Sinus of Valsalva Dimension and Clinical Outcomes in Patients Undergoing Transcatheter Aortic Valve Implantation

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Background Ascending aortic root anatomy is routinely evaluated on pre-procedural multi-detector computed tomography (MDCT). However, its clinical significance has not been adequately studied. We aimed to investigate the impact of the sinus of Valsalva (SOV) dimension on clinical outcomes in patients undergoing transcatheter aortic valve implantation (TAVI).

Methods In a prospective TAVI registry, we retrospectively assessed SOV dimensions by pre-procedural MDCT. Patients were stratified according to tertiles of SOV diameter indexed to body surface area (SOVi). The primary endpoint was all-cause mortality at 1 year.

Results Among 2066 consecutive patients undergoing TAVI between August 2007 and June 2018, 1554 patients were eligible for the present analysis. Patients in the large SOVi group were older (83 ± 6 vs 82 ± 6 vs 81 ± 6; $P < .001$) and had a higher Society of Thoracic Surgeons Predicted Risk of Mortality (6.3 ± 3.8 vs 5.1 ± 3.1 vs 4.9 ± 3.5; $P < .001$) than those in the other groups. Patients in the large SOVi group had a higher incidence of moderate or severe paravalvular regurgitation (11.9% vs 4.5% vs 3.5%; $P < .001$). At 1 year, a large SOVi was independently associated with an increased risk of mortality (HR: 1.62; 95% CI: 1.19-2.21; $P = .002$) and major or life-threatening bleeding (HR: 1.30; 95% CI: 1.02-1.65; $P = .035$).

Conclusions Dilatation of the aortic root at the SOV was associated with adverse outcomes after TAVI. The assessment of the aortic root should be integrated into the risk stratification system in patients undergoing TAVI. (Am Heart J 2022;244:94–106.)

Keywords: aortic valve stenosis; transcatheter aortic valve implantation; sinus of Valsalva, aortic root; paravalvular regurgitation

Introduction

Progressive dilatation of the aortic root, consisting of the aortic annulus, the cusps, the sinus of Valsalva (SOV), the offtake of the coronary arteries, and the sinotubular junction, is a common finding in patients with aortic stenosis (AS).[1-4] The hemodynamic stress caused by AS, involving high velocity and turbulent flow downstream of the stenosis, and intrinsic pathology of the aortic wall have been proposed as potential mechanisms.[5-8] The aortic root is routinely assessed in pre-procedural multidetector computed tomography (MDCT) before transcatheter aortic valve implantation (TAVI) with a particular focus on annular dimensions. In contrast, SOV dimensions are frequently disregarded. Clinical and procedural implications of the dilated aortic root in patients undergoing TAVI have not been adequately studied.[3,4,9] Thus, we sought to describe the patient characteristics according to SOV dimensions, and investigate the association of the dilated SOV with clinical outcomes in patients undergoing TAVI.

Methods

Study design and population

Between August 2007 and June 2018, consecutive patients undergoing TAVI for AS at Bern University

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Abbreviations: AS, aortic stenosis; BSA, body surface area; MDCT, multi-detector computed tomography; PVR, paravalvular regurgitation; SOV, sinus of Valsalva; SOVi, sinus of Valsalva index to BSA; TAVI, transcatheter aortic valve implantation.

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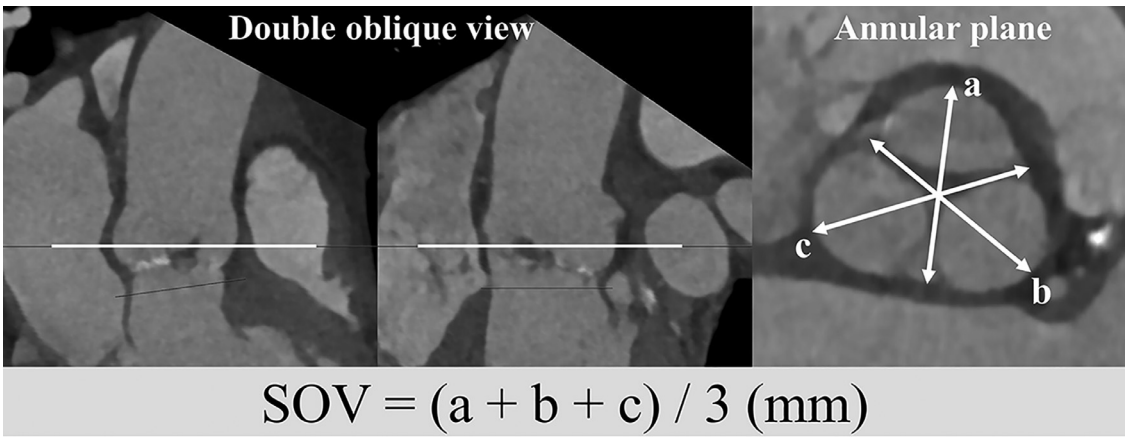
Figure 1



Measurement of sinus of Valsalva diameter. SOV diameter was assessed on a transverse double oblique plane at its widest dimensions. The distance from cusp to commissure were measured from inner edge to inner edge in the annular plane for every cusp, and the three values were averaged. SOV = sinus of Valsalva.

Hospital, Switzerland, were enrolled into a prospective institutional registry, which forms part of the SwissTAVI registry (registered at clinicaltrials.gov with NCT01368250)[10], and were considered eligible for the present analysis. For the purpose of the present study, patients with a history of previous aortic valve surgery/intervention or inadequate MDCT images for the assessment of the aortic root were excluded. Patients with bicuspid anatomy or a diameter of the ascending aorta >55 mm requiring surgical correction were also excluded. The prospective registry was approved by the local ethics committee, and patients provided written informed consent to participate. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Aortic root assessment

Aortic root dimensions were evaluated by experienced imaging specialists in a dedicated Corelab. The pre-procedural MDCT was performed as previously described, and acquired images were transferred to a dedicated workstation (3mensio Structural Heart, 3mensio Medical Imaging BV, Bilthoven, The Netherlands).[11] The systolic phase of MDCT with the least motion artifact was selected and assessed in multiplanar views reconstructed by the built-in module. The SOV diameter was assessed on a transverse double oblique plane at its widest dimension. The distances from cusp to commissure from inner edge to inner edge in the annular plane for each cusp were measured, and the three values were averaged[12] (**Figure 1**). The diameter of SOV was indexed (SOVi) to body surface area (BSA).[13] Device landing zone calcium volume was quantified in the contrast images by using a predefined Hounsfield unit threshold of 850, as previously validated for the prediction of paravalvular regugitation.[14,15]

Data collection and clinical endpoints

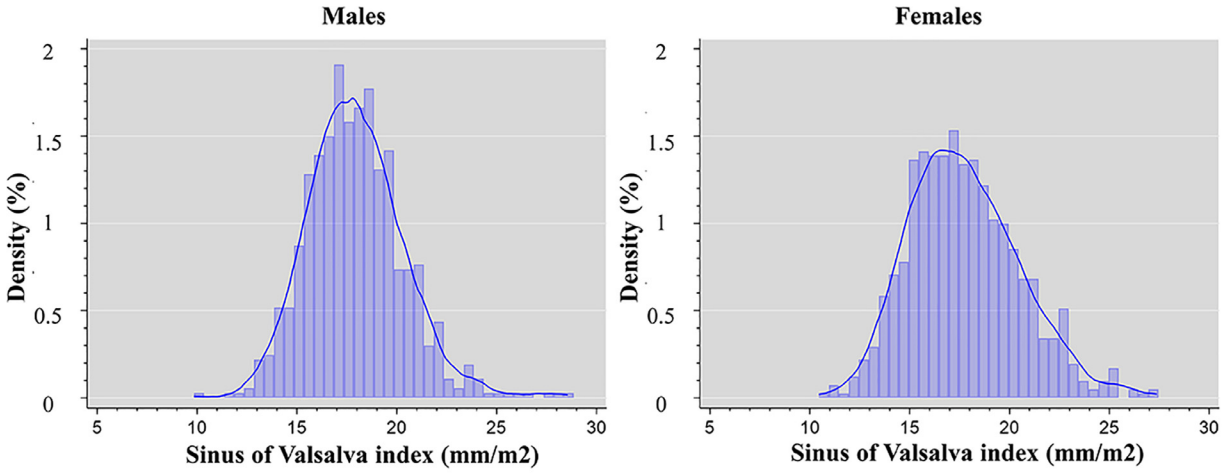
All baseline clinical, procedural, and follow-up data were prospectively recorded in a dedicated database, independently held at the Clinical Trials Unit of the University of Bern, Switzerland. Clinical follow-up data at 30 days and at 1 year were obtained by standardized interviews, documentation from referring physicians, and hospital discharge summaries. All adverse events were systematically collected and adjudicated by a dedicated clinical event committee, involving cardiologists and cardiac surgeons, based on the updated Valve Academic Research Consortium criteria.[16]

The primary endpoint of the present study was all-cause death at 1 year after TAVI. Secondary endpoints included all-cause and cardiovascular death, cerebrovascular events (including disabling and non-disabling stroke, and transient ischemia attack), myocardial infarction, major or life-threatening bleeding at 30 days and 1 year after TAVI.

Statistical analysis

Categorical variables were represented as frequencies and percentages, and the differences between groups were evaluated with the chi-square test or Fisher's exact test. Continuous variables were presented as mean values ± standard deviation (SD) and compared between groups using Student's *t* test. Time-to-event curves were

Figure 2



Distribution of patients according to sinus of Valsalva index. Histogram shows the distribution of patients according to sinus of Valsalva index.

constructed using the Kaplan-Meier method. Kernel density estimations were used to assess the relationship between aortic root dimensions and primary endpoint. Univariable and multivariable Cox proportional hazards model was used to calculate hazard ratios (HR) and 95% confidence intervals (95% CI) for the clinical outcomes. Multivariable analysis was performed with baseline variables selected based on the potential association with the outcomes of interest. All statistical tests were two-sided and *P*-values of <.05 were considered significant. Statistical analyses were performed using Stata 15.1 (StataCorp, College Station, TX, USA).

Results

Studied population and baseline characteristics

Among 2066 consecutive patients enrolled into the institutional TAVI registry, 1554 patients met the inclusion criteria. The distributions of the SOVi dimensions in males and females are shown in the **Figure 2**. Patients were stratified according to tertiles of SOVi: tertile 1 (small SOVi group: mean SOVi = 15.1 mm/m^2, n = 518); tertile 2 (medium SOVi group: mean SOVi = 17.7 mm/m^2, n = 518); and tertile 3 (large SOVi group: mean SOVi = 20.7 mm/m^2, n = 518).

Baseline characteristics according to the tertiles of SOVi are shown in Table I. Patients in the large SOVi group were older (age: 83.6 ± 5.7 vs 82.4 ± 5.8 vs 80.8 ± 6.1; P < .001), had a smaller body surface area (BSA: 1.68 ± 0.18 m^2 vs 1.84 ± 0.19 m^2 vs 1.99 ± 0.22 m^2; P < .001), and had an increased surgical risk (Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM): 6.26 ± 3.83 vs 5.07 ± 3.10 vs 4.85 ± 3.50; P < .001) as compared to patients in the small and medium SOVi groups. While hypertension and diabetes mellitus were less frequently documented (83.0% vs 84.2% vs 88.6%; P = .027 and 17.4% vs 28.4% vs 31.7%; P < .001, respectively), chronic kidney disease (estimated glomerular filtration rate <60 ml/min/1.73 m^2) (80.9% vs 63.8% vs 55.3%; P < .001) and peripheral artery disease (17.4% vs 12.4% vs 12.4%; P = .027) were more frequently observed in patients in the large SOVi group than those in the small and medium SOVi groups.

Echocardiographic and MDCT measurements are summarized in **Table II**. Patients in the large SOVi group had a smaller aortic valve area (0.61 ± 0.22 cm^2 vs 0.66 ± 0.24 cm^2 vs 0.7 ± 0.25 cm^2; P < .001), a lower left ventricular ejection fraction (53.7 ± 14.9% vs 55.4 ± 13.8% vs 56.3 ± 13.7%; P = .015), and a higher left ventricular mass index (142.3 ± 50.4 g/m^2 vs 141.1 ± 49.4 g/m^2 vs 131.4 ± 44.1 g/m^2; P = .006) than those in the small and medium SOVi group. Moderate or severe aortic regurgitation (12% vs 8% vs 6%; P = .002) and moderate or severe mitral regurgitation (27% vs 14% vs 18%; P < .001) were more commonly observed in patients in the large SOVi group compared with those in the small and medium SOVi groups. Patients in the large SOVi group had larger aortic root dimensions including annulus area (469.8 ± 87.0 mm^2 vs 456 ± 82.9 mm^2 vs 423.9 ± 76.2 mm^2; P < .001), ascending aorta diameter (34.1 ± 3.5 mm vs 33.0 ± 3.2 mm vs 32.3 ± 3.1 mm; P < .001), left coronary height (15.4 ± 3.6 mm vs 14.4 ± 3.4 mm vs 13.9 ± 3.2 mm; P < .001), and right coronary height (17.9 ± 3.2 mm vs 17.2 ± 3.3 mm vs 16.5 ± 3.1 mm; P < .001), and a higher device landing zone calcium volume (439.5 ± 426.3 mm^3 vs 344.2 ± 333.2 mm^3 vs 116.8 ± 113.9

Table I. Baseline characteristics according to SOVi tertile.

	All patients ($n = 1554$)	Small ($n = 518$)	Medium ($n = 518$)	Large ($n = 518$)	*P* value
Age, years	82.3 ± 6.0	80.8 ± 6.1	82.4 ± 5.8	83.6 ± 5.7	<.001
Female, n (%)	821 (52.8%)	301 (58.1%)	250 (48.3%)	270 (52.1%)	.006
Body mass index, kg/m	26.62 ± 5.28	30.40 ± 5.55	26.44 ± 3.75	23.03 ± 3.41	<.001
Body surface area, m^2	1.84 ± 0.23	1.99 ± 0.22	1.84 ± 0.19	1.68 ± 0.18	<.001
STS-PROM (%)	5.39 ± 3.54	4.85 ± 3.50	5.07 ± 3.10	6.26 ± 3.83	<.001
NYHA functional class III or IV, n (%)	1083 (69.8%)	355 (68.7%)	356 (68.9%)	372 (71.8%)	.465
Comorbidities					
Hypertension n (%)	1325 (85.3%)	459 (88.6%)	436 (84.2%)	430 (83.0%)	.027
Diabetes mellitus, n (%)	401 (25.8%)	164 (31.7%)	147 (28.4%)	90 (17.4%)	<.001
Renal failure (eGFR < 60 ml/min/1.73 m^2), n (%)	1034 (66.7%)	286 (55.3%)	330 (63.8%)	418 (80.9%)	<.001
Coronary artery disease, n (%)	985 (63.4%)	315 (60.8%)	335 (64.7%)	335 (64.7%)	.330
Past medical history					
Previous PCI, n (%)	424 (27.3%)	141 (27.2%)	148 (28.6%)	135 (26.1%)	.662
Previous CABG, n (%)	136 (9.0%)	48 (9.4%)	51 (10.1%)	37 (7.3%)	.273
History of cerebrovascular accident, n (%)	182 (11.7%)	58 (11.2%)	59 (11.4%)	65 (12.5%)	.765
Atrial fibrillation, n (%)	530 (34.1%)	174 (33.6%)	169 (32.6%)	187 (36.1%)	.476
Previous permanent pacemaker, n (%)	139 (8.9%)	44 (8.5%)	47 (9.1%)	48 (9.3%)	.902
Peripheral artery disease, n (%)	218 (14.0%)	64 (12.4%)	64 (12.4%)	90 (17.4%)	.027
Medication at baseline					
Use of OAC (VKA or NOAC), n (%)	458 (29.5%)	153 (29.5%)	149 (28.8%)	156 (30.2%)	.883
Medication at discharge					
Use of OAC (VKA or NOAC), n (%)	558 (36.5%)	199 (38.9%)	183 (35.8%)	176 (34.9%)	.366

Values are mean ± SD or n (%).
CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; NOAC, non vitamin K antagonist oral anticoagulant agent; NYHA, New York heart association; OAC, oral anticoagulant agent; PCI, percutaneous coronary intervention; SOVi, sinus of Valsalva index; STS-PROM, society of thoracic surgeons predicted risk of mortality; VKA, vitamin K antagonist.

Table II. Baseline echocardiographic and computed tomographic data according to SOVi tertile.

	All patients ($n = 1554$)	Small ($n = 518$)	Medium ($n = 518$)	Large ($n = 518$)	*P* value
Echocardiography					
Aortic valve area, cm^2	0.66 ± 0.24	0.70 ± 0.25	0.66 ± 0.24	0.61 ± 0.22	<.001
Indexed aortic valve area, cm^2/m^2	0.24 ± 0.08	0.25 ± 0.08	0.24 ± 0.08	0.23 ± 0.08	<.001
Mean aortic valve gradient, mm Hg	40.86 ± 17.40	39.88 ± 16.70	41.70 ± 17.06	41.01 ± 18.40	.247
Peak aortic valve gradient, mm Hg	66.65 ± 25.72	65.04 ± 23.71	68.48 ± 25.35	66.44 ± 27.98	.152
LVEF, %	55.15 ± 14.18	56.28 ± 13.67	55.41 ± 13.83	53.74 ± 14.94	.015
Low-gradient AS, n (%)	767 (51%)	262 (52%)	243 (48%)	262 (53%)	.299
Stroke volume index, mL/m^2	30.17 ± 9.76	30.34 ± 10.23	30.17 ± 9.35	30.03 ± 9.72	.904
LVMI, g/m^2	138.5 ± 48.37	131.4 ± 44.11	141.1 ± 49.38	142.3 ± 50.35	.006
Moderate/severe AR, n (%)	123 (9%)	27 (6%)	39 (8%)	57 (12%)	.002
Moderate/severe MR, n (%)	281 (19%)	85 (18%)	65 (14%)	131 (27%)	<.001
Computed tomography					
Annulus area, mm^2	449.9 ± 84.32	423.9 ± 76.18	456.0 ± 82.92	469.8 ± 86.98	<.001
Annulus area index, mm^2/m^2	246.7 ± 44.76	213.1 ± 30.48	247.6 ± 32.69	279.5 ± 42.59	<.001
Ascending aorta diameter, mm	33.13 ± 3.34	32.30 ± 3.06	33.02 ± 3.18	34.08 ± 3.52	<.001
Ascending aorta diameter index, mm/m^2	18.30 ± 2.74	16.35 ± 1.84	18.10 ± 1.99	20.43 ± 2.60	<.001
Left coronary height, mm	14.58 ± 3.45	13.89 ± 3.21	14.44 ± 3.37	15.40 ± 3.59	<.001
Right coronary height, mm	17.20 ± 3.23	16.47 ± 3.07	17.21 ± 3.26	17.93 ± 3.19	<.001
Device landing zone calcium, mm^3	338.8 ± 348.8	231.8 ± 225	344.2 ± 333.2	439.5 ± 426.3	<.001
Device landing zone calcium index, mm^3/m^2	188.9 ± 200.3	116.8 ± 113.9	186.4 ± 177.4	262.8 ± 255.6	<.001

Values are mean ± SD or n (%).
AR, aortic regurgitation; AS, aortic stenosis; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MR, mitral valve regurgitation; SOVi, sinus of Valsalva index.

mm^3; $P < .001$) than those in the small and medium SOVi groups.

Procedural characteristics and complications

Procedural characteristics and complications are summarized in **Table III**. TAVI was performed by transfemoral access in 88.8% of patients without differences among the three groups. There was no difference in the type of valve implanted, whereas the valve size was larger in the order of large SOVi, medium SOVi, and small SOVi group (26.9 ± 2.3 mm vs 26.7 ± 2.3 mm vs 25.9 ± 2.2 mm; $P < .001$). Pre-dilation was most

Table III. Procedural characteristics and results according to SOVi tertile.

	All patients (n = 1554)	Small (n = 518)	Medium (n = 518)	Large (n = 518)	P value
Procedural characteristics					
Fluoroscopy time, min	18.07 ± 15.91	16.66 ± 11.21	19.09 ± 23.24	18.47 ± 9.78	.057
General anesthesia, n (%)	345 (22.2%)	110 (21.2%)	113 (21.8%)	122 (23.6%)	.647
Femoral main access site, n (%)	1380 (88.8%)	467 (90.2%)	463 (89.4%)	450 (86.9%)	.216
Device generation, n (%)					
Old-device	579 (37.3%)	137 (26.4%)	197 (38.0%)	245 (47.4%)	<.001
Newer-device	974 (62.7%)	381 (73.6%)	321 (62.0%)	272 (52.6%)	<.001
Type of valve, n (%)					
Balloon-expandable	702 (45.2%)	223 (43.1%)	255 (49.2%)	224 (43.3%)	.078
Self-expanding	739 (47.6%)	260 (50.2%)	230 (44.4%)	249 (48.2%)	.166
Mechanically-expandable	112 (7.2%)	35 (6.8%)	33 (6.4%)	44 (8.5%)	.366
Valve size, n (%)					
Mean valve size, mm	26.50 ± 2.29	25.90 ± 2.21	26.67 ± 2.25	26.94 ± 2.30	<.001
Pre-dilation, n (%)	1131 (72.8%)	354 (68.3%)	383 (74.1%)	394 (76.1%)	.015
Post-dilation, n (%)	429 (27.6%)	130 (25.1%)	138 (26.6%)	161 (31.1%)	.082
Procedural results					
Valve in series, n (%)	22 (1.4%)	5 (1.0%)	10 (1.9%)	7 (1.4%)	.416
Valve dislocation/embolization, n (%)	29 (1.9%)	7 (1.4%)	12 (2.3%)	10 (1.9%)	.513
Annular rupture, n (%)	9 (0.6%)	3 (0.6%)	1 (0.2%)	5 (1.0%)	.262
Cardiac tamponade, n (%)	14 (0.9%)	5 (1.0%)	4 (0.8%)	5 (1.0%)	.930
Coronary artery occlusion, n (%)	6 (0.4%)	4 (0.8%)	1 (0.2%)	1 (0.2%)	.222
Moderate/severe PVR at discharge, n (%)	95 (6.6%)	17 (3.5%)	22 (4.5%)	56 (11.9%)	<.001

Values are mean ± SD or n (%). Old-device included Medtronic Corevalve and SAPIEN THV/XT. Newer-device included SAPIEN 3/SAPIEN 3 Ultra, Evolut R/PRO, Symetis Accurate/Accurate neo, Portico, and BSC Lotus/ Lotus Edge.
PVR, paravalvular regurgitation; SOVi, sinus of Valsalva index.

frequently performed in the large SOVi group (76.1% vs 74.1% vs 68.3%; P = .015), while the rate of post-dilation was comparable across groups (31.1% vs 26.6% vs 25.1%; P = .082). Procedural complications including valve dislocation/embolization, annular rupture, cardiac tamponade, and coronary artery obstruction were similarly observed across groups. At discharge, moderate or severe PVR as assessed by echocardiography was more frequently observed in the large SOVi group than in the small and medium SOVi groups (11.9% vs 4.5% vs 3.5%; P < .001).

Clinical outcomes

Clinical follow-up at 1 year was completed in 1,533 patients (98.6%). Clinical outcomes at 30 days and 1 year according to the SOVi tertiles are summarized in **Table IV**. At 30 days, patients in the large SOVi group had a higher incidence of all-cause (4.8%) and cardiovascular death (4.1%), and major or life-threatening bleeding (23.8%) compared to those in the small (1.9%, P = 0.013; 1.5%; P = .019; 15.3%, P = .001; respectively) and medium SOVi groups (2.5%, P = .053; 2.1%, P = .079; 17.6%; P = .020; respectively). There were no significant differences in the incidence of cerebrovascular events, myocardial infarction, kidney injury stage 3 (AKIN classification)[16], and new permanent pacemaker implantation among the three groups.

At 1 year, all-cause death occurred in 10.5% of patients in the small SOVi group, in 10.6% of the medium SOVi group, and in 17.5% of patients in the large SOVi group (**Figure 3**). Patients in the large SOVi group had an increased risk of all-cause and cardiovascular death compared to patients in the small (HR 1.73; 95% CI 1.24-2.43; P = .001, and HR 2.04; 95% CI 1.34-3.13; P = .001, respectively) and medium SOVi groups (HR 1.72; 95% CI 1.23-2.41; P = .002, and HR 1.67; 95% CI 1.12-2.48; P = .012, respectively). Major or life-threatening bleeding occurred more frequently in patients in the large SOVi group (26.7%) compared to those in the small (19.2%, HR 1.45; 95% CI 1.12-1.88; P = .005) and medium SOVi groups (21.9%, HR 1.26; 95% CI 0.98-1.62; P = .066). In a probability plot for 1-year all-cause death, mortality increased with increasing SOVi in both males and females, while its relationship with aortic annulus area index was not prominent (**Figure 4**). In a sensitivity analysis conducted in a contemporary cohort of patients treated with newer-generation devices (n = 974), patients in the large SOVi group had an increased risk of all-cause death compared with those in the small (HR 1.74; 95% CI 1.11-2.72; P = .016) and the medium SOVi groups (HR 1.69; 95% CI 1.06-2.70; P = .028), consistent with the main analysis.

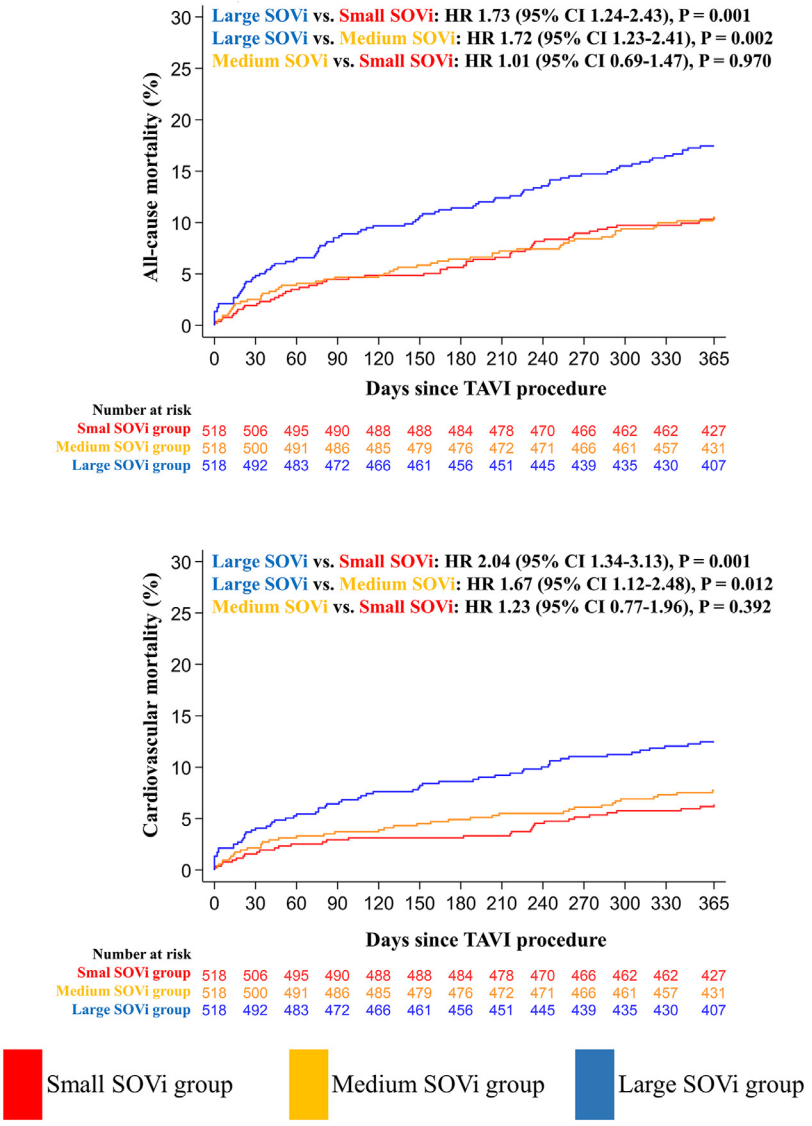
In multivariable analyses, the highest tertile of SOVi was independently associated with an increased risk of all-cause death (HR: 1.62; 95% CI: 1.19-2.21; P = .002) (**Table V**) and major or life-threatening bleeding (HR: 1.30; 95% CI: 1.02-1.65; P = .035) (**Supplementary Table I**) at 1 year after TAVI. In contrast, SOVi did not emerge as an independent predictor of PVR (HR: 1.44;

Table IV. Clinical outcomes at 30 days and 1 year according to SOVi tertile.

	Small ($n = 518$)	Medium ($n = 518$)	Large ($n = 518$)	Medium vs Small		Large vs Small		Large vs Medium	
				HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
At 30 days									
All-cause death (n, %)	10 (1.9%)	13 (2.5%)	25 (4.8%)	1.31 (0.57-2.98)	.523	2.53 (1.22-5.27)	.013	1.94 (0.99-3.78)	.053
Cardiovascular death (n, %)	8 (1.5%)	11 (2.1%)	21 (4.1%)	1.38 (0.56-3.44)	.486	2.66 (1.18-6.00)	.019	1.92 (0.93-3.99)	.079
CVE (n, %)	17 (3.3%)	22 (4.3%)	23 (4.5%)	1.30 (0.69-2.45)	.416	1.38 (0.74-2.58)	.319	1.06 (0.59-1.90)	.851
Disabling stroke (n, %)	9 (1.7%)	11 (2.1%)	15 (2.9%)	1.23 (0.51-2.96)	.648	1.69 (0.74-3.87)	.212	1.38 (0.63-3.00)	.419
Non-disabling stroke (n, %)	7 (1.4%)	7 (1.4%)	3 (0.6%)	1.00 (0.35-2.84)	.997	0.43 (0.11-1.67)	.222	0.43 (0.11-1.67)	.224
Transient ischemic attack (n, %)	1 (0.2%)	4 (0.8%)	5 (1.0%)	4.01 (0.45-35.91)	.214	5.07 (0.59-43.38)	.138	1.26 (0.34-4.70)	.728
Myocardial infarction (n, %)	4 (0.8%)	5 (1.0%)	2 (0.4%)	1.25 (0.34-4.67)	.737	0.50 (0.09-2.74)	.426	0.40 (0.08-2.06)	.274
Major or life-threatening bleeding (n, %)	79 (15.3%)	91 (17.6%)	123 (23.8%)	1.16 (0.86-1.56)	.346	1.60 (1.20-2.12)	.001	1.38 (1.05-1.81)	.020
Kidney injury Stage 3 (n, %)	11 (2.1%)	11 (2.1%)	6 (1.2%)	1.00 (0.43-2.31)	.996	0.55 (0.20-1.48)	.237	0.55 (0.20-1.48)	.235
Permanent pacemaker implantation (n, %)	100 (19.4%)	92 (17.9%)	117 (23.0%)	0.92 (0.69-1.22)	.558	1.21 (0.92-1.58)	.165	1.31 (1.00-1.73)	.050
At 1 year									
All-cause death (n, %)	54 (10.5%)	54 (10.6%)	90 (17.5%)	1.01 (0.69-1.47)	.970	1.73 (1.24-2.43)	.001	1.72 (1.23-2.41)	.002
Cardiovascular death (n, %)	32 (6.4%)	39 (7.7%)	63 (12.5%)	1.23 (0.77-1.96)	.392	2.04 (1.34-3.13)	.001	1.67 (1.12-2.48)	.012
CVE (n, %)	30 (6.0%)	31 (6.2%)	31 (6.2%)	1.04 (0.63-1.71)	.884	1.06 (0.64-1.75)	.814	1.02 (0.62-1.68)	.929
Disabling stroke (n, %)	17 (3.4%)	15 (3.0%)	21 (4.2%)	0.88 (0.44-1.77)	.729	1.27 (0.67-2.41)	.465	1.44 (0.74-2.78)	.285
Non-disabling stroke (n, %)	10 (2.0%)	10 (2.0%)	6 (1.3%)	1.00 (0.42-2.40)	1.000	0.61 (0.22-1.68)	.340	0.61 (0.22-1.68)	.339
Transient ischemic attack (n, %)	4 (0.8%)	6 (1.2%)	5 (1.0%)	1.51 (0.43-5.35)	.524	1.28 (0.34-4.78)	.709	0.85 (0.26-2.79)	.790
Myocardial infarction (n, %)	8 (1.6%)	13 (2.7%)	6 (1.3%)	1.64 (0.68-3.95)	.273	0.78 (0.27-2.24)	.640	0.47 (0.18-1.25)	.131
Major or life-threatening bleeding (n, %)	98 (19.2%)	112 (21.9%)	137 (26.7%)	1.15 (0.88-1.51)	.310	1.45 (1.12-1.88)	.005	1.26 (0.98-1.62)	.066

Events (percentages from lifetable estimates). HR (95% CI) from Cox's regressions.
CI, confidence intervals; CVE, cerebrovascular event; HR, hazard ratio; SOVi, sinus of Valsalva index.

Figure 3



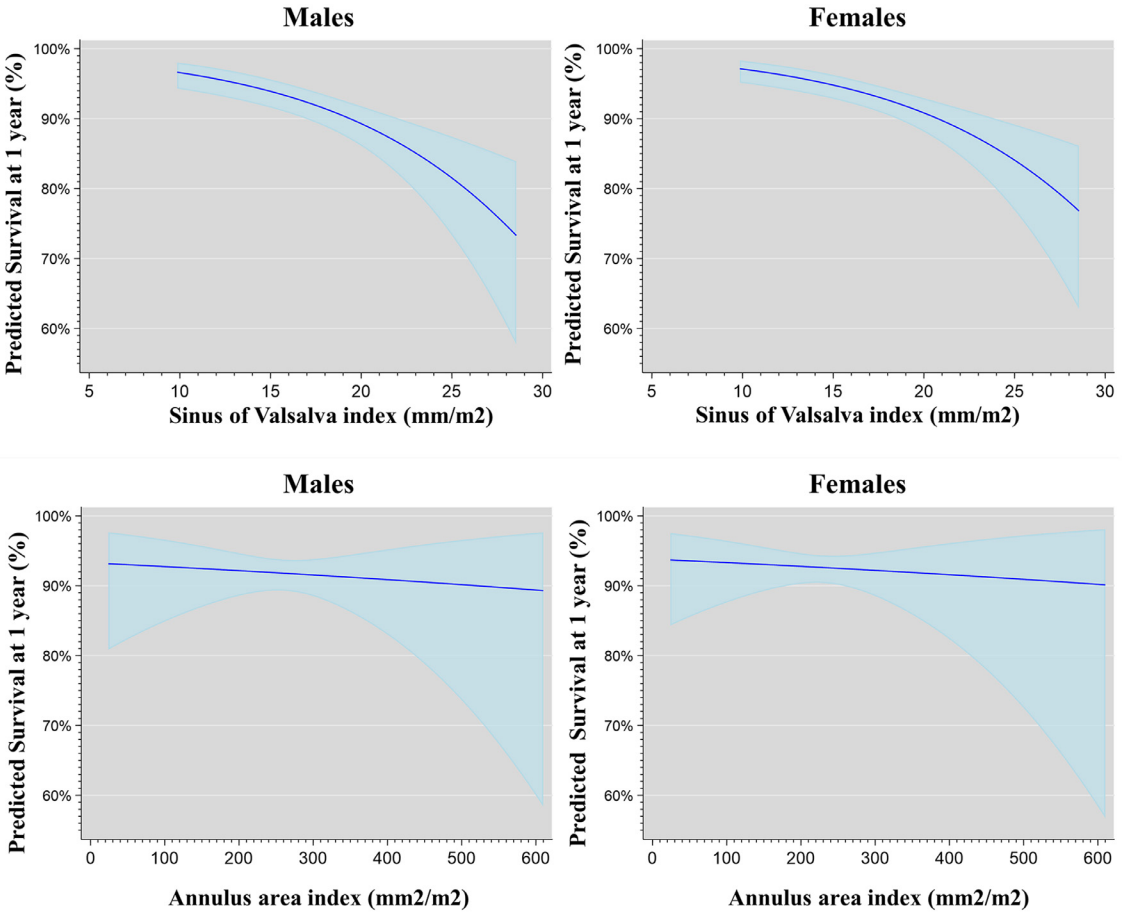
Kaplan-Meier curves for all-cause death and cardiovascular death in all patients. Kaplan-Meier curves for all-cause (upper) and cardiovascular mortality (lower) according to tertiles of SOVi. Hazard ratios and p-values were calculated with the use of Cox proportional hazards models. CI = confidence interval; HR = hazard ratio; SOVi = sinus of Valsalva index.

95% CI: 0.95-2.20; $P = .087$). Device landing zone calcium volume and use of self-expanding devices were independent predictors of PVR (**Supplementary Table II**). In a sensitivity analysis excluding patients with moderate or severe PVR, patients in the large SOVi group had a higher incidence of all-cause (HR: 1.51; 95% CI: 1.02-2.22; $P = .038$) and cardiovascular death (HR: 1.75; 95% CI: 1.06-2.9; $P = .030$) compared to those in the small SOVi group, but not compared to those in the medium SOVi group (Figure 5).

Discussion

The main findings of the present study are as follows: 1) Patients with a large SOVi tended to be older and have an increased surgical risk, advanced left ventricular remodeling, and mixed valve disease; 2) PVR after TAVI occurred more frequently in patients with large SOVi; 3) A large SOVi was independently associated with an increased risk of mortality and major or life-threatening bleeding at 1 year after TAVI, and the effect on mortality

Figure 4



Prognostic value of sinus of Valsalva (and annulus area): probability plot for 1 year survival in patients undergoing TAVI. Probability plot for 1-year survival of SOVi (upper) and annulus area (lower). Solid lines represent the estimated probability of 1-year survival; the shaded area is the 95% confidence interval. Cox's model included SOVi, gender, STS-PROM, diabetes, atrial fibrillation, peripheral artery disease, indexed aortic valve area, and femoral access. SOVi = sinus of Valsalva index; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality; TAVI = transcatheter aortic valve implantation.

was consistent even after excluding patients with moderate or severe PVR.

The prevalence of aortic root dilatation has been reported to be 4.2% to 25% in hypertensive patients and 13.7% to 29.2% in patients with AS, depending on the definition.[2,3,17-19] In echocardiographic studies, normal ranges for aortic root diameter measured at the SOV indexed to BSA were reported to be 15 to 19 mm and 16 to 20 mm in men and women, respectively.[13,20,21] Thus, the large SOVi group (tertile 3: mean SOVi = 21 mm/m^2) in the present study is likely to represent patients with dilated aortic root anatomy. Several epidemiological studies deemed age as the principal determinant of aortic root remodeling.[22-25] In the Framingham Heart Study, aortic root diameter increased with age (0.89 mm in men and 0.68 mm in women per 10-year).[23] Age-related vascular structural changes, reduced elastin fibers, increased collagen deposition, and increased calcification are considered mechanisms of aortic root remodeling.[26,27] In line with these findings, patients with a large SOVi were older than those with a small and medium SOVi in the present study.

Although aortic root dilatation is more commonly observed in patients with AS, the underlying etiology remains unclear. Genetic and hemodynamic factors have been suggested to contribute to aortic root dilatation in patients with AS. It is well known that patients with Marfan syndrome and congenital bicuspid aortic valve are more prone to develop aortic root dilatation[5]. Hemodynamic stress on the aortic wall caused by valve steno-

Table V. Multivariable analysis: all-cause death at 1 year after TAVI.

Variables	Univariable analysis		Multivariable analysis	
	Hazard ratio (95%CI)	*P* value	Hazard ratio (95%CI)	*P* value
Small or medium SOVi	Reference		Reference	
Large SOVi	1.73 (1.31-2.29)	<.001	1.62 (1.19-2.21)	.002
Age	1.01 (0.99-1.04)	.277	1.01 (0.98-1.04)	.489
Female	0.82 (0.62-1.08)	.162	0.82 (0.59-1.15)	.259
STS-PROM	1.09 (1.06-1.11)	<.001	1.04 (1.01-1.08)	.014
Diabetes mellitus	1.79 (1.34-2.38)	<.001	1.67 (1.22-2.26)	.001
eGFR (ml/min/1.73 m^2)	0.99 (0.98-1.00)	<.001	1.00 (0.99-1.01)	.595
Atrial fibrillation	1.71 (1.29-2.26)	<.001	1.57 (1.18-2.08)	.002
Peripheral artery disease	1.96 (1.41-2.72)	<.001	1.37 (0.94-2.00)	.10
LVEF (%)	0.98 (0.97-0.99)	<.001	0.98 (0.97-0.99)	.001
Indexed aortic valve area (cm^2/m^2)	2.60 (0.50-13.51)	.257	3.18 (0.48-20.95)	.228
Baseline AR moderate or severe	1.02 (0.61-1.70)	.949	0.84 (0.50-1.41)	.506
Device landing zone calcium index (10 mm^3/m^2 increase)	1.00 (1.00-1.01)	.240	1.00 (1.00-1.01)	.468
Femoral access	0.51 (0.35-0.72)	<.001	0.70 (0.46-1.06)	.091
Size of valve (mm)	1.01 (0.95-1.07)	.838	0.95 (0.88-1.02)	.160
Low-gradient AS	1.34 (1.01-1.78)	.042	1.10 (0.78-1.54)	.588

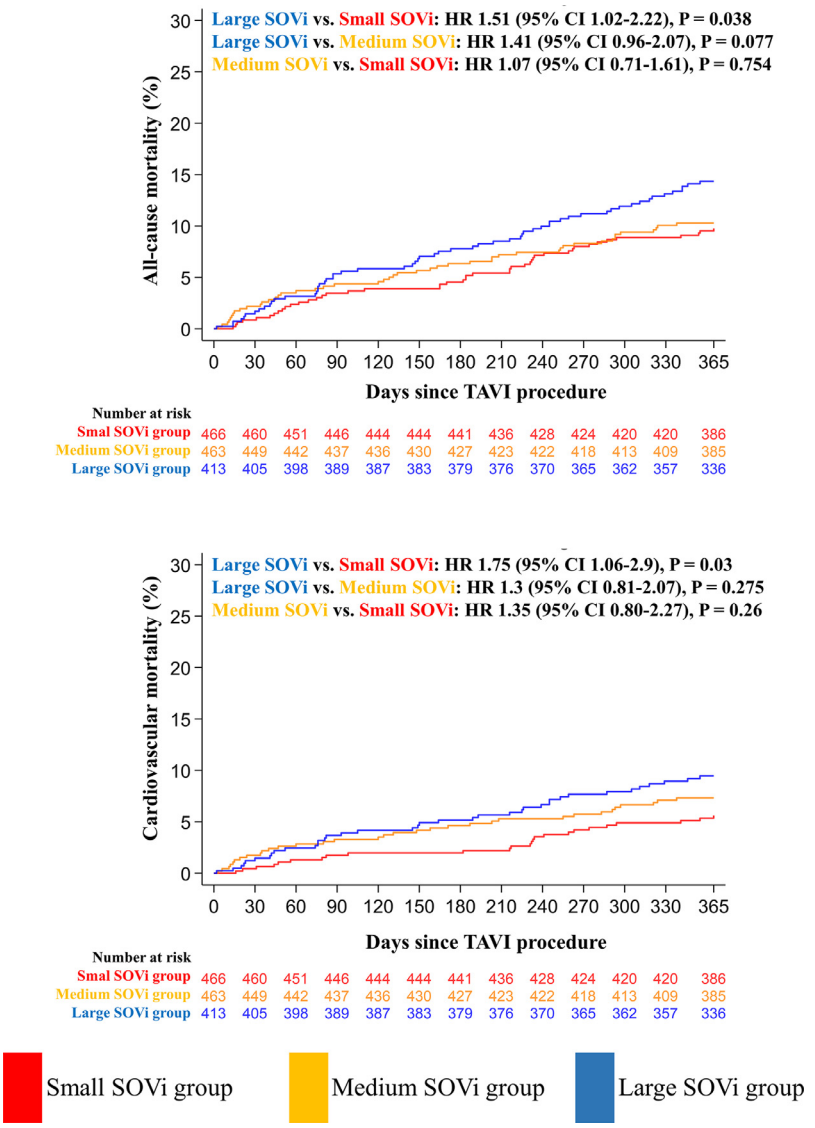
AR, aortic regurgitation; AS, aortic stenosis; CI, confidence interval; Egfr, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; SOVi, sinus of Valsalva index; STS-PROM, society of thoracic surgeons predicted risk of mortality.

sis is another potential contributor to the high prevalence of aortic root dilatation in patients with AS. Four-dimensional flow cardiac magnetic resonance imaging in 37 patients with AS and 37 healthy controls suggested that AS leads to abnormal blood flow patterns with regards to helical and vortical flow formations and eccentricity in the ascending aorta.[6] Abnormal blood flow was associated with increased wall shear stress in the aortic wall, which may lead to aortic root remodeling.[6,7,24] In another study using 4-dimensional flow cardiac magnetic resonance imaging, regions of increased wall shear stress were associated with extracellular matrix dysregulation and elastic fiber degeneration in the ascending aorta in patients with bicuspid aortic valve, implicating valve-related hemodynamics as a contributing factor in the development of aortopathy.[28] A more advanced stage of the disease suggested by more frequent comorbidities, a smaller aortic valve area, and advanced left ventricular remodeling in the present cohort may support the latter hypothesis.[29-31]

Previous studies suggested that aortic root remodeling was associated with cardiovascular events and all-cause mortality in general and elderly populations.[24,25,32] The association between aortic root remodeling and mortality has recently been shown also in patients undergoing TAVI. In a single-center study including 1,426 patients with tricuspid AS who underwent TAVI, patients with ascending aorta dilatation (>40 mm) had more advanced left ventricular remodeling, higher incidence of PVR, and higher 2-year mortality.[3] The present study corroborate these findings in a large prospective TAVI registry, where aortic root dimensions were independently re-evaluated in a standardized method.[12] Furthermore, the association was consistent even after adjusting for baseline confounders or excluding the potential adverse effect of PVR which more commonly occurred in patients with a large SOVi.[33] Nevertheless, in patients undergoing TAVI, the dilated anatomy of the aortic root has been rarely taken into consideration during pre-procedural planning unless it requires surgical correction. Although the aortic root including the SOV, left and right coronaries, the sinotubular junction, and the ascending aorta, is routinely evaluated by pre-procedural MDCT, the impact of SOV dimensions is frequently neglected.[34,35] Our findings suggest that the SOV dimension can be used for risk stratification without additional testing or effort, and is helpful for decision-making in high-risk patients as well as optimizing treatment strategies following TAVI.

In the present analysis, patients in the large SOVi group had a higher incidence of PVR after TAVI than those in the small and medium SOVi groups. However, in a multivariable analysis, large SOVi did not emerge as an independent predictor. Thus, the higher incidence in patients with a large SOVi may be attributed to higher device landing zone calcium volume and use of self-expanding devices, that were previously identified as predictors of PVR.[36-41] Interestingly, patients with a large SOVi had an increased risk of major or life-threatening bleeding at both 30 days and 1 year after TAVI. Even in a multivariable analysis including previously identified risk factors for bleeding (age, obesity, STS-PROM, renal failure, atrial fibrillation, use of oral anticoagulants, and use of alternative access), a large SOVi was significantly associated with an increased risk of major or life-threatening bleeding. A large SOVi may suggest a vulnerable condition to bleeding, such as frailty, that was not systematically

Figure 5



Kaplan-Meier curves for all-cause death and cardiovascular death in patients without moderate or severe paravalvular regurgitation. Kaplan-Meier curves for all-cause (upper) and cardiovascular mortality (lower) according to tertiles of SOVi in patients without ≥moderate paravalvular regurgitation at discharge. Hazard ratios and *P*-values were calculated with the use of Cox proportional hazards models. Abbreviations as in Figure 3.

captured in this prospective registry.[42] Indeed, patients in the large SOVi group were older and smaller, and had a higher surgical risk in the present cohort.

Study limitations

The present analysis is a retrospective observational study with inherent limitations. First, more than 20% of patients were excluded due to inadequate MDCT images for the assessment of SOVi. In turn, we provide comprehensive data from a large prospective registry adhering to high standards of data quality with rigorous data collection, standardized follow-up, and independent event adjudication. Second, as there is no standard definition of dilated SOV on MDCT, we divided patients based on tertiles of SOV diameter indexed to BSA. The optimal cut-off to define SOV dilatation needs to be delineated in future studies. Third, the studied population in the present analysis was limited to elderly patients (mean

age >80 years) with tricuspid aortic stenosis undergoing TAVI; the results are hence not generalizable to other populations such as younger patients with bicuspid anatomy. Finally, sophisticated statistical methods, including multivariable analysis, sensitivity analysis, and Kernel density estimations, were used to confirm the robustness of our findings; however, the potential effect of unmeasured variables could not be eliminated as a nature of observational studies. Thus, the findings of the present analysis are hypothesis-generating and the pathophysiological correlations between the dilated SOV and AS need to be further investigated in future studies.

Conclusion

Dilatation of the aortic root at the sinus of Valsalva may suggest a more advanced stage of AS and was associated with adverse outcomes after TAVI. The assessment of the aortic root should be integrated into the risk stratification system in AS patients undergoing TAVI.

Data availability

The data underlying this article were provided by CTU, University of Bern, by permission. Data will be shared on request to the corresponding author with permission of CTU, University of Bern.

Clinical trial registration

https://www.clinicaltrials.gov. NCT01368250.

Disclosure

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2021.11.004.

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