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Transcatheter Aortic Heart Valve Thrombosis: Incidence, Predisposing Factors, and Clinical Implications

Nicolaj C. Hansson, MD, Erik L. Grove, MD, PhD, Henning R. Andersen, MD, DMSc, Jonathon Leipsic, MD, Ole N. Mathiassen, MD, PhD, Jesper M. Jensen, MD, PhD, Kaare T. Jensen, MD, PhD, Philipp Blanke, MD, Tina Leetmaa, MD, Mariann Tang, MD, Lars R. Krusell, MD, Kaj E. Klaaborg, MD, Evald H. Christiansen, MD, PhD, Kim Terp, MD, Christian J. Terkelsen, MD, DMSc, Steen H. Poulsen, MD, DMSc, John Webb, MD, Hans Erik Bøtker, MD, DMSc, Bjarne L. Nørgaard, MD, PhD

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Nicolaj C. Hansson, MD[a], Erik L. Grove, MD, PhD[a,b], Henning R. Andersen, MD, DMSc[a], Jonathon Leipsic, MD[c], Ole N. Mathiassen, MD, PhD[a], Jesper M. Jensen, MD, PhD[a], Kaare T. Jensen, MD, PhD[a], Philipp Blanke, MD[c], Tina Leetmaa, MD[a], Mariann Tang, MD[d], Lars R. Krusell, MD[a], Kaj E. Klaaborg, MD[d], Evald H. Christiansen, MD, PhD[a], Kim Terp, MD[d], Christian J. Terkelsen MD, DMSc[a], Steen H. Poulsen, MD, DMSc[a], John Webb, MD[c], Hans Erik Bøtker, MD, DMSc[a,b], Bjarne L. Nørgaard, MD, PhD[a]

[a]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark
[b]Institute of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark
[c]Department of Medical Imaging and Division of Cardiology, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia
[d]Department of Cardiothoracic Surgery, Aarhus University Hospital, Aarhus, Denmark

Brief title: THV Thrombosis: Incidence and Clinical Implications

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Address for correspondence:
Nicolaj C. Hansson, MD
Department of Cardiology
Aarhus University Hospital Skejby
Palle Juul-Jensens Boulevard 99
8200 Aarhus N, Denmark
Telephone: +45-284-94-483
Fax: +45-78452260
Email: nh@dadlnet.dk

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Abstract

Background: There is increasing focus on transcatheter heart valve (THV) thrombosis. However, there are limited data on incidence, clinical implications and predisposing factors of THV thrombosis following transcatheter aortic valve replacement (TAVR).

Objectives: We assessed the incidence, potential predictors, and clinical implications of THV thrombosis determined by contrast-enhanced multidetector computed tomography (MDCT) after TAVR.

Methods: Among 460 consecutive patients undergoing TAVR with the Edwards Sapien XT or Sapien 3 (Edwards Lifesciences, Irvine, CA, USA) valves, 405 (88%) underwent MDCT in addition to transthoracic and transesophageal echocardiography 1-3 months post-TAVR. MDCT scans were evaluated for hypo-attenuated leaflet thickening indicating THV thrombosis.

Results: MDCT verified THV thrombosis in 28 of 405 (7%) patients. A total of 23 patients had subclinical THV thrombosis, while 5 (18%) patients experienced clinically overt obstructive THV thrombosis. THV thrombosis risk did not differ between the Edwards Sapien XT and the Sapien 3 valves, 8% (14/173) vs. 6% (14/232) (p=0.42). The risk of THV thrombosis in patients not receiving warfarin was higher compared to patients receiving warfarin, 10.7% vs. 1.8%; RR, 95%CI: 6.09, 1.86-19.84. A larger THV was associated with an increased THV thrombosis risk (p=0.03). In multivariable analysis, 29 mm THV (RR, 95%CI: 2.89, 1.44-5.80) and no post-TAVR warfarin treatment (RR, 95%CI: 5.46, 1.68-17.7), independently predicted THV thrombosis. Treatment with warfarin effectively reverted THV thrombosis and normalized THV function in 85% of patients as documented by follow-up transesophageal echocardiography and MDCT.

Conclusions: The incidence of THV thrombosis in this large study was 7%. Larger THV size may predispose to THV thrombosis, whereas treatment with warfarin appears to have a protective effect. Although often subclinical, THV thrombosis may have important clinical implications.

Key words: Aortic stenosis; multidetector computed tomography; platelet aggregation inhibitors transcatheter aortic valve replacement; warfarin

Abbreviations

eGFR: estimated glomerular filtration rate
EOA: effective orifice area
LVEF: left ventricular ejection fraction
NOAC: non-vitamin K antagonist oral anticoagulants
MR: mitral regurgitation
PAR: paravalvular regurgitation
TAVR: transcatheter aortic valve replacement
TEE: transesophageal echocardiography
THV: transcatheter heart valve
TTE: transthoracic echocardiography

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Introduction

Transcatheter aortic valve replacement (TAVR) is a well-established treatment of severe aortic stenosis. Owing to technical improvements, increased operator experience and refined preprocedural imaging, it is an increasingly safe and successful procedure (1,2). However, there is increasing awareness of prosthesis valve thrombosis after TAVR (3-6). Accordingly, recent reports have demonstrated that conventional post-TAVR transthoracic echocardiography (TTE) follow-up is inferior for the detection of transcatheter heart valve (THV) thrombosis when compared to contrast-enhanced multidetector computed tomography (MDCT). Indeed, post-TAVR MDCT has the ability to detect THV thrombosis in asymptomatic patients with no evidence of THV obstruction on TTE (3-5). Although often subclinical, THV thrombosis may potentially lead to increased risk of stroke, THV obstruction with heart failure or reduced long-term THV durability, making early detection pivotal to guide treatment. Current evidence regarding THV thrombosis mainly builds on case series and small studies of non-consecutive patients with short follow-up time (3-6). Consequently, the incidence, clinical implications and predisposing factors of THV thrombosis remain to be fully understood. The aim of this study was to assess the incidence, potential predictors, and clinical implications of THV thrombosis after TAVR with a balloon-expandable THV.

Methods

Study population and transcatheter aortic valve replacement procedure

Among 460 consecutive patients undergoing TAVR with the Edwards Sapien XT or Sapien 3 (Edwards Lifesciences, Irvine, CA, USA) at Aarhus University Hospital between January 2011 and January 2016, a total of 405 (88%) underwent MDCT in addition to TTE and transesophageal echocardiography (TEE) 1-3 months after the TAVR procedure (routine follow-

up visit 1). These 405 patients form the basis of the present study. In the remaining 55 patients undergoing TAVR, MDCT was not performed because of death before follow-up (n=19), severely impaired renal function (n=7) or patient refusal/frailty (n=29). Clinical and TTE assessment were performed in our outpatient clinic 12 months post-TAVR (routine follow-up visit 2). All procedures were performed as part of standard clinical care.

TAVR was performed according to standard practice (7). THV size selection was based on MDCT analysis, and balloon under-/overfilling and post-dilatation was performed in selected cases (8,9).

Standard post-TAVR antithrombotic treatment comprised dual antiplatelet therapy with aspirin (75 mg/day) and clopidogrel (75 mg/day) for 12 months followed by lifelong aspirin (75 mg/day) (3).In patients with atrial fibrillation, the decision on treatment with warfarin alone or in combination with one platelet inhibitor was at the discretion of the treating physician.

Echocardiographic assessment

TTE was performed before discharge and at routine follow-up visit 1 and 2. THV function was assessed by the mean trans-THV gradient and the effective orifice area (EOA_{THV}). Paravalvular regurgitation (PAR) was graded *mild*, *moderate* or *severe* according to the Valve Academic Research Consortium-2 criteria (10). Furthermore, at routine follow-up visit 1 and after THV thrombosis treatment, TEE was performed to further delineate the aortic root, THV anatomy, and THV leaflet mobility (3).

Multidetector computed tomography acquisition

Pre- and post-TAVR contrast-enhanced MDCT examinations were performed using a second-generation dual-source CT system (Siemens Somatom Definition Flash, Siemens Healthcare, Erlangen, Germany) as previously described (3). Post-TAVR MDCT scans were

performed using a prospectively electrocardiographic (ECG)-gated sequential acquisition protocol in all patients.

Multidetector computed tomography analysis

MDCT examinations were analyzed using commercially available software (syngo.via and Multimodality Workplace, Siemens Healthcare, Forcheim, Germany). On pre-TAVR MDCT scans, aortic root dimensions and degree of calcification was determined as previously described (7). Post-TAVR MDCT scans were evaluated for hypo-attenuated leaflet thickening indicating THV thrombosis (3). Leaflet thrombus was defined as hypo-attentuating leaflet thickening or a more focal hypo-attenuating abnormality attached to the THV leaflet and/or diffuse thickening of 1 or more THV leaflets. The finding had to be identifiable on at least two reconstructed planes (double-oblique axial and multiplanar reformatted reconstructions). In the event of THV thrombosis, the number of leaflets involved as well as maximal leaflet thickening was assessed. THV dimensions, eccentricity, and expansion were assessed as previously described (3). THV underexpansion was defined as an expansion ratio of ≤90% at both the inflow, midportion and outflow. The THV was deemed noncircular if eccentricity was >10% at both the inflow, midportion and outflow.

Transcatheter heart valve thrombosis diagnosis, treatment and follow-up

Follow-up MDCT and echocardiography were performed by separate operators, but all imaging and clinical information were available to the threating physician. As per institutional policy, initiation of warfarin alone or in combination with antiplatelet therapy was recommended in patients with MDCT evidence of THV thrombosis, but the final decision was at the discretion of the treating physician taking into account the patient´s bleeding risk and preferences.

Additional TTE, TEE and MDCT was performed 3 months after the diagnosis of THV thrombosis.

Statistical analysis

The risk ratio (RR) with 95% confidence intervals and the chi-square are calculated to compare THV thrombosis risks (**Tables 1-3**). Left ventricular ejection fraction [LVEF] ≤35% at hospital discharge, use of a 29 mm THV and no post-TAVR warfarin treatment were entered into a log-linear model for binary data to estimate adjusted RRs for THV thrombosis (3-5). Clinical implications of THV thrombosis were studied by comparing the distribution of various factors between THV thrombosis and non-THV thrombosis patients (**Table 4 and 5**). Continuous normally distributed variables are presented as mean±standard deviation (SD) and compared using the unpaired or paired Student´s t-test. Other distributed continuous variables are presented as median [interquartile range] and compared using the Mann-Whitney-U test. Categorical variables are presented as frequencies (percentages) and compared using Fisher´s exact test or chi-square as appropriate. A two-tailed p value <0.05 was considered statistically significant. All analyses were performed using Stata 12 (StataCorp LP, College Station, TX, USA).

Results

Predictors of transcatheter heart valve thrombosis

Baseline characteristics

Table 1 depicts the risk of THV thrombosis in relation to pre-TAVR clinical characteristics, while THV thrombosis risk in relation to pre-TAVR echocardiographic and MDCT characteristics are shown in Online Table 1. Median (IQR) age of the study cohort was 83 (78-86) years, 54% were female and median (IQR) Society of Thoracic Surgeons predicted

risk of mortality (STS PROM) was 5.3 (3.6-7.1). THV thrombosis risk was higher in patients with atrial fibrillation and eGFR ≤30 ml/min, and tended to be higher in males.

Procedural data, THV and pre-discharge echocardiographic characteristics

Information on THV thrombosis risk related to procedural data and pre-discharge echocardiographic characteristics are provided in **Table 2.** A larger THV were associated with THV thrombosis (p=0.03). Otherwise, there were no differences in THV thrombosis risk in relation to procedural characteristics or THV function between groups. THV oversizing ≤17% vs >17% did not affect THV thrombosis risk significantly. Of note, the risk of THV thrombosis did not differ between the Edwards Sapien XT and the Sapien 3 valve.

Post-procedural antithrombotic regimen

Antithrombotic regimens from the TAVR procedure until routine follow-up visit 1 are outlined in **Table 3**. The risk of THV thrombosis in patients not receiving warfarin was higher compared to patients receiving warfarin, 10.7% vs. 1.8%; RR, 95%CI: 6.09, 1.86-19.84. In patients receiving mono antiplatelet therapy, the risk of THV thrombosis was 18.8% (6/32).

Multivariable analysis of predictors of transcatheter heart valve thrombosis

In multivariable analysis, a 29 mm THV (RR, 95%CI: 2.89, 1.44-5.80) and no post-TAVR warfarin treatment (RR, 95%CI: 5.46, 1.68-17.7), but not LVEF ≤35% at discharge (RR, 95%CI: 2.21, 0.93-5.26), independently predicted THV thrombosis.

Incidence and clinical implications of transcatheter heart valve thrombosis

<u>Routine follow-up visit 1</u>

There was no difference in median (IQR) interval from the TAVR procedure to follow-up in the non-THV thrombosis group vs. the THV thrombus group, 42 (25-59) vs. 43 (28-57) days

(p=0.55). Post-TAVR MDCT effective radiation dose (mSv) was similar in the non-THV thrombosis group vs. the THV thrombus group, 3.1±1.6 vs. 2.9±1.7 (p=0.63).

There was no difference between the mean trans-THV gradient at predischarge vs. at routine follow-up visit 1 in the THV thrombosis group, 10±5 vs. 10±4 mmHg (p=1.00). The trans-THV mean gradient was higher among THV thrombosis patients (**Table 4**). Left ventricular ejection fraction ≤35% was two-fold more frequent among patients with THV thrombosis compared to those without, 5 (18%) vs. 30 (8%) patients (p=0.08). There was no difference in 30-day complication rates between the two groups.

Follow-up and treatment of transcatheter heart valve thrombosis

At routine follow-up visit 1, post-TAVR MDCT demonstrated THV thrombosis in 24 patients. Additionally, 4 patients presented with THV thrombosis before or after routine follow-up visit 1. Thus, the THV thrombosis group comprised 28 of 405 (7%) patients. TEE demonstrated leaflet thickening and/or restrictive leaflet movement in 24 (86%) patients. In 2 (7%) patients, there were no abnormal findings on TEE, while 2 (7%) patients did not undergo TEE. No patients without THV thrombus determined by MDCT had compromised leaflet motility by TEE.

Warfarin alone or in addition to antiplatelet therapy was prescribed in 4 (14%) and 17 (61%) patients, respectively. In the 3 (11%) patients already receiving warfarin, the target INR level was raised to 2.5-3. In 4 (14%) patients, routine antithrombotic therapy without warfarin was maintained, and additional downstream TEE and MDCT imaging were planned. Of these four patients, two experienced spontaneous THV thrombus regression, whereas two had THV thrombosis progression and warfarin was initiated. TEE and MDCT follow-up after 3 months of treatment showed complete thrombus resolution in 85% of cases (**Figures 2 and 3**).

Obstructive transcatheter heart valve thrombosis

Five (18%) patients developed obstructive THV thrombosis with heart failure symptoms during the 12-month follow-up period. Details regarding these cases are presented in Online Table 2. In 1 patient, obstructive THV thrombosis was diagnosed at routine follow-up visit 1, whereas 1 presented with symptoms of heart failure before and 3 patients 3-8 months after the routine follow-up visit 1. Four (80%) of these patients received mono antiplatelet therapy. No cases of THV obstruction were observed among patients without THV thrombosis.

Selected clinical characteristics, THV thrombus characteristics and outcomes in patients with non-obstructive versus obstructive THV thrombosis are presented in the supplementary Table S3. No patients with obstructive THV thrombosis received warfarin as part of post-TAVR antithrombotic therapy. Patients with obstructive THV thrombosis had involvement of more THV leaflets than patients with non-obstructive thrombus (1.3±0.5 vs. 2.4±0.5; p=0.0001), and the mean maximal leaflet thickness was significantly higher (4.2±1.8 mm vs. 7.5±1.3 mm; p=0.0007).

Routine follow-up visit 2

The median time from the TAVR procedure to routine follow-up visit 2 in the non-THV thrombosis group vs. the THV thrombus group was 360 (341-383) vs. 363 (348-375) days (p=0.45).

As shown in **Figure 1**, routine follow-up visit 2 data including clinical and echocardiographic assessment as well as mortality status were available in 335 (83%) patients. Twelve-month all-cause mortality was 17% (54/316) in the non-THV thrombosis group vs. 11% (2/19) among patients with THV thrombosis (p=0.75). Twelve-month follow-up data with echocardiography and information on stroke were available for 229 patients in the control group

and 17 patients with THV thrombosis (Table 5). In patients with THV thrombosis, mean trans-THV gradient was lower at routine follow-up visit 2 vs. routine follow-up visit 1, 9±4 mmHg vs. 11±4 mmHg (p=0.03). Antithrombotic regimens at follow-up visit 2 are outlined in Online Table 4.

Discussion

In this study comprising the largest to date and the first consecutive cohort having MDCT performed following TAVR with the Edwards XT or Edwards S3 THVs, the incidence of THV thrombosis was 7%. While in the vast majority of cases there were no signs of THV obstruction on TTE, 18% of patients with THV thrombosis formation developed clinically overt obstructive THV thrombosis. Other main findings were that the use of a 29 mm THV and no warfarin post-TAVR treatment were independently associated with an increased risk of THV thrombosis. Treatment with warfarin effectively reversed THV thrombosis findings and normalized THV function.

Two recent smaller studies assessed the presence of THV thrombosis with MDCT as the diagnostic modality. Makkar et al (5) and Pache et al (4) performed retrospective ECG-gated MDCT scans allowing assessment of THV leaflet morphology as well as leaflet mobility throughout the cardiac cycle. In contrast, the present study evaluated THV leaflet morphology by performing low-radiation dose prospective ECG-gated MDCT imaging, while THV leaflet mobility was assessed by TEE. We believe that TEE provides the most comprehensive evaluation of THV function. THV leaflet mobility assessment is most likely improved compared to MDCT assessment due to the superior temporal resolution of TEE. Additionally, TEE is a valuable supplement to TTE for evaluation of PAR. We found that the agreement between MDCT-verified THV thrombosis and restricted THV leaflet mobility on TEE was high, and

importantly, no patients without THV thrombosis on MDCT had restricted THV leaflet mobility on TEE. Taken together these findings suggests that a frontline diagnostic strategy for THV thrombosis may consist of TTE and THV leaflet morphology assessment by MDCT with supplementary TEE in cases of equivocal MDCT findings or contraindications to MDCT. In our experience, MDCT offers several potential advantages over TEE regarding detection of THV thrombosis, e.g. it is less invasive, less operator-dependent and, in fact, it detected a few more cases of THV thrombosis in this study.

The pooled data presented by Makkar et al (5) demonstrated reduced leaflet motion and hypo-attenuating opacities in 40% of 55 TAVR patients in a clinical trial and 13% of 132 patients (105 THVs, 27 bioprosthetic surgical valves) in two registries. Pache et al.(4) detected hypo-attenuated leaflet thickening in 10.3% of 156 patients (from a cohort of 249 consecutive patients) undergoing TAVR with the Edwards S3 THV. In none of these studies, cases of THV dysfunction attributable to THV thrombosis were presented. The present study extends these findings to a larger cohort with more extensive follow-up, and furthermore illustrates the important clinical implications of THV thrombosis. Additionally, we included 88% of all patients undergoing TAVR at our institution, thus reducing the risk of selection bias compared to the aforementioned studies. The differences in THV thrombosis incidence between studies may result from major differences in crucial determinants of outcomes. First, the interval from TAVR procedure to MDCT follow-up differs significantly between studies ranging from 5 days to 3 months. Moreover, the proportion of patients receiving post-TAVR anticoagulant therapy varied between 20% and 40%. Finally, different THV types were investigated (4,5). Of note, Latib et al.(11) recently reported an incidence of THV thrombosis of 0.61% in a multicenter retrospective registry including >4000 patients. However, the majority of these patients had progression of

symptoms and the diagnosis of THV thrombosis was based mainly on TTE, thus the true incidence of THV thrombosis was likely underestimated (3).

There is limited evidence on the optimal antithrombotic therapy following TAVR, and current recommendations regarding post-TAVR antithrombotic therapy have been empirically determined (12-14). In a recent metaanalysis comparing aspirin vs. aspirin+clopidogrel following TAVR, there was no difference in the 30-day clinical and cerebrovascular adverse event rate, however a trend towards more bleeding in the aspirin+clopidogrel group was demonstrated (15). In this context, it should be acknowledged that in this study, mono therapy with aspirin was associated with a THV thrombosis risk of 25% and, importantly, all patients experiencing obstructive THV thrombosis, received mono antiplatelet therapy. Moreover, the present study indicates that a post-TAVR antithrombotic regimen without warfarin seems to predispose to THV thrombosis (5). In line with these findings are recent data from a multicenter registry demonstrating that lack of anticoagulant therapy following TAVR seems associated with THV dysfunction (16). The protective effect of anticoagulant therapy may explain the lower incidence of THV thrombosis among patients with atrial fibrillation in this study. Several ongoing randomized trials, such as the GALILEO trial (NCT02556203) and the POPular-TAVI trial (NCT02247128), will provide data on the use of non-vitamin K antagonist oral anticoagulants (NOAC) and antiplatelets after TAVR.

Currently, there is no consensus on how to treat THV thrombosis. As in previous studies, anticoagulation with warfarin was effective in the vast majority of patients in the present study (4,5,11,17). We and others have observed recurrence of THV thrombosis after discontinuation of warfarin, thus indicating that short-term warfarin treatment of THV thrombosis may not suffice in patients prone to developing THV thrombosis (5). Furthermore, there is still uncertainty

regarding the natural history of THV thrombosis. Hypothetically, spontaneous THV thrombosis resolution may explain the discrepancy observed between the incidence of incidental THV thrombosis and clinically overt obstructive THV thrombosis. The data provided in this and previous studies suggest that follow-up MDCT in patients with THV thrombus will show either no regression or even progression in most patients who continue antiplatelet therapy only (4,5). Moreover, we observed cases of incidental THV thrombosis progressing to clinically overt THV thrombosis with accompanying THV obstruction and symptoms of heart failure. These findings suggest that early detection and anticoagulation may be crucial in order to prevent deterioration of THV function. An alternative strategy to the one used in this study is "watchful waiting" including serial clinical and imaging follow-up with anticoagulation being initiated only in the event of clinical THV thrombosis. However, 1 of 5 patients with obstructive THV thrombosis in this study did deteriorate despite initiation of anticoagulation. Furthermore, the clinical consequences of non-obstructive THV thrombosis may also include decreased long-term THV durability and increased risk of stroke, although assessment of the latter association is challenging due to the potential multiple mechanisms underlying TAVR-related stroke (5,18). The safety of a "watchful waiting" strategy needs delineation in future studies.

We demonstrated for the first time an association between larger THV size and THV thrombosis. *Ex vivo* data have shown that local flow dynamics in the sinuses of Valsalva are modified upon THV implantation (19). Whether these local flow dynamics are further modified by THV size/type, and thus play a causative role in development of THV thrombosis may be speculated. Additional procedural manipulation of the THV (e.g. post-dilatation), post-deployment THV geometry and degree of THV oversizing did not affect the incidence of THV thrombosis in this or in other studies (4,5,11). Whether the rate of THV thrombosis varies with

different types of THVs remains unclear, but different designs (e.g. suprannular vs. intraannuluar) leading to differences in local flow dynamics and variations in leaflet material (ie. porcine vs. bovine) may potentially account for differences in thrombogenicity. Recently, it was shown that platelet activation appears to be less enhanced in the Sapien 3 compared with Sapien XT, possibly due to the lower rate of post-TAVR aortic regurgitation. However, in the present study the incidence of THV thrombosis did not differ between these two THVs (20). Studies including a larger number of THV thrombosis cases are needed in order to further elucidate specific risk factors for THV thrombosis.

Limitations

This study has the inherent limitations of an observational single-center design. The diagnosis of THV thrombosis was not confirmed by histology or autopsy, however THV leaflet thickening and restricted mobility was rapidly reversible by anticoagulation as documented by follow-up TEE and MDCT strongly underlining the thrombotic nature of these findings. The selection of variables included in the multivariable model for prediction of THV thrombosis, although based on knowledge from previous studies, was posthoc in nature. The present study design does not allow for conclusions on the natural history and management of THV thrombosis. Data in this real-world observational study were collected in a nonselected cohort of patients and involved multiple MDCT, echocardiography, and TAVR operators unblinded to the test results. There is no established consensus on the interpretation and management of imaging findings indicative of THV thrombus. In our center, the diagnostic strategy has previously been described (3). It should be acknowledged that treatment decisions may have varied among observers taking into account also clinical observations, e.g. symptoms, bleeding risk and patient preferences. However, this study included all patients in a defined time period and represents

consecutive data from a contemporary and relevant study cohort in a real-world setting. As well, impact of untreated THV thrombosis on clinical outcomes and structural valve degeneration is not answered by our data. This study is confined to the first 12 months after THV and therefore does not provide data on long-term impact or the occurrence of late THV thrombosis. Concerning warfarin-treated patients, the International Normalized Ratio (INR) levels from discharge to routine follow-up visit 1 were not available. Finally, our findings may not be generalizable to other types of THVs.

Conclusion

The incidence of THV thrombosis in this large study was 7%. Larger THV size may predispose to THV thrombosis, whereas treatment with warfarin appears to have a protective effect. Although often subclinical, THV thrombosis may have important clinical implications. Future studies are warranted to assess whether tailored post-TAVR antithrombotic therapy can reduce the incidence of THV thrombosis.

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Figure Legends

Central Illustration. Transcatheter heart valve thrombosis was detected by MDCT in 28 (7%) of 405 patients. In this study cohort, larger THV size and no post-TAVR warfarin treatment was found to be associated with increased risk of THV thrombosis. Warfarin effectively reverted THV thrombosis and normalized THV function.

LVEF: left ventricular ejection fraction, MDCT: multidetector computed tomography, TAVR: transcatheter aortic valve replacement, THV: transcatheter heart valve

Figure 1. Flow-chart of study population. Flow-chart depicting the inclusion and follow-up of patients in the study cohort.

Figure 2. Case of incidental THV thrombosis. A and B) At one-month routine post-TAVR follow-up, MDCT demonstrated hypo-attenuated leaflet thickening on two leaflets consistent with THV thrombosis. There were no signs of THV obstruction on TTE (mean gradient 9 mmHg, EOA_{THV} 1.6 cm^2). C and D) Full thrombus resolution after 3 months of warfarin and aspirin treatment. EOA: effective orifice area, MDCT: multidetector computed tomography, THV: transcatheter heart valve, TTE: transthoracic echocardiography

Figure 3. Case of obstructive THV thrombosis. A and B) At one-month routine post-TAVR follow-up, this patient presented with heart failure symptoms. MDCT demonstrated hypo-attenuated leaflet thickening involving tow leaflets. THV obstruction (mean gradient 23 mmHg, EOA_{THV} 1.0 cm^2) was detected by TTE. C and D) After 3 months of warfarin and aspirin therapy there was full thrombus resolution at MDCT and THV obstruction had resolved (mean gradient 9mmHg, EOA_{THV} 1.8cm^2).

EOA: effective orifice area, MDCT: multidetector computed tomography, THV: transcatheter heart valve, TTE: transthoracic echocardiography.

Table 1. The risk of THV thrombosis in relation to pre-TAVR baseline clinical characteristics

		Risk of THV thrombosis	RR (95%CI)	p value
Clinical characteristics				
Age	<80y	6.4% (8/125)	1.12 (0.51-2.46)	0.79
	≥80y	7.1% (20/280)		
Gender	Female	4.6% (10/216)	2.06 (0.98-4.35)	0.05
	Male	9.5% (18/189)		
BMI	<20kg/m^2	12.2% (5/41)	Reference	
	20-30kg/m^2	6.7% (18/269)	0.55 (0.22-1.40)	0.21
	>30kg/m^2	5.3% (5/95)	0.43 (0.13-1.41)	0.16
Diabetes	No	7.3% (23/313)	0.74 (0.23-1.89)	0.52
	Yes	5.4% (5/92)		
COPD	No	7.4% (21/285)	0.80 (0.36-1.81)	0.58
	Yes	5.8% (7/120)		
Atrial fibrillation	No	10.1% (22/217)	0.31 (0.13-0.76)	0.006
	Yes	3.2% (6/188)		
Peripheral	No	7.7% (26/337)	0.38 (0.10-1.57)	0.16

vascular disease	Yes	2.9% (2/68)		
Previous cerebrovascular disease	No	6.1% (19/313)	1.61 (0.75-3.44)	0.22
	Yes	9.8% (9/92)		
Previous myocardial infarction	No	6.6% (20/305)	1.22 (0.55-2.68)	0.62
	Yes	8.0% (8/100)		
Previous open heart surgery	No	7.2% (22/304)	0.82 (0.34-1.97)	0.65
	Yes	5.9% (6/101)		
Permanent pacemaker	No	6.6% (23/351)	1.41 (0.56-3.56)	0.47
	Yes	9.3% (5/54)		
eGFR	>30 ml/min	6.0% (22/365)	2.49 (1.07-5.77)	0.03
	≤30 ml/min	15.0% (6/40)		
STS PROM	<3	11.3% (6/53)	Reference	
	3-8	6.0% (17/281)	0.53 (0.22-1.29)	0.16
	>8	7.0% (5/71)	0.62 (0.20-1.93)	0.41

BMI: body mass index, COPD: chronic obstructive pulmonary disease, eGFR: estimated glomerular filtration rate, STS PROM: Society of Thoracic Surgeons predicted risk of mortality

Table 2. Risk of THV thrombosis in relation to procedural and pre-discharge echocardiographic characteristics

		Risk of THV thrombosis	RR (95%CI)	p value
Procedural characteristics				
Access route	Femoral	8.5% (21/246)	0.54 (0.24-1.25)	0.14
	Apical	4.6% (7/151)		
	Aortic	0% (0/8)	-	-
THV model	Edwards Sapien XT	8.1% (14/173)	0.74 (0.37-1.52)	0.42
	Edwards Sapien 3	6.0% (14/232)		
THV size	23 mm	2.3% (2/88)	Reference	
	26 mm	6.1% (12/198)	2.67 (0.61-11.66)	0.17
	29 mm	11.8% (14/119)	5.17 (1.20-22.19)	0.011
THV oversizing*	≤17%	9.0% (18/201)	0.55 (0.26-1.16)	0.11
	>17%	4.9% (10/204)		
Post-dilatation	No	6.4% (24/375)	2.08 (0.77-5.61)	0.15
	Yes	13.3% (4/30)		
THV underexpansion†	No	6.9% (27/392)	1.12 (0.16-7.60)	0.91
	Yes	7.7% (1/13)		
Noncircular	No	6.9% (28/403)	-	-

THV†	Yes	0% (0/2)		
Echocardiography				
LVEF	>35%	6.3% (23/365)	1.98 (0.80-4.93)	0.14
	≤35%	12.5% (5/40)		
Mean trans-THV gradient*	≤8 mmHg	7.1% (15/210)	0.93 (0.46-1.91)	0.85
	>8 mmHg	6.7% (13/195)		
EOA_{THV}*	≤1.5 cm^2	7.0% (17/244)	0.98 (0.47-2.04)	0.96
	>1.5 cm^2	6.8% (11/161)		
MR	<Moderate	6.7% (26/388)	1.76 (0.45-6.80)	0.42
	≥Moderate	11.8% (2/17)		
PAR	None	4.5% (9/199)	Reference	
	Mild	9.6% (17/178)	2.11 (0.97-4.62)	0.06
	Moderate	8.3% (2/24)	1.84 (0.42-8.03)	0.42
	Severe	0% (0/4)	-	-

EOA: effective orifice area, LVEF: left ventricular ejection fraction, MR: mitral regurgitation, PAR: paravalvular regurgitation, THV: transcatheter heart valve

* For continuous variables, the presented thresholds were based on medians or means as appropriate

† As evaluated by post-TAVR CT at routine follow-up visit 1

Table 3. Risk of THV thrombosis in relation to post-TAVR antithrombotic therapy until 1- to 3-month post-TAVR follow-up (routine follow-up visit 1).

		Risk of THV thrombosis [95%CI]
None		0% (0/1) [0.0-97.5%]
Aspirin only		25.0% (4/16) [7.2-52.3%]
Clopidogrel only		12.5% (2/16) [1.5-38.3%]
Aspirin+clopidogrel		9.7% (19/195) [6.0-14.8%]
Warfarin only		7.1% (2/28) [0.9-23.5%]
Warfarin+aspirin		1.0% (1/96) [0.0-5.7%]
Warfarin+clopidogrel		0% (0/41) [0.0-8.6%]
Warfarin+aspirin+clopidogrel		0% (0/6) [0.0-45.9%]
NOAC only		0% (0/5) [0.0-52.2%]
Warfarin part of post-TAVR antithrombotic therapy*	Yes	1.8% (3/171) [0.4-5.0%]
	No	10.7% (25/234) [7.0-15.4%]

NOAC: non-vitamin K antagonist oral anticoagulants, TAVR: transcatheter aortic valve replacement

* The risk of THV thrombosis in patients not receiving warfarin vs. patients receiving warfarin: 10.7% vs. 1.8% (p=0.0005); RR, 95%CI: 6.09, 1.86-19.84

Table 4. Echocardiographic at 1- to 3-month post-TAVR follow-up (routine follow-up visit 1) and 30-day complication rate

	Total (n=405)	THV thrombosis		p value
		- (n=377)	+ (n=28)	
Echocardiography				
LVEF ≤35%	35 (9)	30 (8)	5 (18)	0.08
Mean trans-THV gradient (mmHg)	8±3	8±3	10±7	0.003
EOA_{THV} (cm^2)	1.6±0.4	1.6±0.4	1.5±0.5	0.21
Moderate/Severe MR	32 (8)	29 (8)	3 (11)	0.48
PAR				
none	181 (45)	174 (46)	7 (25)	
mild	196 (48)	177 (47)	19 (68)	0.16
moderate	26 (6)	24 (6)	2 (7)	
severe	2 (0.5)	2 (0.5)	0	
30-day complications				
Stroke	5 (1)	4 (1)	1 (4)	0.30
Major vascular complications	19 (5)	18 (5)	1 (4)	1.00
Major bleeding	16 (4)	14 (4)	2 (7)	0.31
Pacemaker	21 (5)	19 (5)	2 (7)	0.65

Values are n(%) or mean ±SD.

EOA: effective orifice area, LVEF: left ventricular ejection fraction, MR: mitral regurgitation, PAR: paravalvular regurgitation, THV: transcatheter heart valve

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Table 5. Twelve-month post-TAVR follow-up 2 (routine follow-up visit 2)

	Total (n=246)	THV thrombosis - (n=229)	THV thrombosis + (n=17)	p value
Stroke	10 (4)	8 (3)	2 (12)	0.15
Echocardiography				
LVEF ≤35%	30 (12)	27 (12)	3 (18)	0.44
Mean trans-THV gradient (mmHg)	8±4	8±4	9±4	0.32
EOA_{THV} (cm^2)	1.7±0.5	1.6±0.5	1.6±0.6	0.43
Moderate/Severe MR	17 (7)	15 (7)	2 (12)	0.33
PAR				
none	162 (66)	154 (67)	8 (47)	0.29
mild	71 (29)	64 (28)	7 (41)	
moderate	12 (5)	10 (4)	2 (12)	
Severe	1 (0.4)	1 (0.4)	0	

Values are n(%) or mean ±SD if not stated otherwise.

EOA: effective orifice area, LVEF: LVEF: left ventricular ejection fraction, MR: mitral regurgitation, PAR: paravalvular regurgitation, THV: transcatheter heart valve

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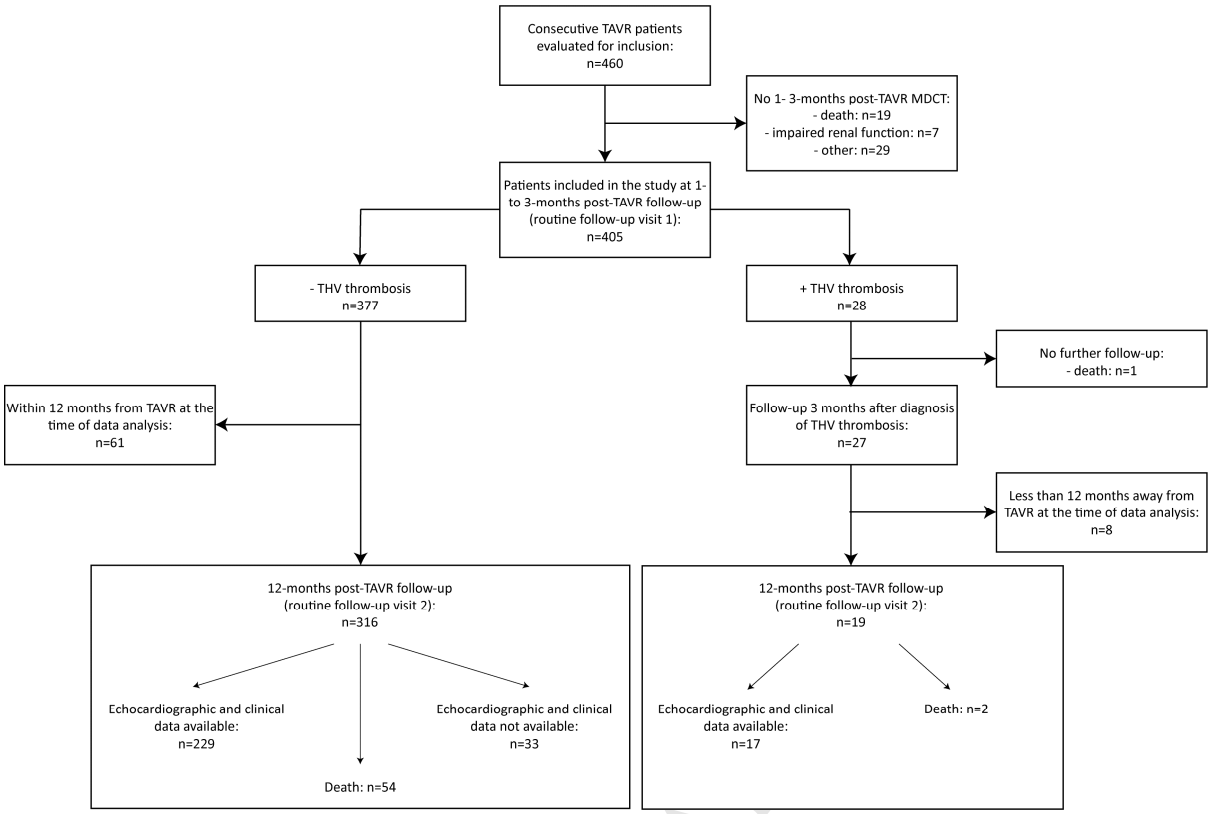

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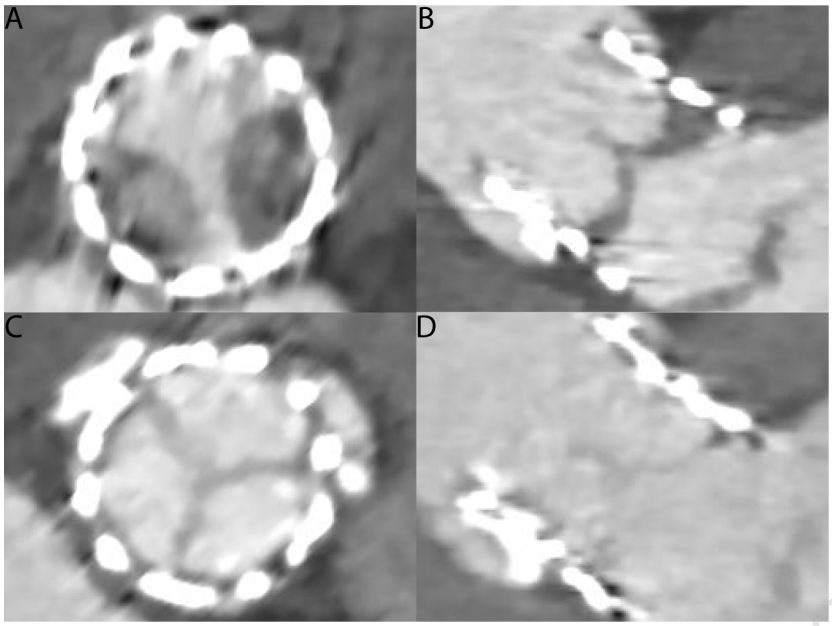

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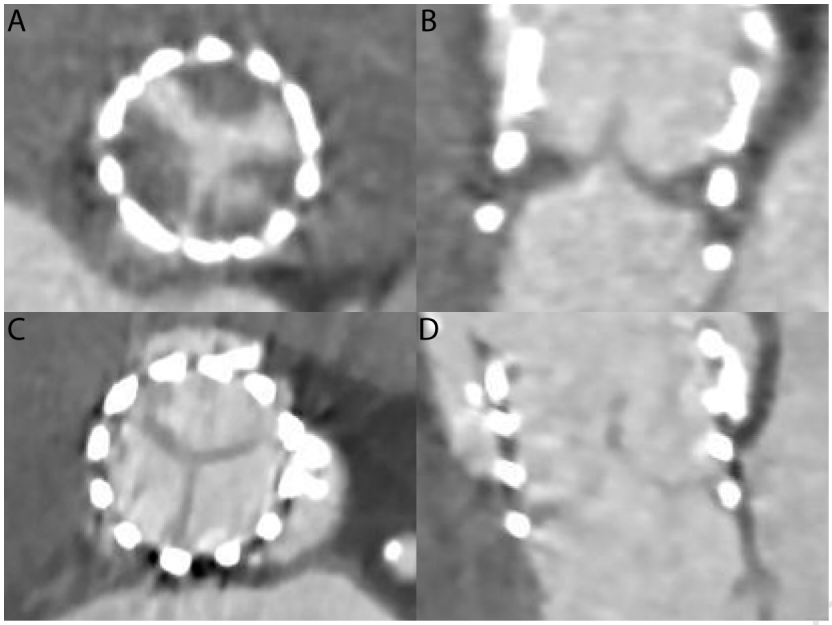

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Online Table 1. Risk of TVH thrombosis in relation to baseline echocardiographic and MDCT characteristics.

		Risk of THV thrombosis	RR (95%CI)	p value
Echocardiography				
LVEF	>35%	6.2% (21/341)	1.78 (0.79-4.00)	0.17
	≤35%	10.9% (7/64)		
Mean transaortic gradient*	≤40 mmHg	6.5% (16/246)	1.16 (0.56-2.39)	0.69
	>40 mmHg	7.5% (12/159)		
EOA*	≤0.7 cm^2	7.8% (20/258)	0.53 (0.22-1.28)	0.15
	>0.7 cm^2	4.1% (6/147)		
MR	<Moderate	6.6% (22/332)	1.24 (0.52-2.95)	0.63
	≥Moderate	8.2% (6/73)		
MDCT assessment				
Mean diameter*	≤25 mm	6.3% (14/222)	1.21 (0.59-2.48)	0.60
	>25 mm	7.7% (14/183)		
Area*	≤5.0 cm^2	6.2% (16/257)	1.30 (0.63-2.68)	0.47
	>5.0 cm^2	8.1% (12/148)		
Eccentricity*	≤20%	8.3% (17/204)	0.66 (0.32-1.37)	0.26
	>20%	5.5% (11/201)		

Aortic root calcium volume*	≤0.60 cm^3	5.5% (11/201)	1.52 (0.73-3.17)	0.26
	>0.60 cm^3	8.3% (17/204)		

EOA: effective orifice area, LVEF: left ventricular ejection fraction, MDCT: multidetector computed tomography, MR: mitral regurgitation

* For continuous variables, the presented thresholds were based on medians or means as appropriate

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Online Table 2. Patients with obstructive THV thrombosis

Case	1- to 3-month follow-up				Antithrombotic regimen until diagnosis of THV obstruction	Time of diagnosis of THV obstruction				
	NYHA	MDCT	TEE	TTE		Timing	NYHA	MDCT	TEE	TTE
1	n/a	n/a	n/a	n/a	Aspirin	before 1- to 3-mo. FU	4	RC_{THV} and LC_{THV} thickened	Thickening and restrictive movement of RC_{THV}	Mean gradient 10 mmHg EOA_{THV} 0.6 cm^2 LVEF 30%
2	1	NC_{THV} and LC_{THV} thickened	Restrictive movement of NC_{THV} AND LC_{THV}		Aspirin (THV thrombosis at 1- to 3-mo. FU treated with warfarin+aspirin, 2 months later complete thrombosis resolution and warfarin discontinued)	5 months after 1- to 3-mo. FU	3	NC_{THV} and LC_{THV} thickened	Restrictive movement of LC_{THV}	Mean gradient 21 mmHg, EOA_{THV} 0.9 cm^2 LVEF 60%
3	2	LC_{THV} mildly thickened, THV thrombosis deemed uncertain	Normal	Mean gradient 10 mmHg, EOA_{THV} n/a, LVEF 60%	Clopidogrel	8 months after 1- to 3-mo. FU	3	All leaflets thickened	n/a	Mean gradient 25 mmHg. EOA_{THV} 0.8 cm^2, LVEF 60%
4	2	NC_{THV} mildly thickened, THV thrombosis deemed uncertain	Normal	Mean gradient 18 mmHg, EOA_{THV} n/a, LVEF 60%	Aspirin (clopidogrel discontinued)	3 month after 1-3 mo. FU	3	All leaflets thickened	Restricted movement and thickening of LC_{THV}	Mean gradient 32 mmHg, EOA_{THV} 0.7, LVEF 60%
5	-	-	-	-	Clopidogrel+aspirin	at 1- to 3-mo. FU	3	NC_{THV} and RC_{THV} thickened	Restricted movement and thickening of NC_{THV} and RC_{THV}	Mean gradient 23 mmHg, EOA_{THV} 1.0, LVEF 20%

Online Table 2- continued. Patients with obstructive THV thrombosis

Case	Post-THV obstruction follow-up				
	Antithrombotic treatment	NYHA	MDCT	TEE	TTE
1	Warfarin+aspirin	n/a (deceased)	n/a	n/a	n/a
2	Warfarin+aspirin	1	THV thrombus regression	Normalized	Mean gradient 10 mmHg, EOA_{THV} 1.4 cm^2, EF 60%
3	Clopidogrel (patient at very high risk of bleeding)	n/a	n/a	n/a	n/a
4	Warfarin	1	THV thrombus regression	Normalized	Mean gradient 10 mmHg, EOA_{THV} 1.5 cm^2, EF 60%
5	Warfarin+aspirin	3	Complete THV thrombus resolution	Normalized	Mean gradient 9 mmHg, EOA_{THV} 1.8 cm^2, EF 20%

LVEF: left ventricular ejection fraction, EOA: effective orifice area, LC_{THV}: THV leaflet located in the native left coronary cusp position, MDCT: multidetector computed tomography, NC_{THV}: THV leaflet located in the native noncoronary cusp position, NYHA: New York Heart Association class, RC_{THV}: THV leaflet located in the native right coronary cusp position, TEE: transesophageal echocardiography, TTE: transthoracic echocardiography

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Online Table 3. Clinical and imaging characteristics, and clinical outcomes in patients with non-obstructive versus obstructive THV thrombosis

	Obstructive THV thrombosis		p value	OR (95%CI)
	+ (n=23)	- (n=5)		
Clinical characteristics				
Age (y), median (IQR)	83 (79-85)	83 (79-85)	0.75	1.02 (0.73-1.41)
STS PROM, median (IQR)	5.1 (2.9-6.4)	6.3 (3.2-10)	0.50	1.21 (0.77-1.89)
Post-TAVR antithrombotic regimen involving warfarin	3 (13)	0	1.00	-
Routine follow-up visit 1*				
LVEF ≤35%	3 (13)	2 (40)	0.21	4.44 (0.55-35.8)
Mean trans-THV gradient (mmHg)	8±4	21±6	>0.0001	1.40 (1.10-2.05)
EOA_{THV} (cm^2)	1.6±0.5	0.8±0.1	0.002	0.40 (0.15-0.80)
Number of involved leaflets	1.3±0.5	2.4±0.5	0.0001	-
Maximal leaflet thickness	4.2±1.8	7.5±1.3	0.0007	1.12 (1.02-1.25)
NYHA III or IV	3 (13)	4 (80)	0.008	26.6 (3.29-215.87)
Death before routine follow-up visit 2†	1 (6)	1 (33)	0.30	7.50 (0.42-135.30)
Routine follow-up visit 2††				
Mean trans-THV gradient (mmHg)	8±3	10±0	-	-

EOA_{THV} (cm^2)	1.6±0.4	1.5±0.1	-	-
NYHA III or IV	2 (13)	0	-	-
Stroke	1 (7)	1 (50)	-	-

Values are n(%) or mean ±SD if not stated otherwise.

* For patients with obstructive THV thrombosis, data acquired at the time of the diagnosis of THV obstruction is used (Table S2 in the Supplement).

† Number of patients within 12 months from TAVR at the time of data analysis: Non-obstructive THV thrombosis: n=16; obstructive THV thrombosis: n=3

†† Number of patients with 12-month follow-up: Non-obstructive THV thrombosis: n=15; obstructive THV thrombosis: n=2

EOA: effective orifice area, IQR: interquartile range, NYHA: New York Heart Association class, LVEF: LVEF: left ventricular ejection fraction, MDCT: multidetector computed tomography, MR: mitral regurgitation, STS PROM: Society of Thoracic Surgeons predicted risk of mortality, TAVR: transcatheter aortic valve replacement, THV: transcatheter heart valve

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Online Table 4. Antithrombotic therapy at 12-month post-TAVR follow-up (routine follow-up visit 2).

	Total (n=246)	**THV thrombosis** - (n=229)	+ (n=17)
None	0	0	0
Aspirin only	2 (0.9)	2 (0.9)	0
Clopidogrel only	2 (0.9)	2 (0.9)	0
Aspirin+clopidogrel	116 (51)	115 (50)	1 (6)
Warfarin only	28 (11)	25 (11)	3 (18)
Warfarin+aspirin	73 (30)	64 (28)	9(53)
Warfarin+clopidogrel	24 (10)	20 (9)	4 (24)
Warfarin+aspirin+clopidogrel	0	0	0
NOAC only	1 (0.4)	1 (0.4)	0

Values are n (%).

NOAC: non-vitamin K antagonist oral anticoagulants, TAVR: transcatheter aortic valve replacement

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