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Silent Valsalva thrombus between the native Valsalva and balloon-expandable transcatheter heart valve: multicentre Japanese registry analysis

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KEYWORDS

- imaging modalities
- MSCT
- TAVI

Abstract

Aims: The newly formed geometry between the native Valsalva and implanted transcatheter heart valve (THV) may induce local thrombogenicity. This study aimed to assess the incidence of and the clinical outcomes associated with Valsalva thrombus formation after transcatheter aortic valve implantation (TAVI).

Methods and results: We retrospectively evaluated the multidetector computed tomography (MDCT) data of 338 patients following transcatheter aortic valve implantation (TAVI) using a balloon-expandable THV. The Valsalva and leaflet thrombi were assessed by MDCT at the left coronary cusp (LCC), right coronary cusp (RCC), and non-coronary cusp (NCC). Combined endpoints such as death, stroke, and readmission for heart failure rates in patients with and without Valsalva and/or leaflet thrombus were examined at two years. The overall incidence of Valsalva and leaflet thrombi was 8.9% and 8.3%, respectively. Significant differences in the location of the Valsalva thrombus in the LCC, RCC, and NCC were noted (5.0%, 4.2%, 8.9%, respectively, p<0.001). The independent predictor for increased risk of Valsalva thrombus was high Valsalva area to implanted THV size ratio (odds ratio 11.8, 95% confidence interval [CI]: 1.67-83.0, p=0.013). Combined endpoints were similar in patients with and without Valsalva thrombus, Valsalva/leaflet thrombus, and leaflet thrombus (p>0.05 for all).

Conclusions: Valsalva thrombus was detected in 8.9% of patients following balloon-expandable THV implantation and was common in the LCC, but it did not increase the risk of adverse events after TAVI.

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Abbreviations

AS aortic stenosis
LCC left coronary cusp
MDCT multidetector computed tomography
NCC non-coronary cusp
OCEAN Optimised CathEter vAlvular interventioN
RCC right coronary cusp
TAVR transcatheter aortic valve replacement
THV transcatheter heart valve
TTE transthoracic echocardiography

Introduction

With the development of devices and technical improvements, the indications for transcatheter aortic valve implantation (TAVI) for severe aortic stenosis (AS) have been expanding to patients considered to be in the intermediate surgical risk category[1]. To date, the existence of leaflet thrombus in patients who underwent TAVI is one of the important remaining issues when considering indications for TAVI[2]. Many recent studies have revealed the incidence, mechanism, and predictive factors of leaflet thrombus following TAVI[3-11]. The majority of patients with leaflet thrombus are free from clinical adverse events, and thus it is called "subclinical" leaflet thrombosis[3-8]. However, clinically relevant leaflet thrombus, although rare, should not be ignored[10,11]. Pivotal research has mentioned the probable increased risk of minor stroke events associated with leaflet thrombosis[12]. We also previously reported a case of huge Valsalva thrombus formation between the native Valsalva and the implanted transcatheter heart valve (THV) after TAVI[13]. Caution must be exercised not only concerning the existence of leaflet thrombus, but also for Valsalva thrombus in patients who have undergone TAVI. Up until now, there are no available data concerning the incidence and prognostic value of Valsalva thrombus following TAVI. This study, therefore, aimed to assess the existence of Valsalva thrombus and to clarify the clinical outcomes of Valsalva thrombus after TAVI using the data from 338 patients enrolled in a Japanese multicentre registry.

Methods

This study used data from an ongoing multicentre registry, the Optimized CathEter vAlvular iNtervention-transcatheter aortic valve implantation (OCEAN-TAVI) registry, involving 14 relatively high-volume centres in Japan[14]. This trial was registered with the University Hospital Medical Information Network (no.: UMIN000020423). Data for a total of 338 aortic stenosis (AS) patients were retrospectively extracted from the OCEAN-TAVI registry for the period from October 2013 to November 2016. All 338 patients had undergone four-dimensional multidetector computed tomography (MDCT) examinations after TAVI (median duration from TAVI to MDCT: 2 days, interquartile range [IQR]: 2 to 7 days). During the hospital stay and follow-up period, experienced echocardiographers in each centre calculated the conventional findings using transthoracic echocardiography (TTE). Information regarding the occurrence of severe adverse events and death was collected from the treating hospitals or by calling the patient's family member(s).

Details of the TAVI procedure have been reported previously[14]. The total number of patients implanted with the SAPIEN XT and SAPIEN 3 (Edwards Lifesciences, Irvine, CA, USA) balloon-expandable prostheses was 229 and 109, respectively. The TAVI procedures were performed with patients under anticoagulant therapy with a bolus of unfractionated heparin administered to achieve an activated clotting time of >250 seconds, which was maintained throughout the procedures. Procedural complications and clinical outcomes, including the cause of death, were evaluated according to the Valve Academic Research Consortium-2 criteria[15].

All 338 patients were scanned using four-dimensional enhanced MDCT with electrocardiography-gated reconstructions. MDCT data sets were previously mentioned in detail[8]. The Valsalva thrombus was defined as a low-density space without enhancement of contrast media between the native Valsalva and implanted THV[13]. The definition of leaflet thrombus was according to that described in our previous report[8]. Baseline characteristics, procedural parameters, and clinical outcomes were compared between the with thrombus (Valsalva or leaflet) and without thrombus groups. Representative images of the Valsalva thrombus and leaflet thrombus are presented in **Figure 1**. Locations of both Valsalva and leaflet thrombi were evaluated for each Valsalva position in the left coronary cusp (LCC), right coronary cusp (RCC), and non-coronary cusp (NCC). The Valsalva length, THV length, and Valsalva length to THV length ratio, Valsalva area, THV area, and Valsalva area to THV area ratio were calculated **(Figure 2)**. The depth of each prosthesis implantation was measured as the maximum distance from the bottom of the stent to the native annulus[9]. The angle of the native commissure to bioprosthetic leaflet orientation was assessed in each coronary cusp. Anti-anatomical position was defined as rotation of the prosthetic valve commissure post on nearly both the coronary artery ostia and interatrial septum according to previous reports[16].

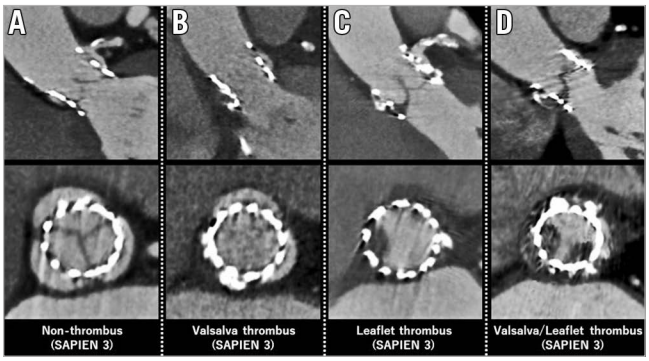

Figure 1. *Representative thrombus images. A) No thrombus. B) Valsalva thrombus. C) Leaflet thrombus. D) Both Valsalva and leaflet thrombi.*

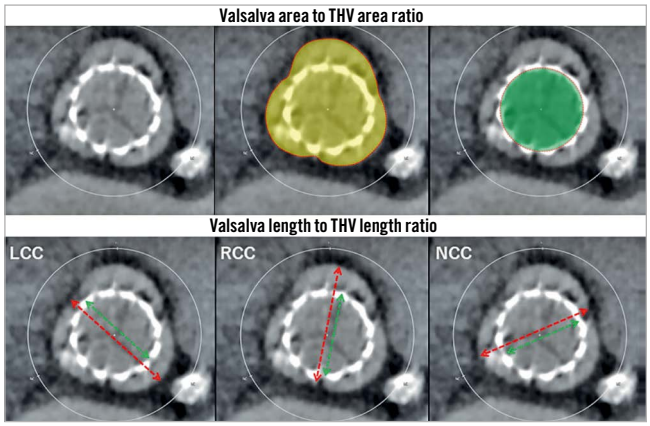

Figure 2. *The Valsalva to transcatheter heart valve (THV) ratios in terms of area and length. Valsalva area to THV ratio was calculated by the yellow area divided by the green area (upper panels). Valsalva length to THV length ratio was calculated by the green distance divided by the red distance for each Valsalva position in the left coronary cusp (LCC), right coronary cusp (RCC), and non-coronary cusp (NCC) (lower panels).*

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS Statistics, Version 22 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as mean±SD and as medians with IQR, depending on the distribution, while the categorical data are expressed as numbers and percentages of the total. Comparisons of the two groups were undertaken using chi-squared or Fisher's exact tests for covariates expressed using mean and SDs, and the Mann-Whitney U test for continuous variables expressed as medians with IQR. The Kaplan-Meier method was used to estimate the combined endpoint of cumulative mortality, stroke and readmission for heart failure in the with and without Valsalva thrombus groups, as well as in the with and without leaflet thrombus groups. A univariate regression analysis predicted the odds ratio regarding the existence of Valsalva thrombus and leaflet thrombus in each variable. Thereafter, a multivariate analysis was performed using the baseline clinical characteristics and other variables with a univariate p-value <0.1 in order to examine independent associations of Valsalva thrombus and leaflet thrombus. All statistical tests were two-sided, and values with $p<0.05$ were considered statistically significant.

Results

Age, sex, body characteristics, comorbidities, blood examinations, and medical treatments were not different between the with Valsalva thrombus and without Valsalva thrombus groups **(Table 1)**, as well as the with leaflet thrombus and without leaflet thrombus groups **(Supplementary Table 1)**. The TTE parameters were similar in the two groups with respect to both Valsalva and leaflet thrombi. Procedural antiplatelet and anticoagulant therapy was not significantly different between the groups.

Table 1. Baseline characteristics.

	Valsalva thrombus		*p*-value
	(+) (n=30)	(–) (n=308)	
Clinical variables			
Age, years	84.8±3.9	84.2±5.1	0.57
Male, n	8 (26.7%)	98 (31.8%)	0.56
Body surface area, m^2	1.38±0.2	1.43±0.2	0.24
Diabetes, n	6 (20.0%)	83 (26.9%)	0.41
Chronic kidney disease, n	14 (46.7%)	181 (58.8%)	0.26
Atrial fibrillation, n	9 (30.0%)	65 (21.1%)	0.28
Previous PCI, n	2 (6.7%)	81 (26.3%)	0.03
Previous cardiac surgery, n	2 (6.7%)	26 (8.4%)	0.74
Peripheral artery disease, n	1 (3.3%)	38 (12.3%)	0.17
Previous stroke, n	2 (6.7%)	28 (9.1%)	0.66
Chronic lung disease, n	6 (20.0%)	99 (32.1%)	0.14
History of cancer, n	1 (3.3%)	64 (20.8%)	0.05
STS score	6.2±2.9	6.8±3.8	0.41
Blood examinations			
Bloodstream haemoglobin, g/dL	11.4±1.3	11.3±1.7	0.90
Serum creatinine, mg/dL	0.91±0.3	0.97±0.3	0.45
eGFR, ml/min/1.73 m^2	53.0±14.8	51.1±16.3	0.71
PT, international normalised ratio	1.08±0.2	1.12±0.3	0.58
Preprocedural echocardiographic variables			
Indexed aortic valve area, cm^2/m^2	0.45±0.1	0.45±0.1	0.87
Left ventricular ejection fraction, %	62.8±13.0	64.2±11.5	0.51
Mean aortic gradient, mmHg	47.1±16.4	48.4±16.4	0.70
Stroke volume, mL	60.5±18.2	65.1±18.3	0.20
Aortic regurgitation ≥mild, n	5 (16.7%)	22 (7.1%)	0.08
Mitral regurgitation ≥mild, n	5 (16.7%)	33 (10.7%)	0.35
Low-flow low-gradient aortic stenosis, n	1 (3.3%)	28 (9.1%)	0.30
Procedural variables			
Transfemoral, n	26 (86.7%)	284 (92.2%)	0.30
Underfilling, n	10 (33.3%)	124 (40.3%)	0.46
Post-dilatation, n	6 (20.0%)	51 (16.6%)	0.60
Antithrombotic therapy			
No antithrombotic therapy, n	0 (0%)	3 (1.0%)	0.80
SAPT, n	8 (26.7%)	56 (18.2%)	
DAPT, n	17 (56.7%)	173 (56.2%)	
OAC therapy, n	1 (3.3%)	11 (3.6%)	
OAC and SAPT, n	4 (13.3%)	61 (19.8%)	
OAC and DAPT, n	0 (0%)	4 (1.3%)	

Values are numbers (%), mean±SD, or median with IQR. DAPT: dual antiplatelet therapy; eGFR: estimated glomerular filtration rate; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; PT: prothrombin time; SAPT: single antiplatelet therapy; STS: Society of Thoracic Surgeons

Preprocedural and post-procedural MDCT parameters are presented in the Valsalva groups **(Table 2)** and in the leaflet groups **(Supplementary Table 2)**. The annulus size as measured by MDCT was not different between the groups. However, the sizes of the LCC, RCC, and NCC were larger in the Valsalva thrombus group than those in the without Valsalva thrombus group. These trends were also confirmed in the leaflet thrombus and without leaflet thrombus groups. The Valsalva length (except for LCC) and area to those of THV ratios were also larger in the Valsalva thrombus group than in the without Valsalva thrombus group (all p<0.05). Similar differences were observed in the with leaflet thrombus and without leaflet thrombus groups (all p<0.05). The angle of the native commissure to bioprosthetic leaflet orientation was approximately 30 degrees rotated, whereas the incidence of Valsalva and leaflet thrombus did not differ. The distributions of the Valsalva and leaflet thrombi were compared overall, and at each Valsalva location **(Figure 3)**. The overall incidence of Valsalva thrombus was 8.9% (30/338). Leaflet thrombus was found in 28 of 338 patients (8.3%). Altogether, 28.6% of the Valsalva thrombi were partially located inside the leaflet (n=8/28). Conversely, 26.7% of the leaflet thrombi overlapped with a Valsalva thrombus (n=8/30). The prevalence of Valsalva thrombus in the LCC and RCC was lower compared with that in the NCC (5.0% [17/338] vs 4.1% [14/338] vs 8.9% [30/338], p<0.001). These trends were similarly found in the SAPIEN XT valve (p<0.001) and SAPIEN 3 valve (p<0.001). The incidences of Valsalva and leaflet thrombi were also compared with respect to the balloon-expandable valve sizes **(Figure 4)**. Among the balloon-expandable valves (20 mm vs 23 mm vs 26 mm vs 29 mm), the incidence of Valsalva thrombus was 6.7% (1/15), 9.0% (19/212), 9.1% (9/99), and 8.3% (1/12), respectively (p=0.75), and that for leaflet thrombus was 6.7% (1/15), 7.1% (15/212), 7.1% (7/99), and 33.3% (4/12), respectively (p=0.27).

Post-procedural echocardiographic parameters and rates of procedural complications are described in the Valsalva groups

Table 2. Preprocedural and post-procedural MDCT.

	Valsalva thrombus		*p*-value
	(+) (n=30)	(–) (n=308)	
Preprocedural MDCT variables			
Annulus area, mm^2	380.3±64.6	384.5±70.0	0.78
Annulus perimeter, mm	70.5±5.9	71.3±5.4	0.46
Post-procedural MDCT variables			
LCC length of Valsalva, mm	27.3±1.7	27.1±1.6	0.091
RCC length of Valsalva, mm	27.3±2.5	28.0±2.1	0.006
NCC length of Valsalva, mm	30.0±1.5	28.6±2.5	0.004
Valsalva area, mm^2	652.7±53.1	612.2±60.9	0.001
THV area, mm^2	393.4±18.6	392.3±21.2	0.79
Length of Valsalva to THV ratio in LCC	1.21±0.1	1.20±0.1	0.41
Length of Valsalva to THV ratio in RCC	1.29±0.1	1.24±0.1	0.011
Length of Valsalva to THV ratio in NCC	1.33±0.1	1.27±0.1	0.007
Area of Valsalva to THV ratio	1.66±0.2	1.56±0.2	0.006
Depth of prosthesis, mm	–1.51±0.9	–1.41±1.3	0.706
Native Valsalva to THV angle in LCC, degrees	32.7±14.6	38.6±18.8	0.23
Native Valsalva to THV angle in RCC, degrees	35.5±19.6	38.6±17.3	0.35
Native Valsalva to THV angle in NCC, degrees	33.7±18.5	35.2±16.1	0.63
Anti-anatomical position, n	10 (33.3%)	138 (44.8%)	0.23
THV design			
SAPIEN XT (N=229), n	16 (7.0%)	213 (93.0%)	0.08
SAPIEN 3 (N=109), n	14 (12.8%)	95 (87.2%)	
THV size ≥26.0 mm, n	10 (3.3%)	101 (3.6%)	0.95
THV size 29.0 mm, n	1 (3.3%)	11 (3.6%)	0.95

Values are numbers (%), mean±SD. LCC: left coronary cusp; MDCT: multidetector computed tomography; NCC: non-coronary cusp; RCC: right coronary cusp; THV: transcatheter heart valve

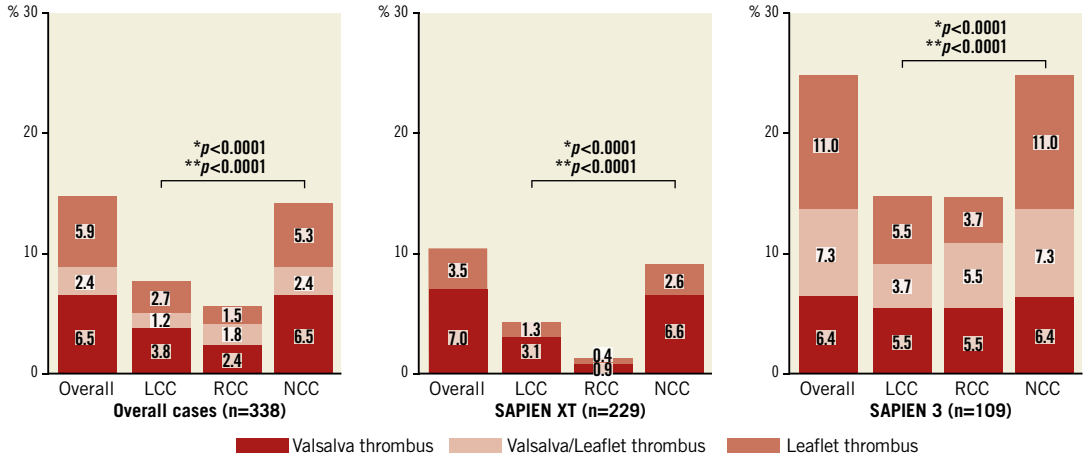

Figure 3. *Distributions of Valsalva, Valsalva leaflet, and leaflet thrombi overall, and in SAPIEN XT valve and SAPIEN 3 valve groups. *p for the incidence of Valsalva thrombus. **p for the incidence of leaflet thrombus.*

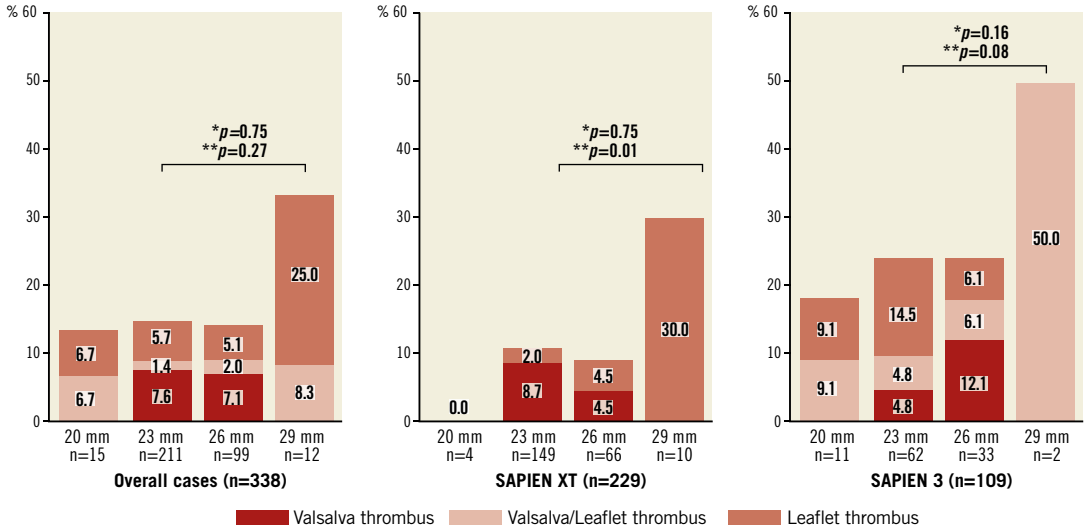

Figure 4. *Comparison of incidences of Valsalva, Valsalva leaflet, and leaflet thrombi in overall, SAPIEN XT, and SAPIEN 3 valve sizes. *p for the incidence of Valsalva thrombus. **p for the incidence of leaflet thrombus.*

(Table 3) and in the leaflet groups **(Supplementary Table 3)**. Post-procedural mean pressure gradient was similar in the Valsalva thrombus and without Valsalva thrombus groups. No significant differences were observed between each group concerning the rates of in-hospital death and procedural complications. Clinical follow-up was performed up to two years after TAVI. Kaplan-Meier analysis showed no significant differences in the combined endpoint in patients in the with Valsalva thrombus and without Valsalva thrombus groups **(Figure 5A)** and in the with leaflet thrombus and without leaflet thrombus groups **(Figure 5B)**. Combining all patients with Valsalva and/or leaflet thrombi (n=51), the incidence of the combined endpoint was similar between the patients with thrombus and without thrombus **(Figure 5C)**. The logistic regression analysis of predictive factors for Valsalva thrombus and leaflet thrombus is shown in **Table 4** and **Supplementary Table 4**, respectively. In the multivariate model, the area of Valsalva to THV ratio was an independent predictive factor of Valsalva thrombus. Low flow, severe prosthesis-patient mismatch, SAPIEN 3 valve, the area of Valsalva to THV ratio, and THV size 29 mm were independent predictive factors for leaflet thrombus.

Table 3. Post-procedural echocardiography and procedural complications.

	Valsalva thrombus		*p*-value
	(+) (n=30)	(–) (n=308)	
Echocardiographic variables			
Indexed effective orifice area, cm^2/m^2	1.17±0.4	1.14±0.3	0.56
Mean aortic pressure gradient, mmHg	10.6±4.7	10.9±4.6	0.71
Peak flow velocity, m/sec	2.13±0.4	2.23±0.4	0.27
Left ventricular ejection fraction, %	64.2±11.8	66.7±10.3	0.21
Stroke volume, mL	66.3±19.0	65.8±16.1	0.52
Aortic regurgitation ≥mild, n	9 (20.5%)	34 (10.7%)	0.71
Severe prosthesis-patient mismatch, n	0 (0.0%)	5 (1.6%)	>0.99
Procedural complications (in-hospital)			
All-cause death, n	0 (0.0%)	0 (0.0%)	>0.99
Major stroke, n	0 (0.0%)	7 (2.3%)	>0.99
Major bleeding, n	1 (3.3%)	14 (4.5%)	0.76
Major vascular complication, n	1 (3.3%)	16 (5.2%)	0.66
Acute kidney injury stage 2 or 3, n	0 (0.0%)	9 (2.9%)	>0.99
New-onset atrial fibrillation, n	2 (6.7%)	9 (2.9%)	0.29

Values are numbers (%), mean±SD.

Discussion

Altogether, the present study demonstrated new findings regarding Valsalva thrombus formation between the native Valsalva and implanted THV following TAVI. Although Valsalva thrombus formation was not significantly associated with all-cause death and stroke events, clinically silent Valsalva thrombus was found in 8.9% of the patients (30/338) who had undergone TAVI. In our study, the timing of MDCT examination was a median of three days after TAVI. The interval from the TAVI procedure to MDCT varied significantly among previous studies, ranging from several days to months (3 to 12). Although the reason why valve thrombosis was recognised in such an early phase was unclear, early leaflet thrombus formation was confirmed by our data and our previous report. In addition, Valsalva thrombus formation was identified during the same early phase after TAVI. Thus, the potential risk of early thrombosis might be affirmed in both the Valsalva and leaflet in patients who underwent TAVI.

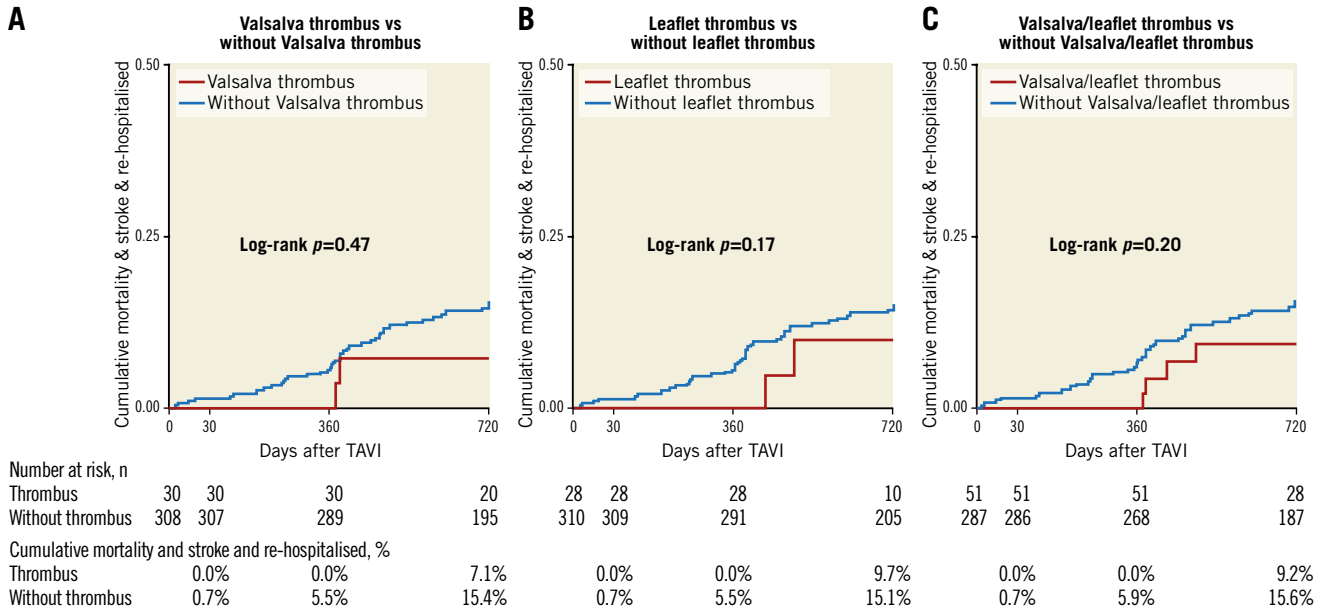

Figure 5. *Cumulative mortality and stroke rates between thrombus and non-thrombus groups. Kaplan-Meier curves showing combined endpoint among the three groups (A-C).*

Table 4. Logistic regression analysis for predicting the Valsalva thrombus.

Variables	Univariable analysis			Multivariable analysis		
	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
Age	1.02	0.95-1.11	0.57			
Male	0.78	0.34-1.81	0.56			
Atrial fibrillation	1.57	0.69-3.59	0.28			
Post aortic regurgitation ≥mild	1.24	0.41-3.77	0.71			
SAPIEN 3	1.96	0.92-4.18	0.08	1.68	0.77-3.64	0.190
THV size 29.0 mm	0.93	0.12-7.47	0.95			
Area of Valsalva to THV ratio	14.70	2.15-99.8	0.006	11.77	1.67-83.0	0.013
Depth of prosthesis, mm	0.94	0.67-1.31	0.71			

CI: confidence interval; THV: transcatheter heart valve

Numerus considerations have been discussed about the causation of leaflet thrombus: these involve speculation regarding the implanted large valve size, balloon-expandable valve type, stent frame geometry, technical aspects, conditions of medical therapy, and fluid mechanics among others[6-10]. The incidence of leaflet thrombus was also significantly higher with SAPIEN 3 valves than with SAPIEN XT valves. However, the sample size was limited in our study and there are arguments both for and against the incidence of leaflet thrombus in the valve differences[5,6,12]. Thus, this topic needs to be investigated in further studies.

The newly formed geometry of the implanted THV affects fluid mechanics negatively in the aorto-valve complex and causes leaflet thrombus formation after TAVI[9]. Fluid mechanics is an important factor when considering the mechanism of THV leaflet thrombosis. An *in vitro* study also proved that the space between the implanted THV and native Valsalva triggered a non-physiological and downstream flow[17,18]. Moreover, the Valsalva space was thought to be a potential risk factor for thrombosis after TAVI[13]. In fact, the area of Valsalva to THV ratios, in terms of both length and area, were significantly larger in the Valsalva thrombus group than in the without Valsalva thrombus group as well as in the leaflet thrombus group. The stent frame design creates more space between the native Valsalva and implanted THV, and thus, as expected, the incidence of Valsalva and leaflet thrombus was higher in the large Valsalva space. The Valsalva thrombus was also located significantly more often in the NCC area. This finding can be explained by the absence of coronary flow in the NCC area in contrast to the other Valsalva cusps. Several factors are related to the increase in local thrombogenicity inside the Valsalva space. As a result, the overall incidence of THV thrombus formation inside the aorto-valve complex might be higher than expected because earlier studies only focused on the existence of leaflet thrombus.

Both Valsalva and leaflet thrombi identified by MDCT were clinically silent. This was classified as subclinical thrombosis in this study, supporting the findings of many past studies[3-8]. The clinical question under debate regards medical intervention using antithrombotic therapy for preventing leaflet thrombus. Anticoagulant therapy is considered to be effective for reducing leaflet thrombosis[3,6,11,12,19]. A recent large-scale multicentre data analysis reported that the lack of anticoagulation therapy post TAVI was associated with significant increments in transvalvular gradient and a greater risk of valve haemodynamic deterioration[20]. However, contradictory data exist suggesting that the natural history of untreated leaflet thrombus is not related to an increase in the pressure gradient after TAVI[4,5,8,21]. When considering medical intervention for valve thrombosis, it is important to assess the clinical relevance of valve thrombus that is associated with valve deterioration, stroke, and heart failure. Although rare, significant elevation of the transvalvular pressure gradient was related to the massive leaflet thrombus detected by MDCT[11]. A study revealed that valve thrombosis was a possible cause of thromboembolic stroke events[22]. In such kinds of high-risk subsets, additional anticoagulant therapy might be useful to treat the adverse clinical events. However, our data demonstrated no significant increased risk of the combined endpoint in patients with leaflet and Valsalva thrombi. The routine use of anticoagulation therapy for its preventive effect against THV thrombus formation should be carefully decided on the basis of the background of each individual patient, especially when considering bleeding risk in the very elderly TAVI patient cohort. Moreover, large-scale data will be required to define an optimal medical therapy after TAVI.

Limitations

Several limitations of this study should be discussed. First, this was a retrospective study without definitive inclusion criteria for MDCT examinations. Patients with renal dysfunction were excluded, thus selection bias in patient enrolment was inevitable. Second, it is difficult to prove the direct relationship between the Valsalva/leaflet thrombus and minor stroke events because the MDCT assessments for the existence of THV thrombosis did not take place when clinical events occurred. In addition, this registry did not have core laboratory centres and neurological specialists who could evaluate the stroke rates properly. Therefore, we should not overstate our conclusions concerning the lack of clinical association between THV thrombus and minor stroke events. Third, the long-term follow-up data of echocardiography were not validated in all patients. Therefore, the clinical influence of Valsalva and/or leaflet thrombus on the occurrence of structural valve deterioration could not be evaluated in this study.

Conclusions

Altogether, Valsalva thrombus was found in 8.9% of patients following TAVR and was especially more common in the LCC. However, both Valsalva and/or leaflet THV thrombi were not related to an increased risk of adverse events. Further clinical investigations will be required to assess the clinical implications of THV thrombosis.

Impact on daily practice

Valsalva thrombus was found in 8.9% of patients following TAVR and was especially more prevalent in the LCC and the large Valsalva space to the implanted THV. Although Valsalva thrombus was subclinical, the optimal management for patients with these TAVR-specific complications needs to be clarified.

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Conflict of interest statement

M. Yamamoto, T. Naganuma, K. Mizutani, and Y. Watanabe are clinical proctors for Edwards Lifesciences and Medtronic. M. Araki, A. Higashimori, and K. Hayashida are clinical proctors of Edwards Lifesciences. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Baseline characteristics.

Supplementary Table 2. Preprocedural and post-procedural echocardiography and MDCT.

Supplementary Table 3. Post-procedural echocardiography and procedural complications.

Supplementary Table 4. Logistic regression analysis for predicting leaflet thrombus.

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Supplementary data

Supplementary Table 1. Baseline characteristics.

	Leaflet thrombus		
	(+) (n=28)	(-) (n=310)	*p*-value
Clinical variables			
Age, years	85.4±3.4	84.2±5.1	0.21
Male, n	9 (32.1%)	90 (29.0%)	0.93
Body surface area, m^2	1.45±0.2	1.42±0.2	0.51
Diabetes, n	11 (39.3%)	70 (22.6%)	0.11
Chronic kidney disease, n	15 (53.6%)	170 (54.8%)	0.77
Atrial fibrillation, n	4 (14.3%)	68 (21.9%)	0.30
Previous PCI, n	7 (25.0%)	67 (21.6%)	0.99
Previous cardiac surgery, n	1 (3.6%)	23 (7.4%)	0.36
Peripheral artery disease, n	2 (7.1%)	34 (11.0%)	0.45
Previous stroke, n	2 (7.1%)	25 (8.1%)	0.74
Chronic lung disease, n	10 (35.7%)	92 (29.7%)	0.68
History of cancer, n	5 (17.9%)	57 (18.4%)	0.85
STS score	6.7±3.4	6.8±3.8	0.88
Blood examinations			
Bloodstream haemoglobin, g/dL	11.2±1.6	11.3±1.5	0.96
Serum creatinine, mg/dL	0.91±0.3	0.96±0.3	0.90
eGFR, ml/min/1.73 m^2	54.7±13.0	50.9±16.3	0.56
PT, international normalised ratio	1.11±0.2	1.12±0.3	0.96
Preprocedural echocardiographic variables			
Indexed aortic valve area, cm^2/m^2	0.43±0.2	0.45±0.1	0.27
Left ventricular ejection fraction, %	63.9±10.7	64.1±11.7	0.94
Mean aortic gradient, mmHg	48.2±14.3	48.2±16.6	1.0
Stroke volume, mL	62.1±21.7	64.9±18.0	0.46
Aortic regurgitation ≥mild, n	1 (3.6%)	22 (7.1%)	0.38
Mitral regurgitation ≥mild, n	1 (3.6%)	34 (11.0%)	0.20
Low-flow low-gradient aortic stenosis, n	7 (25.0%)	15 (4.8%)	0.003
Procedural variables			
Transfemoral, n	28 (100.0%)	265 (85.5%)	1.0
Underfilling, n	8 (28.6%)	119 (38.4%)	0.22
Post-dilatation, n	3 (10.7%)	51 (16.5%)	0.39
Antithrombotic therapy			

No antithrombotic therapy, n	0 (0%)	3 (1.0%)	0.80
SAPT, n	8 (28.6%)	56 (18.1%)	
DAPT, n	14 (50.0%)	176 (56.8%)	
OAC therapy, n	1 (3.6%)	11 (3.5%)	
OAC and SAPT, n	5 (17.9%)	60 (19.4%)	
OAC and DAPT, n	0 (0%)	0 (0%)	

Values are numbers (%), mean±SD, or median with IQR.

DAPT: dual antiplatelet therapy; eGFR: estimated glomerular filtration rate; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; PT: prothrombin time; SAPT: single antiplatelet therapy; STS: Society of Thoracic Surgeons

Supplementary Table 2. Preprocedural and post-procedural echocardiography and MDCT.

	Leaflet thrombus		
	(+) (n=28)	(-) (n=310)	*p*-value
Preprocedural MDCT variables			
Annulus area, mm^2	409.1±71.4	382.4±69.1	0.11
Annulus perimeter, mm	72.9±6.1	71.1±5.4	0.18
Post-procedural MDCT variables			
LCC length of Valsalva, mm	27.1±2.6	27.1±1.6	0.75
RCC length of Valsalva, mm	29.4±2.6	28.0±2.1	0.001
NCC length of Valsalva, mm	29.8±2.1	28.7±2.4	0.028
Valsalva area, mm^2	649.5±64.2	612.7±60.2	0.003
THV area, mm^2	391.9±21.7	392.5±20.9	0.88
Length of Valsalva to THV ratio in LCC	1.20±0.1	1.20±0.1	0.96
Length of Valsalva to THV ratio in RCC	1.31±0.1	1.24±0.1	0.002
Length of Valsalva to THV ratio in NCC	1.32±0.1	1.28±0.1	0.03
Area of Valsalva to THV ratio	1.66±0.2	1.57±0.2	0.009
Depth of prosthesis, mm	-1.30±1.6	-1.43±1.3	0.59
Native Valsalva to THV angle in LCC, degrees	37.0±19.3	36.5±18.5	0.90
Native Valsalva to THV angle in RCC, degrees	32.9±20.0	38.8±17.2	0.09
Native Valsalva to THV angle in NCC, degrees	35.8±17.7	35.0±16.2	0.83
Anti-anatomical position, n	11 (39.3%)	137 (44.2%)	0.62
THV design			
SAPIEN XT (N=229), n	9 (3.9%)	220 (96.1%)	<0.001
SAPIEN 3 (N=109), n	19 (17.4%)	90 (82.6%)	
THV size ≥26.0 mm, n	11 (14.3%)	100 (2.3%)	0.45
THV size 29.0 mm, n	4 (14.3%)	7 (2.3%)	0.005

Values are numbers (%), mean±SD.

LCC: left coronary cusp; MDCT: multidetector computed tomography; NCC: non-coronary cusp; RCC: right coronary cusp; THV: transcatheter heart valve

Supplementary Table 3. Post-procedural echocardiography and procedural complications.

	Leaflet thrombus		
	(+) (n=28)	(-) (n=310)	*p*-value
Echocardiographic variables			
Indexed effective orifice area, cm^2/m^2	1.11±0.4	1.14±0.4	0.56
Mean aortic pressure gradient, mmHg	11.8±4.8	10.8±4.5	0.29
Peak flow velocity, m/sec	2.33±0.5	2.21±0.4	0.12
Left ventricular ejection fraction, %	64.6±8.8	66.6±10.6	0.32
Stroke volume, mL	63.0±17.2	66.0±16.3	0.64
Aortic regurgitation ≥mild, n	5 (16.1%)	147 (11.48%)	0.93
Severe prosthesis-patient mismatch, n	3 (10.7%)	2 (0.6%)	0.002
Procedural complications (in-hospital)			
All-cause death, n	0 (0.0%)	0 (0.0%)	>0.99
Major stroke, n	1 (3.6%)	6 (1.9%)	0.57
Major bleeding, n	2 (7.1%)	13 (4.2%)	0.47
Major vascular complication, n	1 (3.6%)	16 (5.2%)	0.71
Acute kidney injury stage 2 or 3, n	0 (0.0%)	9 (2.9%)	>0.99
New-onset atrial fibrillation, n	1 (3.6%)	10 (3.2%)	0.92

Values are numbers (%), mean±SD.

Supplementary Table 4. Logistic regression analysis for predicting the leaflet thrombus.

	Leaflet thrombus					
	Univariable analysis			Multivariable analysis		
Variables	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Age	1.06	0.97-1.16	0.21			
Male	1.04	0.45-2.38	0.93			
Atrial fibrillation	0.56	0.19-1.67	0.30			
Low-flow low-gradient aortic stenosis	4.36	1.67-11.4	0.003	4.44	1.46-13.5	0.008
Post aortic regurgitation ≥mild	0.94	0.27-3.33	0.93			
Severe prosthesis-patient mismatch	18.5	2.95-115.8	0.002	15.7	1.85-133.1	0.012
Valve design SAPIEN 3	5.16	2.25-11.8	<0.001	5.24	2.04-13.5	0.001
THV size 29.0 mm	6.29	1.77-22.4	0.005	15.6	3.49-69.7	<0.001
Area of Valsalva to THV ratio	13.9	1.95-98.7	0.009	11.6	1.35-99.0	0.025
Depth of prosthesis, mm	1.07	0.83-1.38	0.59			

CI: confidence interval; OR: odds ratio; THV: transcatheter heart valve