.5)	1.38 (0.75-2.55)	0.297
At 5 years				
All-cause mortality	52 (50.4)	38 (39.6)	1.26 (0.84-1.90)	0.269
Cardiovascular mortality	35 (39.0)	32 (35.0)	1.00 (0.62-1.60)	0.996
Any stroke (disabling and nondisabling)	18 (12.3)	10 (7.2)	1.78 (0.87-3.65)	0.114
Disabling stroke	10 (6.6)	1 (0.6)	10.01 (1.25-80.01)	0.030
Myocardial infarction	1 (0.6)	5 (5.0)	0.20 (0.02-1.73)	0.143
Life-threatening or major bleeding	33 (22.2)	26 (21.1)	1.28 (0.77-2.14)	0.336
Structural valve deterioration	2 (1.6)	4 (3.2)	0.46 (0.08-2.51)	0.367
Repeat aortic valve intervention[b]	3 (2.1)	2 (1.2)	1.44 (0.24-8.56)	0.689
NYHA functional class III or IV	3/ 27 (11.1)	4/ 34 (11.8)	0.94 (0.23-3.86)	0.937

Values are n (%) or n/N (%) unless otherwise indicated. VARC-3 device success/assessed patients and NYHA/assessed patients (%), both with rate ratio from robustified Poisson regression with 95% CIs in parentheses. The matched cohort is cluster robustified for the matched sets (171 sets: each set contains 1 SEV and 1 BEV patient). [a]VARC-3 device failure: death within 30 days from procedure, surgery, or intervention related to: 1) the device; 2) a major vascular or access-related complication; or 3) a cardiac structural complication; VARC3 technical failure; and using 1-month visit echo or closest post-TAVR echo if 1-month echo is missing: mean aortic valve gradient ≥20 mmHg; moderate or severe aortic regurgitation. Mean gradient was not available in 5 patients, 3 of whom died so they were a device failure by default, and 2 were alive and had none or mild aortic regurgitation, technical success, and no surgery or interventions and were assumed to have VARC-3 device success. [b]Unplanned repeat aortic intervention includes valve-in-series, surgical revision, and aortic valve treatment.

NYHA = New York Heart Association; VARC-3 = Valve Academic Research Consortium-3; other abbreviations as in Table 1.

SENSITIVITY ANALYSIS IN THE SWISS TAVI REGISTRY. In the entire Swiss TAVI registry, 1,132 patients treated with a self-expanding THV and 1,155 patients with a balloon-expandable THV met the inclusion criteria and were analyzed. Consistent with the primary analysis, there were no significant differences in clinical outcomes, including mortality, myocardial infarction, major or life-threatening bleeding, structural valve deterioration, repeat aortic valve intervention, and residual heart failure symptoms (NYHA functional class III/IV) up to 5 years. Consistent with the main analysis, we observed a higher rate of disabling stroke in patients with a self-expanding THV compared with a balloon-expandable THV at 5 years (5.3% vs 2.0%; HR: 2.38; 95% CI: 1.37-4.10); in contrast to the primary analysis, the difference was already apparent at 30 days (2.8% vs 0.9%; HR: 2.72; 95% CI: 1.29-5.72; $P = 0.009$). Moreover, there was a higher rate of any stroke in patients with a self-expanding THV compared with a balloon-expandable THV at 30 days (4.2% vs 2.1%; HR: 1.77; 95% CI: 1.06-2.98; $P = 0.030$) and 5 years (8.3% vs 5.8%; HR: 1.47; 95% CI: 1.00-2.14; P = 0.047) (Supplemental Table 2).

CENTRAL ILLUSTRATION **5-Year Clinical Outcomes Between Self-Expanding Transcatheter Heart Valves vs Balloon-Expandable Transcatheter Heart Valves in Patients With Small Annuli**



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HRs and *P* values were calculated with the use of Cox proportional hazards survival models. BEV = balloon-expandable valve; SEV = self-expanding valve; TAVR = transcatheter aortic valve replacement.

DISCUSSION

The salient findings of the present analysis comparing self-expanding (supra-annular) THVs and balloon-expandable (intra-annular) THVs in patients with small annuli are as follows:

1. The VARC-3 technical success rate was >85% for both devices, with no difference between groups.
2. Self-expanding THVs demonstrated better echocardiographic hemodynamic performance in terms of a larger EOA, a lower mean transvalvular gradient, and a lower incidence of prosthesis-patient mismatch than balloon-expandable THVs.
3. The incidence of moderate or severe paravalvular regurgitation was rare in both devices; however, any paravalvular regurgitation, including mild and moderate, was more common in patients with a

self-expanding THV than those with a balloon-expandable THV.
4. Patients with a self-expanding THV received new permanent pacemaker implantation more frequently than those with a balloon-expandable THV.
5. VARC-3 device success was achieved in about 80% for both devices, with no difference between groups.
6. There were no significant differences in clinical outcomes, except for stroke, between the devices up to 5 years.
7. Disabling stroke occurred more frequently in patients with a self-expanding THV than in those with a balloon-expandable THV at 5 years.

A small aortic annulus is one of the important anatomical features that may put patients at risk of high residual gradients and prosthesis-patient mismatch after aortic valve replacement.[19] Self-expanding THVs have consistently shown better forward flow hemodynamics than balloon-expandable THVs and are likely to be preferred for patients with small annuli.[3-6] Indeed, in the present study, prosthesis-patient mismatch was documented in more than half of patients treated with a balloon-expandable THV, and a high residual gradient (≥20 mm Hg) was documented in 7% of the patients, both of which were higher than in patients treated with a self-expanding THV. However, it is noteworthy that the echocardiographic hemodynamic advantage of self-expanding THVs did not translate into a higher VARC-3 device success rate or improved clinical outcomes up to 5 years.

The incidence and clinical impact of prosthesis-patient mismatch in TAVR populations remain a subject of debate because of differences in the methods to document prosthesis-patient mismatch.[20,21] Earlier studies in surgical aortic valve replacement (SAVR) populations have generally shown a significant impact of severe prosthesis-patient mismatch on clinical outcomes.[22,23] However, it should be noted that prosthesis-patient mismatch in these studies has been based on predicted EOA but not on measured EOA. In a recent study in a TAVR population, the use of predicted EOA downgraded the severity of prosthesis-patient mismatch compared with measured EOA and had a stronger association with hemodynamic outcomes than "measured" prosthesis-patient mismatch.[14] In line with the study, the incidence of severe "predicted" prosthesis-patient mismatch was not documented in both devices in our cohort.

In contrast to the SAVR studies, previous TAVR studies mainly used "measured" prosthesis-patient mismatch and yielded conflicting results.[4,9,24-26] Several methodological pitfalls in "measured" prosthesis-patient mismatch have been suggested.[20,21] First, the indexation of the EOA to body surface area may result in overestimation of the prevalence of prosthesis-patient mismatch in obese patients.[14] Thus, more recent TAVR studies used adjusted cutoff values of EOA in obese patients according to the updated VARC-3 definitions,[12] as with the present study.[4,25,26] Second, discordance between echocardiographic and invasive measurements for hemodynamic performance of bioprostheses has been shown in several studies.[27-30] In general, transvalvular gradients are higher and EOAs are smaller when measured by Doppler echocardiography than by cardiac catheterization because of the pressure recovery phenomenon and the limitations and simplifications of the Bernoulli formula and continuity equation when applied in normal-functioning TAVR.[20] Our group previously showed that adjustment for pressure recovery using the energy loss index resulted in a downgrade of prosthesis-patient mismatch in a significant proportion of patients undergoing TAVR.[31] Furthermore, we previously reported comparable invasive gradients despite significantly lower echocardiographic gradients with self-expanding THVs compared with balloon-expandable THVs, which may be explained, at least in part, by different flow types (laminar vs turbulent) across THVs.[32-34] Third, the assumption that the cross-sectional area of the LVOT is circular may lead to underestimation of the EOA and overestimation of prosthesis-patient mismatch in 2-dimensional echocardiography. The use of the CT-derived LVOT area substantially downgraded the prevalence of prosthesis-patient mismatch after TAVR in previous studies.[35,36] Finally, measured EOA is flow dependent, and a low-flow state may lead to underestimation of the EOA, resulting in pseudosevere prosthesis-patient mismatch.

Considering all of these together, the hemodynamic performance of both devices may have been underestimated by the use of Doppler echocardiography. Clinically meaningful residual high gradients and prosthesis-patient mismatch might be less frequent even in patients with small annuli treated with an intra-annular THV. Indeed, the incidence of prosthesis-patient mismatch was lower after TAVR than SAVR even when intra-annular THVs were used, possibly because of the thinner stent frame and the absence of a bulky sewing ring.[9,25]

Furthermore, the increased risk of mild or moderate paravalvular regurgitation, new permanent pacemaker implantation, and disabling stroke in patients with a self-expanding THV compared with those with a balloon-expandable THV may have diluted a potential clinical benefit as a result of favorable hemodynamics. The effect of even mild paravalvular regurgitation has been shown to accrue over time and results in an increased risk of death at 5 years.[37] New permanent pacemaker implantation may also have an adverse effect on long-term clinical outcomes, although the data remain conflicting.[38] The reason for the higher risk of stroke in patients with a self-expanding THV may be related to partial repositionability that increases manipulation in the AVC. However, there is conflicting evidence on reported stroke rates in self-expanding and balloon-expandable THVs. In a recent randomized clinical trial comparing the Medtronic Evolut R and the Edwards SAPIEN 3 (N = 447), the 30-day stroke rate was lower in the self-expanding THV group than in the balloon-expandable THV group.[6] In contrast, stroke occurred more frequently in patients with a self-expanding THV than in those with a balloon-expandable THV after propensity score matching in the CENTER registry (N = 12,381).[39] At this stage, we cannot exclude the possibility of chance or residual confounding.

The impact of high residual gradients or prosthesis-patient mismatch on clinical outcomes may possibly become apparent in the long-term because the impaired forward hemodynamics may lead to faster degeneration of bioprostheses and the need for reintervention.[40] Nevertheless, in the present study, the occurrences of structural valve deterioration and unplanned repeat intervention were low in both groups with no significant differences up to 5 years, which underpins the current finding that there was no clear benefit of self-expanding THVs in terms of mortality and symptoms.

Because of the observational nature of the present study, the findings are exploratory and need to be corroborated in the ongoing SMART trial.[10] However, while waiting for definitive data in the coming years, the present study provides important insights into current optimal device selection. Because our preliminary data did not show a clear clinical benefit of the echocardiographic hemodynamic advantage of self-expanding THVs until 5 years, balloon-expandable THVs should not necessarily be avoided in patients with small annuli, particularly when other anatomical and clinical features favor the intra-annular design or the balloon-expandable deployment system.

STUDY LIMITATIONS. First, although the study was based on a large TAVR registry, the number of patients in the final propensity-matched cohort was modest, thus limiting the power to detect small differences in clinical outcomes of patients with small annuli. However, the findings were corroborated by 2 sensitivity analyses using IPTW both in the Bern TAVI registry and the Swiss TAVI registry. Furthermore, the robustness of the findings was reinforced by the use of detailed CT-imaging data (only in the Bern TAVI registry) and granularity in terms of procedural and clinical outcomes from the prospective TAVR registry. Second, although we used propensity score matching based on 33 variables including the detailed imaging data, the potential of bias caused by unmeasured or unrecognized confounding cannot be eliminated, as with all observational studies. Third, postprocedural echocardiographic data were not adjudicated by a core laboratory. Nevertheless, the measurement methods were standardized, and the measurements reflect current clinical practice in a high TAVR volume center. Fourth, flow data such as stroke volume, which may have an impact on the incidence of prosthesis-patient mismatch, were not systematically captured and could not be considered in the present analysis. Fifth, although the occurrences of structural valve deterioration and repeat aortic valve intervention were systematically collected and adjudicated, the absence of systematic echocardiographic follow-up is likely to have led to under-reporting of structural valve deterioration in the cohort. Finally, although the study cohort reflects current TAVR practice, the mean age was over 80 years. Thus, the findings may not be generalizable to younger patients with a longer life expectancy.

CONCLUSIONS

Supra-annular, self-expanding THVs demonstrated better echocardiographic hemodynamic performance compared with intra-annular, balloon-expandable THVs in patients with small annuli. Nevertheless, the hemodynamic advantage was not associated with a significant improvement in mortality or symptoms up to 5 years. The findings need to be corroborated in the ongoing randomized clinical trial (NCT04722250) in the coming years.

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PERSPECTIVES

WHAT IS KNOWN? Supra-annular, self-expanding THVs were associated with better hemodynamic performance compared with intra-annular, balloon-expandable THVs.

WHAT IS NEW? In a propensity score–matched analysis conducted in a prospective TAVR registry, the superior hemodynamic performance of self-expanding THVs compared with balloon-expandable THVs in patients with small annuli was not associated with a significant improvement in mortality or symptoms up to 5 years.

WHAT IS NEXT? The ongoing SMART trial (NCT04722250) will provide more definitive data in the coming years.

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