Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Balloon Versus Self-Expandable Valve for the Treatment of Bicuspid Aortic Valve Stenosis

Insights From the BEAT International Collaborative Registry

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BACKGROUND: Large data comparing the performance of new-generation self-expandable versus balloon-expandable transcatheter heart valves in bicuspid aortic stenosis are lacking. We aim to compare the safety and performance of balloon-expandable and self-expandable transcatheter heart valves in the treatment of bicuspid aortic stenosis.

METHODS: The BEAT (balloon versus self-expandable valve for the treatment of bicuspid aortic valve stenosis) registry included 353 consecutive patients who underwent transcatheter aortic valve implantation using new-generation Evolut R/PRO or Sapien 3 valves in bicuspid aortic valve.

RESULTS: A total of 353 patients (n=242 [68.6%] treated with Sapien 3 and n=111 [68.6%] treated with Evolut R (n=70)/PRO [n=41]) were included. Mean age was 77.8±8.3 years and mean Society of Thoracic Surgeons Predicted Risk of Mortality was 4.4±3.3%. Valve Academic Research Consortium-2 device success was similar between Sapien 3 and Evolut R/PRO (85.6% versus 87.2%; *P*=0.68). In the Sapien 3 group, 4 patients experienced annular rupture whereas this complication did not occur in the Evolut R/PRO group. After propensity score matching, Valve Academic Research Consortium-2 device success was similar between both groups (Sapien 3=85.7% versus Evolut R/Pro=84.4%; *P*=0.821). Both in the overall and in the matched population, no differences in the rate of permanent pacemaker implant were observed. At 1-year follow-up, the rate of overall death and cardiovascular death were similar between the 2 groups. In the unmatched population, the 1-year echocardiographic follow-up demonstrated similar rate of moderate-to-severe paravalvular aortic regurgitation (Evolut R/PRO 10.5% versus Sapien 3 4.2%, *P*=0.077); however, after propensity matching, the rate of moderate-to-severe paravalvular leak became significantly higher among patients treated with self-expandable valves (9.3% versus 0%; *P*=0.043).

CONCLUSIONS: Our study confirms the feasibility of both Sapien 3 and Evolut R/PRO implantation in bicuspid aortic valve anatomy; a higher rate of moderate-severe paravalvular aortic regurgitation was observed in the Evolut R/PRO group at 1-year follow-up in the matched cohort, although patients treated with balloon-expandable valve had a higher rate of annular rupture.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: aortic valve ■ bicuspid valve ■ pacemaker ■ propensity score ■ surgeons ■ transcatheter aortic valve replacement

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The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCINTERVENTIONS.119.008714.

For Sources of Funding and Disclosures, see page 10.

Circulation: Cardiovascular Interventions is available at www.ahajournals.org/journal/circinterventions

WHAT IS KNOWN

- Transcatheter aortic valve implantation in bicuspid anatomic has a favorable outcome with new second-generation devices.
- Bicuspid anatomy poses some therapeutic challenges related to anatomic differences compared with tricuspid valve anatomy. Few data are available comparing the performance of different transcatheter heart valves in bicuspid anatomy.

WHAT THE STUDY ADDS

- Our registry demonstrates for the first time differences in device performances when patients with bicuspid aortic valve stenosis are treated using new-generation balloon- or self-expandable valves.
- Balloon-expandable valves have higher gradients when used in bicuspid anatomies and a trend toward a higher rate of annular ruptures.
- Self-expandable valves have higher rate of residual moderate-to-severe perivalvular regurgitation.

Nonstandard Abbreviations and Acronyms

AV	aortic valve
BAV	bicuspid aortic valve
BEV	balloon-expandable valve
PAR	paravalvular aortic regurgitation
PS	propensity score
SEV	self-expandable valve
TAVI	transcatheter aortic valve implantation
THV	transcatheter heart valve
VARC-2	Valve Academic Research Consortium-2

Transcatheter aortic valve implantation (TAVI) is a valid alternative to surgical aortic valve (AV) replacement in patients with severe symptomatic aortic stenosis regardless of risk level.[1–3] Nowadays, percutaneous options are offered to a younger population in which the prevalence of bicuspid aortic valve (BAV) anatomy is higher. BAV has an estimated prevalence of 0.5% to 2% of the general population, with a peak of prevalence of 47.5% reported in the Chinese population enrolled in the Venus-A trial.[4] In this study, BAV anatomy was associated with greater aortic angulation, leaflet calcium burden, and ascending aorta dimensions compared with patients with tricuspid aortic valves (TAVs).[4] These anatomic peculiarities pose a challenge for the percutaneous treatment of BAV, as TAVI can be at higher risk of suboptimal result because of a high rate of paravalvular regurgitation, annular rupture, device underexpansion, need for a second transcatheter heart valve (THV), and aortic dissection.[5] These complications, frequently observed with first-generation devices, were mitigated with the introduction of new-generation THVs that show a safer profile and a higher rate of device success.[6] Even if retrospective registries confirm that new-generation THVs offer a similar device success rate both in BAV and TAV, these reports are still limited by the relatively low number of patients treated with such devices. Moreover, large data comparing the performance of new-generation self-expandable valves (SEVs) versus balloon-expandable valves (BEVs) are lacking. The aim of our international registry is to compare the procedural and clinical outcome of patients treated with the balloon-expandable Sapien 3 valve (Edwards Lifesciences, Irvine, CA) with those treated with the self-expandable Evolut R/PRO valve (Medtronic, Minneapolis, MN).

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

The balloon versus self-expandable valve for the treatment of bicuspid aortic valve stenosis registry is an international, multicenter registry including 353 consecutive patients treated for aortic stenosis in BAV with TAVI using Sapien 3 (n=242) or Evolut R/PRO systems (n=111) in 18 different European Centres (Figure I in the Data Supplement).

BAV morphology was classified according to the description by Sievers and Schmidtke[7] considering the number of cusps and the presence of raphes: type 0 refers to BAV characterized by the presence of 2 cusps and 1 commissure without evidence of a raphe, type 1 identified valve morphologies with 1 raphe, and type 2 was characterized by the presence of 2 raphes. The diagnosis of BAV was confirmed by the local heart team based on the review of the medical records, multi-slice computed tomography, and transthoracic/transesophageal echocardiography analysis when available. Authors declare that this study has been approved by institutional review committee and that the subjects gave informed consent.

Study Procedure

Patients were scheduled for TAVI after a multidisciplinary approach as indicated by the current recommendations. The preoperative workout included the execution of multi-slice computed tomography scan to plan the most appropriate route of intervention and to establish the aortic size and dimensions. Aortic sizing and valve measurements were performed by the local team. The degree of both annular and left ventricular outflow tract calcifications were graded according to previous methods.

All centers adopted a transfemoral-first approach policy; other vascular accesses (transapical, transaortic, transsubclavian) were considered in case of severe peripheral vascular disease involving the iliofemoral axis, which precluded a safe advancement of the delivery system. According to the local policy, TAVIs were performed under local or general anesthesia. The selection of prosthesis type and size was at the discretion of the treating physician at each center.

Study Devices

The Sapien 3 BEV incorporates a cobalt chromium stent that mounts bovine pericardial leaflets; as previously reported, the

valve has both an inner and an outer polyethylene terephthalate fabric seal to minimize the risk of perivalvular leaks. The delivery system has an active 3-dimensional coaxial positioning catheter and a 16-Fr expandable sheath.[8]

The Evolut R SEV is constituted by a nitinol frame mounting 3 bovine pericardial leaflets. The valve is repositionable, partially recapturable, and it is deliverable using a dedicated delivery system 14/16-Fr compatible depending on valve size. The Evolut PRO device represents an evolution of its predecessor and features a porcine pericardial outer wrap that contributes to reduce the risk of residual paravalvular leakage. Evolut R covers a wide range of sizes and is available in 23, 26, 29, and 34 mm sizes[9]; the PRO valve is currently available in 23, 26, and 29 mm sizes.[10]

Study End Points

The primary end point of the study was postprocedural device success, defined according to Valve Academic Research Consortium–2 (VARC-2) criteria.[11] Secondary end points included procedural complications, the rate of permanent pacemaker implantation, and the assessment of clinical outcomes at 30-day follow-up. Clinical events were reported according to the VARC-2 criteria. The severity of paravalvular aortic regurgitation (PAR) was qualitatively assessed and graded using transthoracic echocardiography at each institution according to established guidelines.

Statistical Analysis

Baseline categorical variables are presented as numbers and percentages; continuous variables are presented as mean±SD. Propensity score (PS) was calculated for each patient to estimate the propensity toward belonging to a specific treatment group (BEV versus SEV). This was done by means of a nonparsimonious multivariable logistic regression including the following covariates: age, sex, body mass index, previous pacemaker or implantable cardioverter defibrillator, chronic obstructive pulmonary disease, Society of Thoracic Surgeons Predicted Risk of Mortality score, baseline creatinine, bicuspid AV type 1, and moderate-severe AV calcification. The C-statistic for the PS model was 0.69, indicating good discrimination. The Hosmer-Lemeshow goodness-of-fit test *P* value was 0.28, confirming good calibration and fit of the multivariable model. A 1-to-1 nearest neighbour matching algorithm without replacement (caliper 0.10) was performed to identify PS matched pairs. All reported *P* values are 2 sided, and a *P* value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using Stata version 13.0 (STATACorp, College Station, TX).

RESULTS

Between June 2013 and October 2018, a total of 353 patients (n=242 [68.6%] treated with Sapien 3 valve and n=111 [31.4%] treated with Evolut R/PRO valve) were included. Baseline characteristics of the entire study population are reported in Table 1. Mean patient age was 77.8±8.3 years. Mean Society of Thoracic Surgeons Predicted Risk of mortality score was 4.4±3.3% without any significant difference between SEV and BEV. Other baseline characteristics of the 2 populations were well balanced. According to multi-slice computed tomography findings, patients receiving BEV had larger valve anatomy (area: 528.9±105.4 versus 493.2±119.5 mm^2; *P*=0.016; perimeter: 82.8±8.5 versus 79.7±9.7 mm; *P*=0.007) and higher burden of AV calcification (*P*=0.029). A 1-to-1 PS matching analysis (for variables listed in Section Methods) resulted in a total of 77 matched pairs. As shown in Table 2, there was no significant difference in any baseline characteristic among the PS-matched SEV and BEV groups, including the degrees of AV calcification.

Procedural Characteristics

Procedural characteristics of the overall population are reported in Table 3. TAVI was performed under conscious sedation in most patients (92.4%), without any significant difference between both groups. In the overall population, SEVs were more frequently implanted through a transfemoral route (94.6 versus 87.6%), although the transsubclavian access was used more frequently in case of BEV implantation (11.6 versus 1.8%; *P*=0.002). Need for pre-dilatation and post-dilatation was significantly higher in the SEV group (pre-dilatation: 58.7% versus 36.5%; *P*=0.001; post-dilatation: 45.9% versus 14.5%; *P*=0.001). VARC-2 device success was 86.7% in the overall population, with a similar rate between the unmatched groups (SEV 85.6% versus BEV 87.2%; *P*=0.68). Patients treated with BEV experienced 4 (1.7%) annular ruptures: among patients with annular rupture, one patient received urgent pericardiocentesis and the immediate implantation of a second Sapien 3 was able to seal the rupture; 3 patients underwent urgent conversion to open surgery, but 2 of them died and one of them survived and was regularly discharged 15 days after the index procedure. No differences were found in terms of permanent pacemaker implantation (SEV 16.0% versus BEV 16.1%; *P*=0.977).

After PS matching, the use of predilatation and post-dilatation remained significantly higher in the SEV group (pre-dilatation: 57.3% versus 37.9%; post-dilatation: 42.7% versus 14.3%; *P*<0.001 for both). VARC-2 device success remained similar between the PS-matched groups (SEV 84.4% versus BEV 85.7%; *P*=0.82). There was no significant difference in any periprocedural complication after PS matching, including pericardial tamponade, second THV implantation, valve embolization, annular rupture, aortic dissection, coronary occlusion, conversion to open surgery, and need of permanent pacemaker (Table 4).

Early Echocardiographic Outcome, 30-Days and 1-Year Follow-Up

Early echocardiographic results in the unmatched population are reported in Table 3. The mean prosthesis gradient

Table 1. Baseline Patient Characteristics (Overall Population)

	Overall (n=353)	SEV (n=111)	BEV (n=242)	*P* Value
Clinical characteristics				
Age, y	77.8±8.3 (n=353)	78.6±7.5 (n=111)	77.4±8.6 (n=242)	0.193
Male sex	229/353 (64.9)	62/111 (55.9)	167/242 (69.0)	0.016
BMI	26.2±5.3 (n=340)	25.7±4.7 (n=108)	26.4±5.5 (n=232)	0.258
COPD	81/353 (23.0)	28/111 (25.2)	52/242 (21.9)	0.490
Diabetes mellitus	75/353 (21.3)	25/111 (22.5)	50/242 (20.7)	0.691
Hypertension	273/351 (77.8)	89/111 (80.2)	184/240 (76.7)	0.462
Serum creatinine, mg/dL	1.14±0.47 (n=352)	1.08±0.41 (n=111)	1.16±0.49 (n=241)	0.166
Prior MI	26/352 (7.4)	9/111 (8.1)	17/241 (7.1)	0.725
Prior PCI	77/353 (21.8)	21/111 (18.9)	56/242 (23.1)	0.373
Prior CABG	29/353 (8.2)	5/111 (4.5)	24/242 (9.9)	0.086
Prior cardiac surgery	28/337 (8.3)	7/105 (6.7)	21/232 (9.1)	0.463
Peripheral vascular disease	63/353 (17.9)	23/111 (20.7)	40/242 (16.5)	0.340
Prior stroke or TIA	54/353 (15.3)	19/111 (17.1)	35/242 (14.5)	0.520
History of atrial fibrillation	85/335 (25.4)	23/104 (22.1)	62/231 (26.8)	0.358
PM or ICD	31/353 (8.8)	11/111 (9.9)	20/242 (8.3)	0.612
NYHA class				0.937
I	5/352 (1.4)	2/111 (1.8)	3/241 (1.2)	
II	103/352 (29.3)	32/111 (28.8)	71/241 (29.5)	
III	215/352 (61.1)	69/111 (62.2)	146/241 (60.6)	
IV	29/352 (8.2)	8/111 (7.2)	21/241 (8.7)	
STS-M score (%)	4.4±3.3 (n=336)	4.2±3.3 (n=110)	4.4±3.3 (n=226)	0.575
Echocardiographic data				
Mean AV gradient, mm Hg	48.3±16.6 (n=343)	49.5±16.6 (n=108)	47.7±16.5 (n=235)	0.352
AVA, cm^2	0.68±0.22 (n=336)	0.72±0.28 (n=101)	0.67±0.18 (n=235)	0.059
Moderate-severe aortic regurgitation	67/345 (19.4)	23/109 (21.1)	44/236 (18.7)	0.592
LVEF (%)	52.0±14.3 (n=353)	53.3±13.6 (n=111)	51.5±14.7 (n=242)	0.268
Severe pulmonary hypertension	48/297 (16.2)	18/103 (17.5)	30/194 (15.5)	0.654
MDCT data				
Annular sizing				
Area, mm^2	519.0±110.4 (n=276)	493.2±119.5 (n=77)	528.9±105.4 (n=199)	0.016
Perimeter, mm	81.9±8.9 (n=287)	79.7±9.7 (n=88)	82.8±8.5 (n=199)	0.007
Area-derived diameter, mm	25.6±2.7 (n=276)	24.9±3.0 (n=77)	25.8±2.6)	0.011
Perimeter-derived diameter, mm	26.1±2.8 (n=287)	25.3±3.1 (n=88)	26.4±2.7 (n=199)	0.007
Aortic valve calcification				0.029
None	6/274 (2.2)	3/89 (3.4)	3/185 (1.6)	
Mild	49/274 (17.9)	24/89 (27.0)	25/185 (13.5)	
Moderate	99/274 (36.1)	26/89 (29.2)	73/185 (39.5)	
Severe	120/274 (43.8)	36/89 (40.5)	84/185 (45.4)	
Sino-tubular junction, mm	31.0±4.3 (n=238)	29.8±4.5 (n=71)	31.4±4.1 (n=167)	0.007
Ascending aorta–major diameter, mm	37.0±5.4 (n=269)	36.1±5.4 (n=85)	37.4±5.4 (n=184)	0.063
Type of bicuspid AV				
Type 0	25/353 (7.1)	9/111 (8.1)	16/242 (6.6)	0.611
Type 1	218/353 (61.8)	64/111 (57.7)	154/242 (63.6)	0.283
Type 2	3/353 (0.9)	1/111 (0.9)	2/242 (0.8)	0.944
Undeterminate/unavailable	105/353 (29.8)	36/111 (32.4)	69/242 (28.5)	0.454

AV indicates aortic valve; AVA, aortic valve area; BEV, balloon-expandable valve; BMI, body mass index; CABG, coronary bypass grafting; COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MDCT, multi detector computed tomography; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PM, pacemaker; SEV, self-expandable valve; STS-M, Society of Thoracic Surgeons Predicted Risk of Mortality; and TIA, transient ischemic attack.

Table 2. Baseline Patients Characteristics (Matched Populations)

	Overall (n=154)	SEV (n=77)	BEV (n=77)	*P* Value
Clinical characteristics				
Age, y	79.3±7.8 (n=154)	79.1±7.8 (n=77)	79.4±7.9 (n=77)	0.780
Male sex	89/154 (57.8)	48/77 (62.3)	41/77 (53.3)	0.253
BMI	25.5±4.9 (n=154)	25.8±4.8 (n=77)	25.1±4.9	0.410
COPD	40/154 (26.0)	19/77 (24.7)	21/77 (27.3)	0.713
Diabetes mellitus	33/154 (21.4)	20/77 (26.0)	13/77 (16.9)	0.169
Hypertension	117/153 (76.5)	63/77 (81.8)	54/76 (71.1)	0.117
Serum creatinine, mg/dL	1.03±0.38 (n=154)	1.07±0.39 (n=77)	1.00±0.37 (n=77)	0.251
Prior MI	12/153 (7.8)	7/77 (9.1)	5/76 (6.6)	0.563
Prior PCI	36/154 (23.4)	18/77 (23.4)	18/77 (23.4)	1.000
Prior CABG	9/154 (5.8)	5/77 (6.5)	4/77 (5.2)	0.731
Prior cardiac surgery	10/154 (6.5)	6/77 (7.8)	4/77 (5.2)	0.513
Peripheral vascular disease	29/154 (18.8)	19/77 (24.7)	10/77 (13.0)	0.064
Prior stroke or TIA	20/154 (13.0)	10/77 (13.0)	10/77 (13.0)	1.000
History of atrial fibrillation	33/146 (22.6)	14/72 (19.4)	19/74 (25.7)	0.368
PM or ICD	12/154 (7.8)	7/77 (9.1)	5/77 (6.5)	0.548
NYHA class				0.743
I	3/154 (2.0)	2/77 (2.6)	1/77 (1.3)	
II	49/154 (31.8)	27/77 (35.1)	22/77 (28.6)	
III	90/154 (58.4)	42/77 (54.6)	48/77 (62.3)	
IV	12/154 (7.8)	6/77 (7.8)	6/77 (7.8)	
STS-M score (%)	4.3±2.8 (n=154)	4.4±3.1 (n=77)	4.2±2.5 (n=77)	0.719
Echocardiographic data				
Mean AV gradient, mm Hg	49.4±16.5 (n=146)	49.3±16.5 (n=74)	49.4±16.7 (n=72)	0.968
Moderate-severe aortic regurgitation	30/149 (20.1)	17/75 (22.7)	13/74 (17.6)	0.438
LVEF (%)	54.6±13.2 (n=154)	53.7±13.8 (n=77)	55.5±12.7 (n=77)	0.383
Severe pulmonary hypertension	18/122 (14.8)	12/69 (17.4)	6/53 (11.3)	0.349
MDCT data				
Annular sizing				
Area, mm^2	506.0±110.9 (n=112)	504.9±118.7 (n=54)	507.0±104.1 (n=58)	0.922
Perimeter, mm	80.9±8.9 (n=122)	80.9±9.6 (n=64)	80.9±8.2 (n=58)	0.976
Area-derived diameter, mm	25.2±2.8 (n=112)	25.2±3.0 (n=54)	25.3±2.6 (n=58)	0.856
Perimeter-derived diameter, mm	25.8±2.8 (n=122)	25.8±3.1 (n=64)	25.8±2.6 (n=58)	0.976
Aortic valve calcification				0.844
None	5/154 (3.3)	3/77 (3.9)	2/77 (2.6)	
Mild	38/154 (24.7)	17/77 (22.1)	21/77 (27.3)	
Moderate	45/154 (29.2)	24/77 (31.2)	21/77 (27.3)	
Severe	66/154 (42.9)	33/77 (42.9)	33/77 (42.9)	
Sino-tubular junction, mm	30.2±4.5 (n=130)	29.8±4.6 (n=64)	30.5±4.5 (n=66)	0.399
Ascending aorta–major diameter, mm	35.7±5.1 (n=133)	35.3±5.0 (n=68)	36.1±5.3 (n=65)	0.377
Type of bicuspid AV				
Type 0	15/154 (9.7)	7/77 (9.1)	8/77 (10.4)	0.786
Type 1	96/154 (62.3)	53/77 (68.8)	43/77 (55.8)	0.096
Type 2	0/154 (0.0)	0/154 (0.0)	0/154 (0.0)	…
Undeterminate/unavailable	42/154 (27.3)	16/77 (20.8)	26/77 (33.8)	0.070

AV indicates aortic valve; BEV, balloon-expandable valve; BMI, body mass index; CABG, coronary bypass grafting; COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MDCT, multi detector computed tomography; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PM, pacemaker; SEV, self-expandable valve; STS-M, Society of Thoracic Surgeons Predicted Risk of Mortality; and TIA, transient ischemic attack.

Table 3. Procedural Outcome (Overall Population)

	Overall (n=353)	SEV (n=111)	BEV (n=242)	*P* Value
Procedural characteristics and in-hospital outcomes				
Conscious sedation	303/328 (92.4)	97/107 (90.7)	206/221 (93.2)	0.569
Access route				0.002
Transfemoral	317/353 (89.8)	105/111 (94.6)	212/242 (87.6)	
Transsubclavian	30/353 (8.5)	2/111 (1.8)	28/242 (11.6)	
Direct transaortic	6/353 (1.7)	4/111 (3.6)	2/242 (0.8)	
Valve size				<0.001
23 mm	48/353 (13.6)	4/111 (3.6)	44/242 (18.2)	
26 mm	120/353 (34.0)	30/111 (27.0)	90/242 (37.2)	
29 mm	151/353 (42.8)	43/111 (38.7)	108/242 (44.6)	
31 mm	2/353 (0.6)	2/111 (1.8)	…	
34 mm	32/353 (9.1)	32/111 (28.8)	…	
Pre-dilatation	152/350 (43.4)	64/109 (58.7)	88/241 (36.5)	<0.001
Post-dilatation	85/350 (24.3)	50/109 (45.9)	35/241 (14.5)	<0.001
Procedural death	4/353 (1.1)	0/111 (0.0)	4/242 (1.7)	0.173
Need of second valve	17/353 (4.8)	7/111 (6.3)	10/242 (4.1)	0.376
Annular rupture	4/353 (1.1)	0/111 (0.0)	4/242 (1.7)	0.173
Cardiac tamponade	8/353 (2.3)	2/111 (1.8)	6/242 (2.5)	0.691
VARC-2 device success	306/353 (86.7)	95/111 (85.6)	211/242 (87.2)	0.680
Moderate-severe AR	14/353 (4.0)	12/111 (10.8)	2/242 (0.8)	<0.001
Mean gradient >20 mm Hg predischarge	21/353 (6.0)	5/111 (4.5)	16/242 (6.6)	0.437
Mean gradient predischarge (mm Hg)	10.8±4.8 (n=314)	9.6±5.1 (n=101)	11.3±4.6 (n=213)	0.003
LVEF predischarge (%)	54±13 (n=325)	56.3±11.0 (n=104)	53.2±13.8 (n=221)	0.047
Need of permanent PM	51/317 (16.1)	16/100 (16.0)	35/217 (16.1)	0.977
Vascular complication				0.521
Major	11/353 (3.1)	2/111 (1.8)	9/242 (3.7)	
Minor	24/353 (6.8)	9/111 (8.1)	15/242 (6.2)	
Bleeding				0.222
Life-threatening	7/345 (2.0)	2/110 (1.8)	5/235 (2.1)	
Major	15/345 (4.4)	5/110 (4.6)	10/235 (4.3)	
Minor	21/345 (6.1)	11/110 (10.0)	10/235 (4.3)	
30-d clinical outcomes				
30-d all-cause death	14/328 (4.3)	3/100 (3.0)	11/228 (4.8)	0.452
30-d cardiovascular death	13/328 (4.0)	3/100 (3.0)	10/228 (4.4)	0.554
30-d stroke	5/315 (1.6)	3/98 (3.1)	2/217 (0.9)	0.160
30-d any hospitalization	21/318 (6.6)	4/99 (4.0)	17/219 (7.8)	0.216
30-d cardiac hospitalization	7/317 (2.2)	2/99 (2.0)	5/218 (2.3)	0.878
1-y echocardiographic outcomes				
Mean gradient, mm Hg	10.5±4.4 (n=203)	8.5±4.0 (n=65)	11.4±4.2 (n=138)	<0.0001
Mean gradient >20 mm Hg	7/203 (3.5%)	1/65 (1.5%)	6/138 (4.4%)	0.306
EOA, cmq	1.8±0.4 (n=149)	2.0±0.5 (n=41)	1.7±0.4 (n=108)	0.0001
Moderate-severe total AR	13/211 (6.2%)	7/67 (10.5%)	6/144 (4.2%)	0.077

AR indicates aortic regurgitation; BEV, balloon-expandable valve; EOA, effective orifice area; LVEF, left ventricular ejection fraction; PM, permanent pacemaker; SEV, self-expandable valve; and VARC-2, Valve Academic Research Consortium-2.

was significantly higher in the BEV group (11.3±4.6 versus 9.6±5.1 mm Hg; *P*=0.003), although the proportion of patients with mean AV gradient ≥20 mm Hg was similar between groups (SEV 4.5% versus BEV 6.6%; *P*=0.437). The overall amount of moderate-severe PAR was significantly higher after SEV implantation (10.8% versus 0.8%; *P*<0.001). After PS matching (Table 4), the proportion for moderate-severe PAR remained higher among patients treated with SEV (10.4% versus 0.0%, *P*=0.004; Figure II in the Data Supplement); in

Table 4. Procedural Outcome (Matched Population)

	Overall (n=154)	SEV (n=77)	BEV (n=77)	*P* Value
Procedural characteristics and in-hospital outcomes				
Conscious sedation	142/154 (92.2)	70/77 (90.9)	75/77 (97.4)	0.176
Access route				0.060
Transfemoral	139/154 (90.3)	72/77 (93.5)	67/77 (87.0)	
Transsubclavian	11/154 (7.1)	2/77 (2.6)	9/77 (11.7)	
Direct transaortic	4/154 (2.6)	3/77 (3.9)	1/77 (1.3)	
Valve size				<0.001
23 mm	21/154 (13.6)	3/77 (3.9)	18/77 (23.4)	
26 mm	50/154 (32.5)	18/77 (23.4)	32/77 (41.6)	
29 mm	56/154 (36.4)	29/77 (37.7)	27/77 (35.1)	
31 mm	2/154 (1.3)	2/77 (2.6)	-	
34 mm	25/154 (16.3)	25/77 (32.5)	-	
Pre-dilatation	61/152 (40.1)	43/75 (57.3)	18/77 (23.4)	<0.001
Post-dilatation	43/152 (28.3)	32/75 (42.7)	11/77 (14.3)	<0.001
Procedural death	2/154 (1.3)	0/77 (0.0)	2/77 (2.6)	0.155
Need of second valve	6/154 (3.9)	5/77 (6.5)	1/77 (1.3)	0.096
Annular rupture	2/154 (1.3)	0/77 (0.0)	2/77 (2.6)	0.155
Cardiac tamponade	4/154 (2.6)	1/77 (1.3)	3/77 (3.9)	0.311
VARC-2 device success	131/154 (85.1)	65/77 (84.4)	66/77 (85.7)	0.821
Moderate-severe AR	8/154 (5.2)	8/77 (10.4)	0/77 (0.0)	0.004
Mean gradient >20 mm Hg predischarge	11/154 (7.1)	4/77 (5.2)	7/77 (9.1)	0.348
Mean gradient predischarge (mm Hg)	10.6±4.7 (n=135)	9.7±4.9 (n=68)	11.5±4.3 (n=67)	0.026
LVEF predischarge (%)	56.6±11.5 (n=147)	56.2±11.7 (n=74)	57.1±11.3 (n=73)	0.649
Need of permanent PM	22/140 (15.7)	10/70 (14.3)	12/70 (17.1)	0.642
Vascular complication				0.439
Major	3/154 (2.0)	1/77 (1.3)	2/77 (2.6)	
Minor	7/154 (4.6)	5/77 (6.5)	2/77 (2.6)	
Bleeding				0.014
Life-threatening	4/151 (2.7)	2/76 (2.6)	2/75 (2.7)	
Major	7/151 (4.6)	3/76 (4.0)	4/75 (5.3)	
Minor	10/151 (6.6)	10/76 (13.2)	0/75 (0.0)	
30-d clinical outcomes				
30-d all-cause death	7/141 (5.0)	3/68 (4.4)	4/73 (5.5)	0.771
30-d cardiovascular death	7/141 (5.0)	3/68 (4.4)	4/73 (5.5)	0.771
30-d stroke	1/132 (0.8)	1/67 (1.5)	0/65 (0.0)	0.323
30-d any hospitalization	7/134 (5.2)	4/67 (6.0)	3/67 (4.5)	0.698
30-d cardiac hospitalization	3/134 (2.2)	2/67 (3.0)	1/67 (1.5)	0.559
1-y echocardiographic outcomes (PS-matched population)				
Mean gradient, mm Hg	9.9±4.5 (n=80)	8.5±4.2 (n=42)	11.5±4.3 (n=38)	0.0019
Mean gradient >20 mm Hg	3/80 (3.8%)	1/42 (2.4%)	2/38 (5.3%)	0.498
EOA, cmq	1.9±0.5 (n=63)	2.1±0.6 (n=28)	1.8±0.2 (n=35)	0.0026
Moderate-severe total AR	4/85 (4.7%)	4/43 (9.3%)	0/42 (0.0%)	0.043

AR indicates aortic regurgitation; BEV, balloon-expandable valve; EOA, effective orifice area; LVEF, left ventricular ejection fraction; PM, permanent pacemaker; PS, propensity score; SEV, self-expandable valve; and VARC-2, Valve Academic Research Consortium-2.

the matched population, we confirmed that BEV had a higher residual mean gradient (11.5±4.3 versus 9.7±4.9 mm Hg; *P*=0.026), whereas the proportion of patients with mean AV gradient ≥20 mm Hg was not significantly different between both groups (SEV 5.2% versus BEV 9.1%; *P*=0.348).

At 1-year follow-up, we did not find differences in all-cause deaths and in cardiovascular deaths both in

the overall population and in the PS-matched cohort (Figure). The 1-year unmatched echocardiographic follow-up showed a nonsignificant difference in moderate-severe PAR between SEV and BEV (10.5 versus 4.2%, *P*=0.077) with a better hemodynamic profile among patients treated with EvolutR/Pro (mean gradient 8.5±4.0 versus 11.4±4.2 mm Hg; *P*<0.0001; effective orifice area 2.0±0.5 versus 1.7±0.4 cm^2; *P*=0.0001). After PS matching, a higher rate of PAR II+ was observed in the SEV group (9.3% versus 0.0%; *P*=0.043).

DISCUSSION

The balloon versus self-expandable valve for the treatment of bicuspid aortic valve stenosis international registry is the first study comparing the most commercially utilized THVs (Sapien 3 versus EvolutR/PRO) in BAV anatomy. The main findings of our study are as follows:

1. VARC-2 device success was obtained in 86.7% of patients, without significant differences after SEV and BEV both in the entire population and in the PS-matched cohort.
2. The rate of moderate-severe PAR after TAVI was acceptable (4%) in the entire cohort; however, it was higher after SEV implantation at 1 year in the PS-matched population.
3. SEV had a better hemodynamic profile at discharge and at 1-year follow-up with lower mean gradient and higher effective orifice area.
4. At 30-day follow-up and at 1-year follow-up, the 2 groups of treatment showed comparable rates of clinical events both in the entire cohort and in the PS-matched population.

Current TAVI practice is mainly based on evidence on TAVI for tricuspid AV, being BAV anatomy excluded from landmark TAVI trials.[12] However, considering the unique morphological characteristics of BAV, TAVI in this setting could be particularly challenging and raise concerns about suboptimal procedural results. Furthermore, as TAVI is rapidly expanding toward younger and lower-risk patients,[13] the frequency of BAV anatomy among TAVI candidates is expected to increase in the future, with the consequence clinical need of optimizing TAVI outcomes in this specific patient subset. The large Bicuspid AS TAVI multicenter registry has recently compared clinical

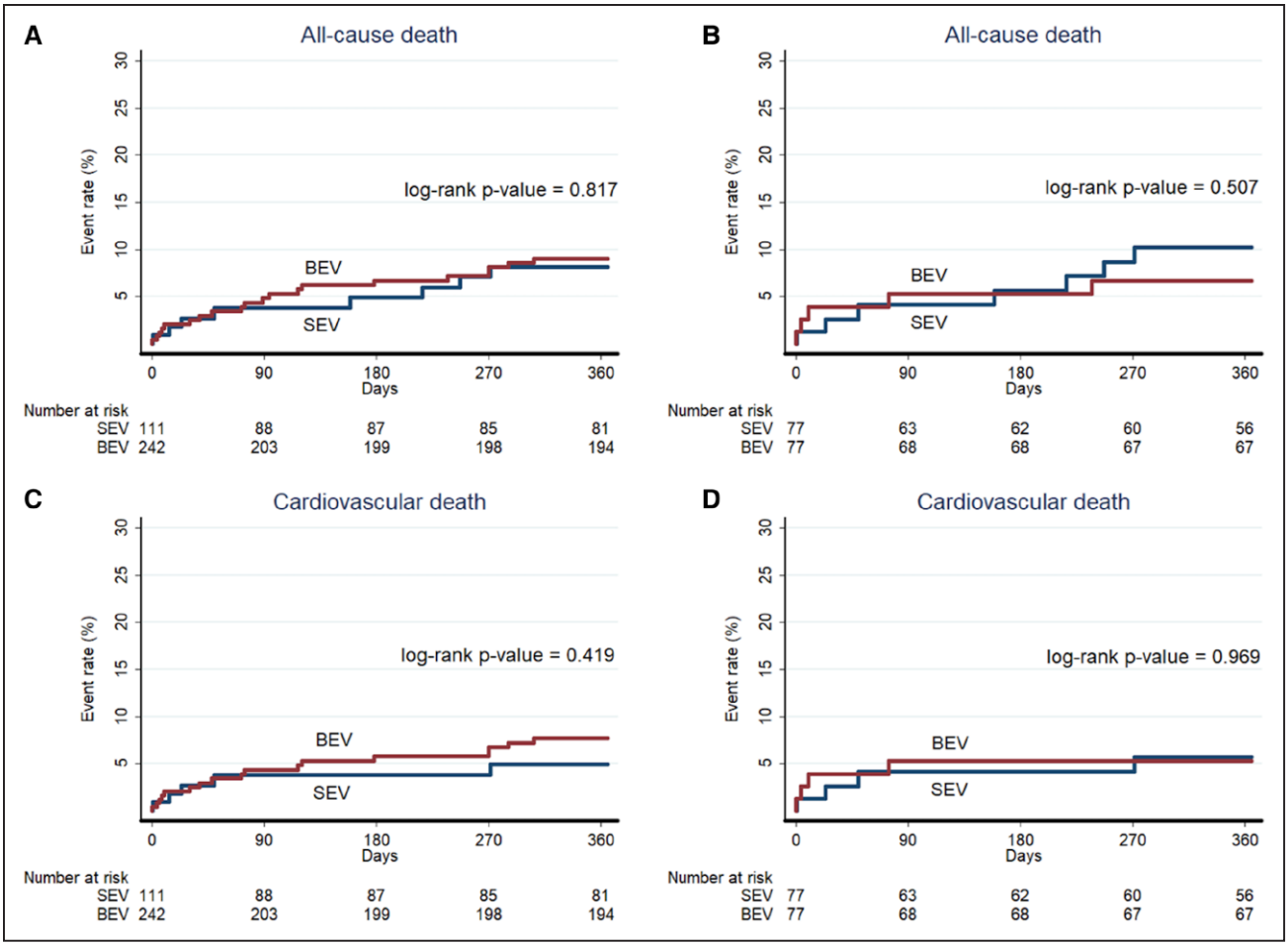

Figure. One-year outcome according to all cause of death and cardiovascular deaths in both matched and unmatched populations.
BEV indicates balloon-expandable valves; and SEV, self-expandable valve.

outcomes of patients undergoing TAVI for bicuspid versus tricuspid aortic stenosis: among 546 matched pairs, VARC-2-defined device success was significantly lower in bicuspid AS patients (85.3% versus 91.4%; *P*=0.002), a difference that was maintained only in the subgroup of patients treated with early-generation devices.[6] A subsequent analysis of the same multicenter registry focused on the type of THV implanted, comparing TAVI with early- versus new-generation devices in patients with BAV. This study included 199 patients treated with early-generation THVs (n=87 Sapien XT; n=112 CoreValve) and 102 patients treated with new-generation THVs (n=91 Sapien 3; n=11 Lotus), reporting a lower rate of moderate-severe PAR (0.0% versus 8.5%; *P*=0.002) and a higher rate of device success (92.2% versus 80.9%; *P*=0.01) in the new-generation group, with similar rates of 30-day mortality and other major clinical end points between the 2 groups. Favorable outcomes with the Sapien 3 THV were also reported in a recent single-arm study, showing a 0% rate of moderate-severe PAR among 51 patients with BAV treated with this new-generation BEV device.[14] Despite this early evidence supporting the use of new-generation THVs for the treatment of bicuspid aortic stenosis, a direct comparison between different new-generation devices could be helpful to optimize procedural results and clinical outcomes in this specific patient subset; furthermore, available studies included a relatively low number of patients treated with Sapien 3 and no data are available for Evolut R/PRO in BAV population.

Our study adds information by evaluating the clinical outcomes of patients with BAV treated with 2 most commonly used new-generation devices that are conceptually different and currently widely implanted worldwide: the Sapien 3 BEV is a low-profile valve with an outer skirt and a higher radial force able to minimize the risk of PAR; the Evolut R/PRO SEVs are higher profile valves with less radial force. The Evolut PRO THV has an adjunctive pericardial wrap that increases valve sealing, thus theoretically reducing the risk of PAR; however, real-world experiences have demonstrated that Evolut R and PRO have similar results in terms of device success.[15]

Sapien 3 has been previously studied in BAV anatomy by Kawamori et al[16] reporting a lower THV expansion at mid, sinus, and outflow levels compared with tricuspid AV patients. Nevertheless, this morphological difference did not correlate with an increase of transvalvular gradients in BAV versus tricuspid AV patients. Conversely, our analysis demonstrated that SEV offered a better hemodynamic profile with larger effective orifice area and lower gradients compared with BEV. Nevertheless, these results should be contextualized as Sapien 3 was implanted in smaller sizes compared with EvolutR/PRO both in overall and PS-matched populations. Moreover, the supra-annular design of SEVs can mitigate the effect of valve asymmetry and under-expansion, thus minimizing the risk of high transvalvular gradients. However, these data need to be carefully confirmed in larger and prospective studies to evaluate the possible clinical impact that residual high gradients have on valve durability.

Our registry confirmed previous studies about the excellent performance of Sapien 3 valve in terms of residual PAR. As already mentioned, Perlman et al[17] reported a 0% rate of moderate-severe PAR among 51 patients with BAV treated with Sapien 3. On the other side, SEV demonstrated a high rate of moderate-severe PAR in the matched populations both at discharge and at 1-year follow-up. The difference is remarkable if compared with the performance of Evolut R and PRO valves in tricuspid AV. The high rate of PAR observed in bicuspid anatomies in the SEV group could be justified by the low radial force of this prosthesis, which does not guarantee an optimal sealing in the pericommissural zone. SEV might be more capable of conforming to the irregular orifice of BAV but less capable of achieving a circular formation after implantation. Moreover, the highly calcified raphes and leaflets can hamper a complete SEV expansion. As matter of fact, SEV required more frequently predilatation and post-dilatation to be optimally implanted and to achieve a satisfactory result. A high rate of post-dilatation was similarly observed for another SEV, the Acurate neo device (Boston Scientific, Marlborough), when implanted in bicuspid anatomies: among 54 patients treated with such THV, the rate of post-dilatation increased proportionally according to the degree of annular calcifications.[5] The Bicuspid Aortic Stenosis With Evolut Platform International Experience (BIVOLUT X) international registry (Clinical trial identifier: NCT03495050) aims to enrol 150 BAV treated with Evolut PRO and will give more definite answers about the performance of SEV in BAV through a detailed analysis of postprocedural multi-slice computed tomography findings.

Limitations

The main limitation of our study is represented by its observational nature, without independent adjunction of adverse events and without an independent core laboratory for the diagnosis of BAV and for the evaluation of echocardiographic outcomes. We performed a PS-matched comparison between the 2 groups to account for demographic and anatomic differences that could bias the interpretation of our results. However, a potential impact of unknown or unmeasured confounding factors on study outcomes cannot be excluded. The device selection was left to the operator's decision and may have affected the observed outcomes. The vast majority of the treated population had a bicuspid type I with and 27% of the patient had an indeterminate bicuspid classification: we cannot exclude that this lack of information had an impact on device selection. Finally, the low number of patients included in the analysis, together with the

multicenter design, may have limited the statistical power of the analysis.

Conclusions

The balloon versus self-expandable valve for the treatment of bicuspid aortic valve stenosis international registry confirms the feasibility of both Sapien 3 and Evolut R/PRO implantation in BAV anatomy, with a similar rate of device success between these new-generation THVs; however, a higher rate of moderate-severe PAR was observed among SEV recipients although patients treated with BEV had a higher rate of annular rupture. Further observational and randomized studies are needed to confirm our findings.

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Received November 21, 2019; accepted April 20, 2020.

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Sources of Funding

None.

Disclosures

Dr Mangieri has received a research grant (to the institution) from Boston Scientific and a and has served on medical advisory boards for Boston Scientific. Dr Kim received proctor fees from Symetis SA/Boston Scientific, St. Jude Medical/Abbott, lecture honoraria from Edwards Lifesciences, Symetis SA/Boston, St. Jude Medical/Abbott. Dr Tchetche is proctor for Edwards LifeSciences, Medtronic and Boston Scientific. Dr De Biase has been supported by a research grant provided by the Cardiopath PhD program. Dr De Marco serves as proctor for Boston Scientific and Kardia. Dr Giannini serves as proctor for Neovasc. Dr Montorfano serves as proctor for Edwards Lifescience, Abbott and Kardia. Dr Schäfer is consultant and proctor for Edwards Lifesciences, Abbott Vascular, Biotronik, Jena Valve Technology, Medtronic, Inc, Symetis SA and Boston Scientific, received speaker honoraria and travel compensation from JenaValve Technology, Edwards Lifesciences, Abbott Vascular, Medtronic, Inc, Biotronik, Direct Flow Medical, Symetis SA and Boston Scientific. Dr Sinning has received speaker honoraria and research grants from Medtronic, Edwards Lifesciences, Abbott, and Boston Scientific. Dr De Backer is consultant for Abbott. Stefan Toggweiler is proctor and consultant for Boston Scientific, proctor and consultant for New Valve Technology, institutional research grant from Boston Scientific. Dr Søndergaard received institutional research grants and has been consultant for Abbott, Medtronic and Boston Scientific, Medtronic, and Symetis SA. Dr Sievert has received study honoraria, travel expenses, and consulting fees from 4tech Cardio, Abbott, Ablative Solutions, Ancora Heart, Bavaria Medizin Technologie GmbH, Bioventrix, Boston Scientific, Carag, Cardiac Dimensions, Celonova, Comed B.V., Contego, CVRx, Edwards Lifesciences, Endologix, Hemoteq, Lifetech, Maquet Getinge Group, Medtronic, Mitralign, Nuomao Medtech, Occlutech, pfm Medical, Recor, Renal Guard, Rox Medical, Terumo, Vascular Dynamics, and Vivasure Medical. Dr Nickenig has received research funding from the Deutsche Forschungsgemeinschaft, the German Federal Ministry of Education and Research, the EU, Abbott, AGA Medical, AstraZeneca, Bayer, Berlin Chemie, Biosensus, Biotronic, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Edwards Lifesciences, Medtronic, Novartis, Pfizer, Sanofi, and St Jude Medical; has received honoraria for lectures or advisory boards from Abbott, AGA Medical, AstraZeneca, Bayer, Berlin, Cardiovalve, Berlin Chemie, Biosensus, Biotronic, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Edwards Lifesciences, Medtronic, Novartis, Pfizer, Sanofi, and St Jude Medical; and has participated in clinical trials for Abbott, AGA Medical, AstraZeneca, Bayer, Berlin Chemie, Biosensus, Biotronic, Bristol-Myers Squibb, Boehringer Ingelheim, Cardiovalve, Daiichi Sankyo, Edwards Lifesciences, Medtronic, Novartis, Pfizer, Sanofi, and St Jude Medical. Dr Latib has served on advisory boards for Medtronic and Abbott; and has been a consultant to Edwards Lifesciences. The other authors report no conflicts.

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