Treatment and Clinical Outcomes of Transcatheter Heart Valve Thrombosis

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Background—Valve thrombosis has yet to be fully evaluated after transcatheter aortic valve implantation. This study aimed to report the prevalence, timing, and treatment of transcatheter heart valve (THV) thrombosis.

Methods and Results—THV thrombosis was defined as follows (1) THV dysfunction secondary to thrombosis diagnosed based on response to anticoagulation therapy, imaging modality or histopathology findings, or (2) mobile mass detected on THV suspicious of thrombus, irrespective of dysfunction and in absence of infection. Between January 2008 and September 2013, 26 (0.61%) THV thromboses were reported out of 4266 patients undergoing transcatheter aortic valve implantation in 12 centers. Of the 26 cases detected, 20 were detected in the Edwards Sapien/Sapien XT cohort and 6 in the Medtronic CoreValve cohort. In patients diagnosed with THV thrombosis, the median time to THV thrombosis post–transcatheter aortic valve implantation was 181 days (interquartile range, 45–313). The most common clinical presentation was exertional dyspnea (n=17; 65%), whereas 8 (31%) patients had no worsening symptoms. Echocardiographic findings included a markedly elevated mean aortic valve pressure gradient (40.5±14.0 mm Hg), presence of thickened leaflets or thrombotic apposition of leaflets in 20 (77%) and a thrombotic mass on the leaflets in the remaining 6 (23%) patients. In 23 (88%) patients, anticoagulation resulted in a significant decrease of the aortic valve pressure gradient within 2 months.

Conclusions—THV thrombosis is a rare phenomenon that was detected within the first 2 years after transcatheter aortic valve implantation and usually presented with dyspnea and increased gradients. Anticoagulation seems to have been effective and should be considered even in patients without visible thrombus on echocardiography. **(*Circ Cardiovasc Interv*. 2015;8:e001779. DOI: 10.1161/CIRCINTERVENTIONS.114.001779.)**

Key Words: anticoagulants ■ aortic valve stenosis ■ bioprosthesis ■ echocardiography ■ thrombosis ■ transcatheter aortic valve replacement

Transcatheter aortic valve implantation (TAVI) has emerged as an alternative to surgical aortic valve replacement (AVR) in high operative risk or inoperable patients.[1,2] Given its minimally invasive nature and acceptable clinical outcomes, TAVI has recently become an established and popular treatment option for high-risk groups with severe aortic stenosis.[3–5] However, because of their rare occurrence, the incidence and characteristics of several causes of prosthetic valve dysfunction, such as valve thrombosis, pannus formation, calcification, endocarditis, etc, have yet to be reported in the literature. Of these, valve thrombosis is of particular interest as the optimal antithrombotic therapy after TAVI remains controversial. Even in the context of surgical

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WHAT IS KNOWN

- The reported incidence of valve thrombosis postsurgical bioprosthetic aortic valve replacement ranges from as low as 0.03% to 5.0%, but data on transcatheter heart valve (THV) thrombosis are limited.

WHAT THE STUDY ADDS

- THV thrombosis occurred in 0.61% of TAVI patients in a large multicentre registry, with the majority of patients presenting with worsening dyspnea and increased THV gradient.
- All THV thrombosis cases occurred within 2 years from transcatheter aortic valve implantation and were not associated with discontinuation of antiplatelet/antithrombotic therapy or with an underlying thrombogenic diathesis.
- Thrombosis should be suspected in cases of premature THV dysfunction, even if a thrombotic mass is not clearly detected.
- Anticoagulation resulted in restoration of normal THV function within 2 months of treatment, and should be considered the treatment of choice when THV thrombosis is suspected.

AVR using bioprosthetic valves, the optimal antithrombotic therapy remains an area of debate.[6,7] The reported incidences of valve thrombosis postsurgical AVR using bioprostheses ranges widely from as low as 0.03% to 5.0%.[8–12] Conversely, data on transcatheter heart valve (THV) thrombosis are scarce and restricted to several case reports and small case series.[13–15] A recent meta-analysis on clinical outcomes after TAVI using Valve Academic Research Consortium definitions reported a 1.2% pooled estimated incidence of THV thrombosis.[16,17] However, this figure was based on only 2 previous articles studying a small number of patients (0% in 305 patients and 2.7% in 130 patients).[18,19] Furthermore, to the best of our knowledge, there are no descriptive articles reporting not only the incidence but also details about THV thrombosis. The aim of this study was to evaluate the prevalence, timing, characteristics, and optimal treatment of THV thrombosis.

Methods

Of 4266 consecutive patients who underwent TAVI with Edwards Sapien/Sapien XT or Medronic CoreValve between January 2008 and September 2013 in 12 centers, 26 patients diagnosed with THV were retrospectively analyzed. A standardized case report form was used by all participating centers; data were collected by retrospective review of hospital records by the site investigators and after quality controls were sent to the coordinating center. These data were collected as part of a formal ongoing registry. Follow-up was performed by outpatient visits or phone calls. Each participating center obtained institutional review board or ethics committee approval according to local standards. Informed consent was obtained from each patient according to institutional standard practice. Antiplatelet and antithrombotic regimes after TAVI were dependent on each hospital's protocol.

Definitions

THV dysfunction was defined as (1) mean aortic valve pressure gradient (AVPG) ≥20 mm Hg or aortic valve area <1.2 cm^2 or peak velocity ≥3 m/s, or (2) moderate or more prosthetic valve regurgitation, which was not recorded post procedure. THV thrombosis was defined as follows: (1) THV dysfunction secondary to thrombosis diagnosed based on response to anticoagulation therapy, imaging modality (echo or computed tomography), or histopathology findings, or (2) mobile mass detected on THV suspicious of thrombus, irrespective of dysfunction, and in the absence of infection. Cases were excluded if other main potential causes for THV dysfunction were suspected (excluding possible THV thrombosis) based on imaging modality or histopathology findings: stent creep; pannus; calcification; support structure deformation, underexpansion or trauma; mal-sizing; endocarditis; native leaflet prolapse impeding prosthetic leaflet motion; malposition; acute mal-coaptation; leaflet wear, tear/perforation, prolapse, or retraction; suture breakage or disruption.[16] Cases with clinical signs (sepsis, fever, embolic, or immunologic phenomena), biochemistry (C-reactive protein, erythrocyte sedimentation rate, white blood cell count), or microbiology (blood cultures) consistent with underlying endocarditis were excluded.

Statistical Analysis

The values were presented as mean±SD or median (interquartile range) for normally and not normally distributed continuous variables, respectively, or as counts and percentages for categorical variables. Changes in AVPG (at the time of THV thrombosis and after anticoagulation) were calculated and analyzed using the paired Student *t* test. The proportion of patients with AVPG <20 mm Hg at the time of diagnosis of THV thrombosis and after anticoagulation were analyzed using McNemar test. Detailed follow-up was available only for patients who were diagnosed with THV thrombosis. All the analyses are retrospective and were performed using SPSS for Windows, version 19.0 (IBM SPSS Inc, Chicago, IL).

Results

Baseline clinical characteristics are shown in Table 1. As far as conditions potentially associated with thrombotic events are concerned, the incidence of previous stroke (19%), atrial fibrillation (19%), and history of cancer (12%) was not higher as compared with historical data.[20–22] Furthermore, mean left ventricular ejection fraction was 59.1±12.1% and only 2 patients (8%) had left ventricular ejection fraction <35%.

Procedural characteristics are shown in Table 2. Valve-in-valve (ie, TAVI in a degenerated aortic prosthesis) procedures were performed in 3 (12%) patients. According to operators' judgment, valve positioning was appropriate in 24 (92%) patients, whereas low implantation occurred in 2 (8%) patients. About echo findings, postprocedural mean AVPG <20 mm Hg was recorded in almost all cases (n=25; 96%), whereas only 1 patient had a slightly higher gradient (23 mm Hg).

Prevalence, Timing, Clinical Presentation, and Echo Findings of THV Thrombosis

Details of THV thrombosis are shown in Table 3. All the cases of THV thrombosis were detected within 2 years after TAVI (median time to THV thrombosis: 181 [interquartile range, 45–313] days; range, 3–735 days). As shown in Figure 1, only 1 patient had discontinued antiplatelet treatment at the time of diagnosis of THV thrombosis. No significant differences in antiplatelet/antithrombotic regimes were observed in patients with acute (within 1 month) and late (after 1 month) THV thrombosis (Table I in the Data Supplement). The majority of patients (n=17/26; 65%) presented with worsening dyspnea, whereas in 31% of the patients THV thrombosis was not associated with worsening symptoms and was detected on routine follow-up echocardiography. A

Table 1. Baseline Clinical Characteristics of Patients With Transcatheter Heart Valve Thrombosis

	n=26
Age, y	79.7±6.9
Sex, male	14 (53.8)
BMI, kg/m^2	27.1±4.4
Logistic EuroSCORE	17.8±14.4
STS PROM score	5.6±4.1
Diabetes mellitus	3 (11.5)
Hypertension	21 (80.8)
Dyslipidemia	15 (57.7)
Smoking history	2 (7.7)
Chronic renal failure (eGFR <60 mL/min per 1.73 m^2)	8 (30.8)
Chronic liver disease	1 (3.8)
Chronic obstructive pulmonary disease	9 (34.6)
Peripheral arterial disease	5 (19.2)
Coronary artery disease (detected at last angiography just before TAVI)	8 (30.8)
Previous MI	3 (11.5)
Previous PCI	3 (11.5)
Previous CABG	7 (26.9)
Previous valve surgery	3 (11.5)
Previous stroke	5 (19.2)
Previous pulmonary embolism	1 (3.8)
Porcelain aorta	1 (3.8)
Atrial fibrillation	5 (19.2)
History of cancer*	3 (11.5)
Echo findings before TAVI	
LVEF, %	59.1±12.1
LVEF <35%	2 (7.7)
Aortic valve area, mm^2	0.71±0.24
Mean aortic valve gradient, mm Hg	50.7±19.4
Maximal aortic valve gradient, mm Hg	83.6±29.3
More than moderate AR	4 (15.4)

Values are mean±SD or n (%). AR indicates aortic regurgitation; BMI, body mass index; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; EuroSCORE, European system for cardiac operative risk evaluation; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; STS PROM, society of thoracic surgeons predicted risk of mortality; and TAVI, trancatheter aortic valve implantation.

*Of all the 3 patients, cancers had been already cured at the time of TAVI.

Table 2. Procedural Characteristics

	n=26
Edwards Sapien or Sapien XT*	20 (76.9)
23 mm	6 (23.1)
26 mm	13 (50)
29 mm	1 (3.8)
Medtronic CoreValve	6 (23.1)
26 mm	2 (7.7)
29 mm	4 (15.4)
Valve-in-valve	3 (11.5)
Postdilatation	4 (15.4)
Appropriate valve positioning	24 (92.3)
Echo findings after TAVI	
Mean aortic valve gradient, mm Hg	11.3±4.5
Mean aortic valve gradient <20 mm Hg†	25 (96.2)
Maximal aortic valve gradient, mm Hg	22.7±8.6
Moderate AR	2 (7.7)
Severe AR	0 (0)

Values are mean±SD or n (%). AR indicates aortic regurgitation; and TAVI, transcatheter aortic valve implantation.

*Sapien in 3 cases; Sapien XT in 17 cases.

†Only 1 patient had 23 mm Hg of mean aortic valve gradient at post procedure.

transesophageal echo was performed in the majority of the cases (20/26), providing detailed anatomic and functional information. None of the patients had neurological events or other evidence of thromboembolic phenomena. Overall, mean AVPG was significantly increased (40.5±14.0 mm Hg) and was >20 mm Hg in 92% (n=24). Of the 2 patients without increased AVPG, 1 had severe AR (postprocedural AR: mild) with thickened leaflets detected on echo and the other had a mobile mass suggestive of thrombus, despite already being on warfarin with optimal international normalized ratio levels (2.0–3.0). The most common morphological presentation of thrombus on echocardiography was thickened leaflets or thrombotic apposition of leaflets (n=20; 77%), whereas only in a minority of cases a thrombotic mass was seen on the leaflets (n=6; 23%). THV thromboses characterized by thrombotic mass tended to occur earlier post-TAVI compared with thromboses because of thickened leaflets or thrombotic apposition (Table II in the Data Supplement). Neither echocardiography nor computed tomography showed geometric deformation or dislocation of the implanted THV or evidence of thrombus on the frame.

Treatment and Clinical Outcomes for THV Thrombosis

Of the 26 patients with THV thrombosis, 23 (88%) patients were treated with medical therapy, such as oral vitamin K antagonists with/without bridging heparin (unfractionated heparin or low-molecular–weight heparin; n=21); heparin without subsequent oral vitamin K antagonists because of high bleeding risk or patient refusal (n=2). Anticoagulation was effective and resulted in significant decrease of the AVPG (Figure 2) or disappearance of the thrombotic mass in all 23 patients (mean AVPG at the time of THV thrombosis, 41.9±12.3 and after anticoagulation, 16.9±6.4 mm Hg; patient number with AVPG <20 mm Hg: 1/23 and 17/23, at the time of THV thrombosis diagnosis and after anticoagulation, respectively; P<0.001). Two patients (8%) underwent percutaneous valve-in-valve, and 1 (4%) surgical AVR at the discretion of the operators or physicians.[23] In both these patients, a trial of anticoagulation was not attempted, as THV thrombosis was not initially suspected.

Examples are shown in Figures 3–5: (1) a case with serial echo findings showing acute resolution of thrombus within 4 days after initiation of anticoagulation therapy for a 29-mm Edwards Sapien XT thrombosis (Figure 3), (2) a case with serial computed tomographic findings of a 29-mm Medtronic CoreValve thrombosis suggesting a beneficial effect of anticoagulation in a case of persistent THV thrombosis that had been diagnosed 1 year before and had only partially responded to dual antiplatelet therapy (Figure 4), and (3) pictures of an explanted valve and its histopathology from a patient who

Table 3. Details of THV Thrombosis

	n=26
Median time to THV thrombosis, d	181 (IQR, 45–313; range, 3–735)
Incidence of THV thrombosis	26/4266 (0.61)
Edwards Sapien or Sapien XT	20/2813 (0.71)
Medtronic CoreValve	6/1453 (0.41)
Clinical presentation	
Dyspnea	17 (65.4)
No worsened symptoms	8 (30.8)
NSTEMI, acute heart failure	1 (3.8)
Echo findings at THV thrombosis	
LVEF, %	58.0±10.6
Mean aortic valve gradient, mm Hg	40.5±14.0
Mean aortic valve gradient <20 mm Hg*	2 (7.7)
Maximal aortic valve gradient, mm Hg	65.1±19.0
Worsened AR (to more than moderate) as compared with post procedure	2 (7.7)
Thrombus morphology	
Thickened leaflets or thrombotic apposition of leaflets	20 (76.9)
Thrombotic mass on leaflets	6 (23.1)

Values are mean±SD or n (%). AR indicates aortic regurgitation; IQR, interquartile range; LVEF, left ventricular ejection fraction; NSTEMI, non–ST-segment–elevation myocardial infarction; and THV, transcatheter heart valve.

*Of the 2 patients without increased aortic valve gradient, one had severe AR (postprocedural AR: mild) with thickened leaflets detected by echo, and the other one had a mobile thrombotic mass, despite already taking warfarin (prothrombin time–international normalized ratio, 2.0–3.0).

underwent surgical AVR for Medtronic CoreValve thrombosis (Figure 5).[23]

Three patients diagnosed with THV thrombosis died. Two patients died, despite being effectively treated with anticoagulation: 1 because of pneumonia and 1 because of acute heart failure (left ventricular ejection fraction: 30%). One patient died because of recurrent valve thrombosis at 3 months after percutaneous valve-in-valve implantation. In the remaining 23 patients, no embolic events originating from thrombi attached to THV leaflets were reported, after initiation of anticoagulation therapy, which was recommended indefinitely.

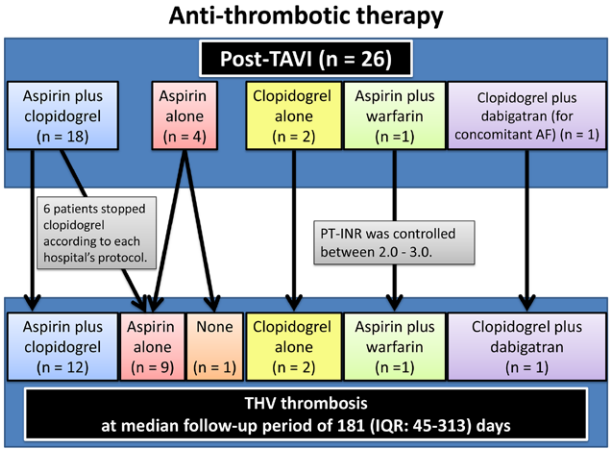

Figure 1. Details of antithrombotic therapy post procedure and at the time of diagnosis of transcatheter heart valve (THV) thrombosis. IQR indicates interquartile range; PT-INR, prothrombin time–international normalized ratio; and TAVI, transcatheter aortic valve implantation.

Discussion

The main findings from this are:

1. The prevalence of THV thrombosis was low (0.61%), however, this figure should be interpreted with caution as it probably underestimates the true prevalence.
2. All cases of THV thrombosis were detected within 2 years from TAVI and were not associated with discontinuation of antiplatelet/antithrombotic therapy, or a thrombogenic diathesis (as indicated by presence of previous stroke, atrial fibrillation, low left ventricular ejection fraction, and history of cancer).
3. Majority of patients presented with worsening dyspnea (65%) and increased THV gradient (92%).
4. Anticoagulation resulted in restoration of normal THV function within 2 months of treatment and should be considered the treatment of choice once THV thrombosis is suspected (thickened leaflets or apposition of leaflets) even without evidence of an obvious thrombotic mass on the valve leaflets.

Prevalence and Timing of THV Thrombosis

To the best of our knowledge, this is the first study reporting details about THV thrombosis. In our study, the prevalence of THV thrombosis was 0.61%. A previous meta-analysis showed a pooled estimated rate of THV thrombosis of 1.2%; however, this was based on only 2 small studies (0% of 305 patients and 2.7% of 130 patients).[6,18,19] In the context of surgical AVR, there is a wide range in the reported incidences of valve thrombosis from as low as 0.03% to 5.0%.[8–12] These reported incidences concur with the one from our study, despite the fact that TAVI patients have more comorbidities predisposing them to prothrombotic states. This suggests that the bioprosthetic material inserted in the aortic valve position rather than other predisposing factors, plays the major role in valve thrombosis. Furthermore, our data showed that all THV thrombosis cases occurred within 2 years after TAVI (the overwhelming majority of cases occurred within 1 year) suggesting that biological processes, such as fibrin deposits and platelet aggregation on foreign

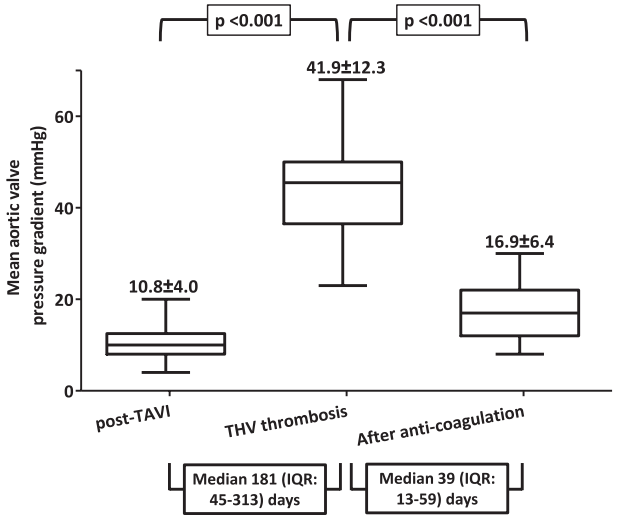

Figure 2. Significant decrease in mean aortic valve pressure gradient after treatment with anticoagulation. IQR indicates interquartile range; TAVI, transcatheter aortic valve implantation; and THV, transcatheter heart valve.

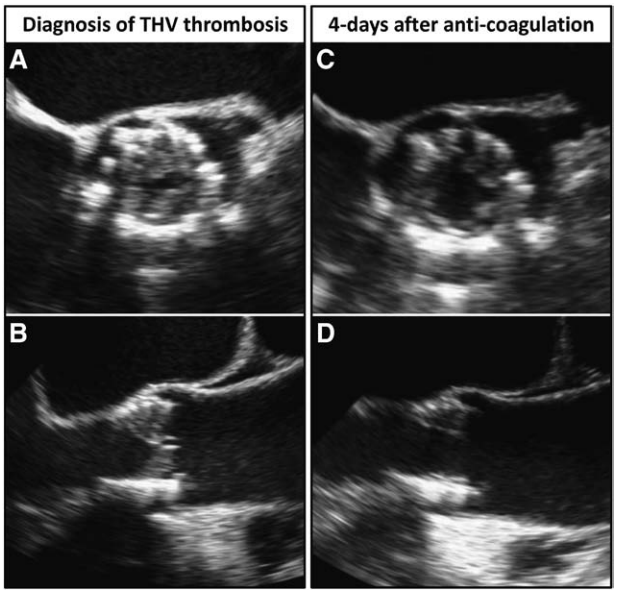

Figure 3. Serial transesophageal echo images showing acute resolution of thrombus 4 days after initiation of anticoagulation. At 8 months after implantation of a 29-mm Edwards Sapien XT, mean aortic valve pressure gradient (AVPG) increased as compared with the one recorded post procedure (from 10 to 47 mm Hg), despite ongoing dual antiplatelet therapy. **A** and **B**, Transesophageal echocardiography showing thickened leaflets suggesting mural thrombosis of all 3 leaflets without evident valve calcification and valve dislocation. **C** and **D**, Transesophageal echocardiography after 4 days of anticoagulation showing all the 3 leaflets thinner with significantly decreased mean AVPG (from 47 to 17 mm Hg). THV indicates transcatheter heart valve.

surfaces (endothelium devoid valve leaflets), occurring in the early period after TAVI, may predispose to valve thrombosis.

Clinical Presentation

Surprisingly, 31% of patients did not present with worsening symptoms at the time of diagnosis of THV thrombosis, highlighting the importance of follow-up echocardiography. This high rate of subclinical THV thrombosis could be explained by the fact that patients who have undergone TAVI have been preconditioned to the severe accompanying symptoms of severe aortic stenosis, hence slight changes in breathlessness may go unnoticed. It is therefore recommended, that regardless of symptomatic status, all patients with TAVI should undergo regular routine follow-up.

Potential Causes for THV Thrombosis

Our data suggest that THV thrombosis may occur without specific underlying circumstances. However, there are several predisposing factors, which should be discussed.

(1) Small valve size leading to patient–prosthesis mismatch is generally considered to be associated with unfavorable outcomes[24,25] and THV underexpansion is one of the possible triggers for THV thrombosis. However, the fact that 77% of THV thrombosis cases in this study occurred in patients who received THV >26 mm with acceptable postprocedural AVPG suggests that small size or underexpanded valves are unlikely to have contributed to THV thrombosis. (2) Even though no consensus exists on optimal antiplatelet/antithrombotic therapy after TAVI implantation, it is commonly accepted that premature cessation of antiplatelet/antithrombotic therapy may lead to thrombotic events. However, in our study, all but 1 patient were on some kind of antiplatelet or antithrombotic agent at the time of THV thrombosis diagnosis, suggesting that THV thrombosis can occur, despite patients' drug compliance. (3) Even though the study was not designed to compare THV thrombosis rates in patients with different types of THV, the fact that THV thrombosis prevalence was comparable between the 2 widely used THV: 0.71% with Sapien/Sapien XT; 0.41% with Medtronic CoreValve, may suggest that thrombosis can occur irrespective of implanted valve type with similar mechanisms of thrombosis (Table III in the Data Supplement). (4) Aggressive postdilation has also been considered one of the potential risks for valve leaflet damage with subsequent higher thrombosis risks. However, in our study, only 15% of THV thrombosis cases had undergone postdilatation after valve implantation. (5) Another possible cause of THV thrombosis is geometric deformation of the aortic valve stent, which may predispose to thrombus formation as a result of flow turbulence.[26] However, once again this was not evident in our study. (6) We cannot exclude the possibility of underlying inherited thrombophilias among THV thrombosis patients, such as antiphospholipid antibody

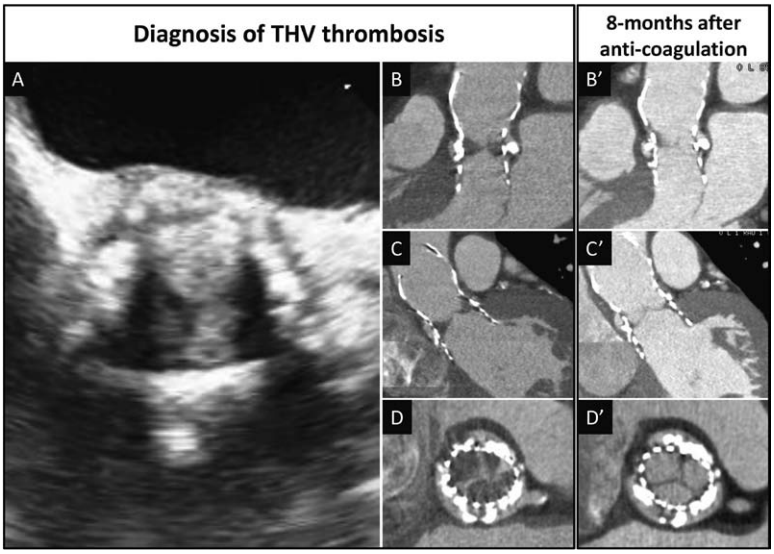

Figure 4. Serial computed tomographic (CT) images showing the effect of oral anticoagulation on chronic valve thrombosis. At 17 months after implantation of a 29-mm Medtronic CoreValve, mean aortic valve pressure gradient (AVPG) assessed by echo, increased as compared with that reported at 5 months (from 10 to 50 mm Hg), despite ongoing aspirin. This patient was treated with dual antiplatelet therapy (DAPT) until 32 months (mean AVPG was still 32 mm Hg), then switched to anticoagulation. **A**, Transesophageal echocardiography showing thrombotic mass on the aortic side of prothetic leaflets at 23 months after transcatheter aortic valve implantation (TAVI; at that time still on DAPT). **B**–**D**, CT showing suspected low-density thrombi on the aortic side of the aortic valve cusps, without evident valve calcification or valve dislocation at 23 months after TAVI (at the time still on DAPT). **B′**–**D′**, Follow-up CT images showing thrombi disappearance after 8 months of anticoagulation (from 32 to 40 months after TAVI) therapy, and associated significantly decreased mean AVPG (8 mm Hg) on echo.

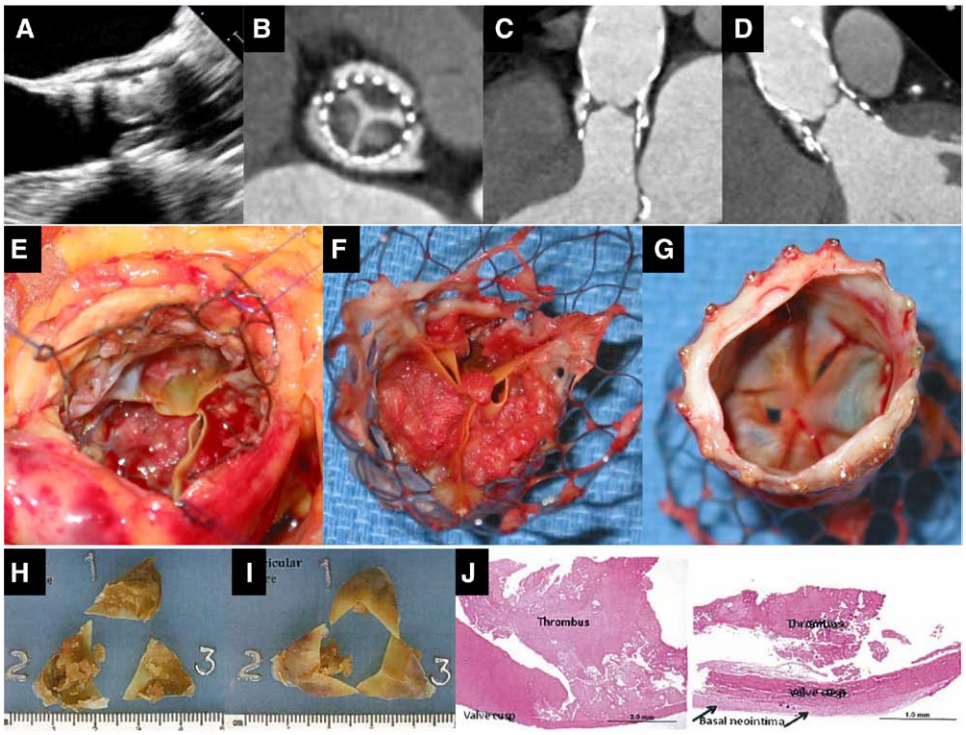

Figure 5. Images demonstrating valve thrombosis on cusps of aortic side. At 12 months after implantation of a 26-mm Medtronic CoreValve, mean aortic valve pressure gradient increased as compared with that observed immediately post procedure (from 8 to 41 mm Hg), in a patient on ongoing aspirin. **A**, Transesophageal echocardiography showing thickened leaflets with restricted motion (aortic valve area 0.69 cm2). **B**–**D**, Computed tomography showing hypo-dense thickened leaflets without change in prosthesis position or significant deformation of the stent by any calcification. **E**, The in situ visual inspection of the implant revealed a normal seating of the CoreValve with a translucent neointimal sheath covering the upper portion of the nitinol frame. The free edges of the valve leaflets were thin, and no calcifications were noted. The leaflets were almost immobile because of the presence of a brown-colored thrombotic host tissue covering exclusively the aortic side. **F** and **G**, Glistening white fibrous-like tissue covered the fabric skirt of the inflow portion of the device on outer and inner surfaces and formed a ridge of pannus extending into the inflow orifice and partially onto the ventricular surface of the valve cusps. **H**, aortic-side surfaces and **I**, ventricular-side surfaces. Specimens of each valve leaflet fixed with formalin. Fragments of friable pink-tan to brown-tan mural thrombus covered the aortic surfaces of the valve cusps. **J**, The valve leaflets showed intact pericardial collagen with few scattered chronic inflammatory cells. There was focal mild neointimal growth on the ventricular surfaces of leaflets and adherent bland fibrin and platelet thrombus on the aortic surfaces. There was no calcification on Vonkossa stain. **A**–**G** and **J**, were reproduced from Lancellotti et al[23] with permission of the publisher. Copyright ©2013, American Heart Association, Inc.

syndrome, antithrombin III, protein C, or S deficiency or Factor V Leiden, which were not investigated in this study. However, when taking into account the absence of previous thromboembolic events, an underlying thrombophilia is less likely to have been the contributing factor to THV thrombosis.

Optimal Treatment for Valve Thrombosis

The most commonly used treatment regimen for THV thrombosis was anticoagulation, which proved to be extremely efficacious. Anticoagulation was effective even for chronic and organized thrombi (Figure 4). This highlights the importance of anticoagulation as soon as valve thrombosis is suspected, not only in cases with visible thrombotic mass on valve leaflets but also in cases with THV dysfunction associated with thickened leaflets or apposition of leaflets with increased AVPG on echocardiography.

Current Guidelines on Antiplatelet/Antithrombotic Agents After TAVI

Although the bioprosthetic valves used in open heart surgery and TAVI are different and patients treated with TAVI are more fragile as compared with those who undergo surgical AVR, there are some inconclusive historical data on antiplatelet/antithrombotic agents after bioprosthetic surgical AVR. After TAVI, current guidelines from American Heart Association/American College of Cardiology/Society of Thoracic Surgeons recommend that (1) aspirin should be used indefinitely, (2) concomitant clopidogrel for 3 to 6 months, and (3) if vitamin K antagonists is indicated, no concomitant clopidogrel.[6] Furthermore, European Society of Cardiology guidelines recommend (1) aspirin or clopidogrel indefinitely, (2) combination of aspirin and clopidogrel early after TAVI, and (3) if vitamin K antagonists is indicated no antiplatelet therapy.[27,28] The main justification for use of antiplatelet and antithrombotic treatments post-TAVI is the prevention of ischemic events, mainly cerebrovascular ones. However, the low THV thrombosis incidence rates and the risks of anticoagulation-related bleeding[7] may not allow recommendation of routine use of anticoagulants after TAVI, not unless concomitant diseases, such as atrial fibrillation, mechanical mitral valve replacement, or previous thromboembolic events are present.

Limitations

First, the lack of data on the entire TAVI population followed in this registry did not allow us to estimate the cumulative risk of

THV thrombosis as a time-related outcome, or to evaluate risk factors for thrombosis. Given the retrospective nature of the study, attrition and selection bias are inherent limitations. In particular, deceased patients with sudden, unknown, or uncertain cause of death may have died secondary to undiagnosed THV thrombosis; hence our data may be underestimating the true prevalence. Furthermore, the discussion points about potential causes of THV thrombosis should only be viewed as speculative. Future large multicenter prospective studies are needed to confirm the prevalence reported in this current study and to identify potential predictors of THV thrombosis in the TAVI population. Another limitation of this study is the absence of data on inherited thrombophilias, even though the absence of previous thrombotic events among patients with THV thrombosis discourages, yet cannot exclude, a potential association with inherited thrombophilias. Moreover, platelet function tests were not undertaken in this study, therefore, it is not possible to assess whether patients with thrombosis were nonresponders to the antiplatelet regimes. A future, large, multicenter prospective randomized controlled study with stringent echocardiographic follow-up monitoring is required to clarify whether a specific antiplatelet regime post-TAVI would reduce the risk of THV thrombosis.

Conclusions

THV thrombosis is a rare phenomenon that was detected within the first 2 years after TAVI and usually presented with dyspnea and increased gradients. Anticoagulation seems to have been effective and should be considered even in patients without visible thrombus on echocardiography.

Disclosures

Dr Latib is a consultant for Medtronic, Valtech, and Direct Flow Medical. Dr Colombo is a minor shareholder in Direct Flow Medical. Dr Alfieri receives royalties from Edwards and is a consultant for Symetis. Dr Maisano is a consultant for Valtech, Edwards, Medtronic, and St Jude. Dr Baumgartner is consultant for Edwards Life Sciences. Dr Abdel-Wahab received an institutional research grant from Medtronic and speaker fees from Edwards Lifesciences and Boston Scientific. Dr Vahanian serves on a Medtronic Advisory Board. Dr Messika-Zeitoun is a consultant to Symetis, and Valtech. The other authors report no conflicts.

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SUPPLEMENTAL MATERIAL

Suppl. Table 1

	Acute thrombosis (within 1 month) (n=3)	Late thrombosis (after 1 month) (n=23)	P value
Edwards Sapien	3 (100)	17 (73.9)	0.313
Valve-in-valve	1 (33)	2 (8.7)	0.209
Anti-thrombotic therapy at the time of THV thrombosis			0.943
DAPT	2 (67)	10 (43.5)	
SAPT	1 (33)	10 (43.5)	
Aspirin plus warfarin	0	1 (4.3)	
Clopidogrel plus dabigatran	0	1 (4.3)	
None	0	1 (4.3)	
Symptomatic	2 (67)	16 (70.0)	0.919

DAPT = dual antiplatelet therapy, SAPT = single antiplatelet therapy, THV = transcatheter heart valve

Suppl. Table 2

	Thickened leaflets or thrombotic apposition of leaflets (n=20)	Thrombotic mass on leaflets (n=6)	P values
Time from TAVI (days)	248±200	115±105	0.132
Post-TAVI AVPG	11.6±4.9	10.3±3.5	0.575
Median AVPG at the time of THV thrombosis diagnosis	41.9±13.6	35.8±15.5	0.366

AVPG = aortic valve pressure gradient, TAVI = transcatheter aortic valve implantation, THV = transcatheter heart valve

Suppl. Table 3

	Edwards Sapien (n = 20)	Medtronic CoreValve (n = 6)	P value
Time to THV thrombosis, days	215 ± 194	226 ± 193	0.906
Clinical presentation			0.245
Dyspnea/NSTEMI, acute heart failure	15 (75.0)	3 (50.0)	
No worsened symptoms	5 (25.0)	3 (50.0)	
Echo findings at THV thrombosis			
LVEF, %	56.1 ± 10.6	64.0 ± 9.1	0.115
Mean aortic valve gradient, mm Hg	40.4 ± 15.7	40.7 ± 6.8	0.968

Maximal aortic valve gradient, mm Hg	64.5 ± 21.1	67.0 ± 11.8	0.786
Worsened AR (to more than moderate) as compared to post-procedure	1 (5.0)	1 (16.7)	0.347
Thrombus morphology			0.671
Thickened leaflets or thrombotic apposition of leaflets	15 (75.0)	5 (83.3)	
Thrombotic mass on leaflets	5 (25.0)	1 (16.7)	

AR = aortic regurgitation, LVEF = left ventricular ejection fraction, NSTEMI = non-ST-elevation myocardial infarction, THV = transcatheter heart valve.

Treatment and Clinical Outcomes of Transcatheter Heart Valve Thrombosis

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