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JACC REVIEW TOPIC OF THE WEEK

Treatment of Transcatheter Aortic Valve Thrombosis

JACC Review Topic of the Week

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ABSTRACT

Transcatheter aortic valve (TAV) thrombosis may manifest as subclinical leaflet thrombosis (SLT) and clinical valve thrombosis. SLT is relatively common (10%-20%) after transcatheter aortic valve replacement, but clinical implications are uncertain. Clinical valve thrombosis is rare (1.2%) and associated with bioprosthetic valve failure, neurologic or thromboembolic events, heart failure, and death. Treatment for TAV thrombosis has been understudied. In principle, anticoagulation may prevent TAV thrombosis. Non–vitamin K oral anticoagulants, as compared to antiplatelet therapy, are associated with reduced incidence of SLT, although at the cost of higher bleeding and all-cause mortality risk. We present an overview of existing literature for management of TAV thrombosis and propose a rational treatment algorithm. Vitamin K antagonists or non-vitamin K oral anticoagulants are the cornerstone of antithrombotic treatment. In therapy-resistant or clinically unstable patients, ultraslow, low-dose infusion of thrombolytics seems effective and safe and may be preferred over redo-transcatheter aortic valve replacement or explant surgery.
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Transcatheter aortic valve replacement (TAVR) is an established treatment for patients with symptomatic severe aortic valve stenosis.[1,2] One concern after TAVR is transcatheter aortic valve (TAV) dysfunction. A distinct entity of TAV dysfunction is TAV thrombosis.[3] TAV thrombosis covers a spectrum ranging from subclinical leaflet thrombosis (SLT) to overt clinical valve thrombosis (CVT).[4] SLT is relatively common and typically diagnosed by multislice computed tomography (MSCT). However, its clinical relevance remains unclear.[5,6] CVT is rare but associated with the cardinal symptoms of severe aortic stenosis or regurgitation (heart failure, angina, syncope) and thromboembolic or neurological events, and may be associated with increased transprosthetic gradients, valve

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HIGHLIGHTS

- Distinction should be made between subclinical leaflet thrombosis and overt clinical valve thrombosis.
- Treatment of transcatheter aortic valve thrombosis is understudied.
- Valid pharmacotherapy options include oral anticoagulant therapy and ultraslow low-dose intravenous thrombolysis.
- Further research should focus on elucidating the clinical significance of subclinical leaflet thrombosis and identifying the optimal antithrombotic strategy for patients with subclinical leaflet thrombosis and overt clinical valve thrombosis.

insufficiency, and bioprosthetic valve failure.[7] Management of TAV thrombosis remains understudied. Herein, we discuss the spectrum of TAV thrombosis with a focus on management strategies and outline a rational treatment algorithm for the different stages of TAV thrombosis using practical case vignettes and existing literature.

INCIDENCE

SLT is characterized by thickening of TAV leaflets (ie, hypoattenuated leaflet thickening [HALT]) and may be associated with reduced leaflet motion (RLM). Reported incidences vary between 12% and 38%.[5,8-12] The SAVORY (Subclinical Aortic Valve Bioprosthesis Thrombosis Assessed With 4D CT) and RESOLVE (Assessment of TRanscathetEr and Surgical Aortic BiOprosthetic Valve Thrombosis and Its TrEatment With Anticoagulation) registries, which include both transcatheter and surgical aortic valve replacements, identified HALT by MSCT in 106 of 890 (12%) patients at a median of 83 days (Q1-Q3: 33-281 days) after TAVR or 58 (Q1-Q3: 32-236 days) after surgical aortic valve replacement (SAVR).[12] MSCT substudies of randomized low-risk trials evaluated HALT and RLM after TAVR.[8,9] The PARTNER-3 (Placement of AoRTic TraNscathetER Valve Trial) MSCT substudy[8] described an incidence of 10% at 30 days and 24% at 1 year in patients with a balloon-expandable valve. All patients with HALT exhibited RLM. For patients with self-expanding valves, the Evolut Low Risk MSCT substudy[9] reported HALT in 31 of 179 (17.3%) patients at 30 days and in 47 of 152 (30.9%) patients at 1 year. HALT in individual patients fluctuated over time without antithrombotic therapy adjustments. RLM occurred in 23 of 157 (14.6%) patients at 30 days and in 45 of 145 (31.0%) patients at 1 year. These MSCT substudies included only patients on antiplatelet therapy with no formal indication for oral anticoagulation.

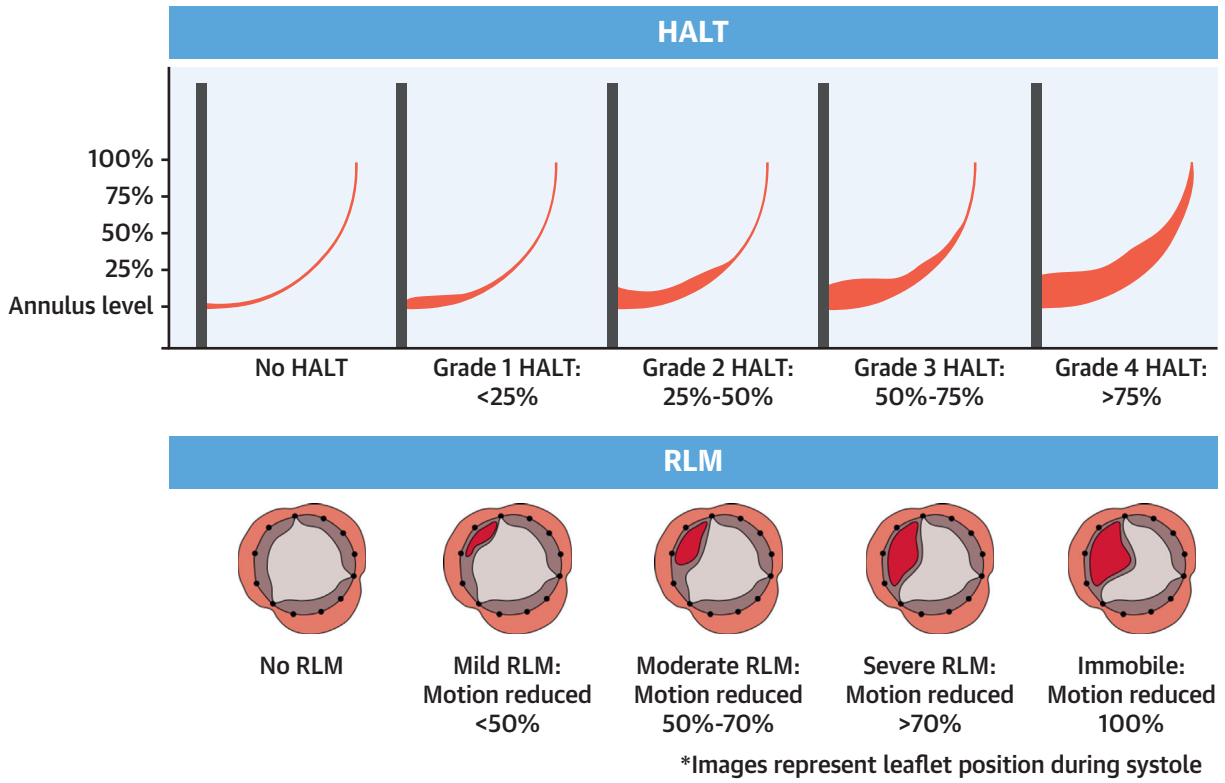
Retrospective studies suggested a lower SLT incidence in patients on oral anticoagulant drugs.[12-18] The prospective randomized GALILEO-4D (Global Study Comparing a rivAroxaban-based Antithrombotic Strategy to an antipLatelet-based Strategy After Transcatheter aortIc vaLve rEplacement to Optimize Clinical Outcomes) trial[19] reported a significantly lower HALT incidence with rivaroxaban 10 mg and 3 months with aspirin at 75 to 100 mg once daily vs dual antiplatelet drugs (aspirin 75-100 mg and clopidogrel 75 mg once daily) in patients without indication for oral anticoagulation (12.4% vs 32.4%, 95% CI of risk difference: -30.9 to -8.5 percentage points). In the ATLANTIS-4D-CT (Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis) substudy,[20] the overall incidence of any HALT was 45.9% in patients receiving apixaban (5 mg twice daily or 2.5 mg twice daily in combination with antiplatelet therapy) and 51% in patients receiving standard-of-care consisting of aspirin with or without clopidogrel. In patients without formal indication for oral anticoagulation, apixaban reduced the incidence of severe RLM from 8.5% to 1.1%.[20] In the ADAPT TAVR (Anticoagulant Versus Dual Antiplatelet Therapy for Preventing Leaflet Thrombosis and Cerebral Embolization After Transcatheter Aortic Valve Replacement) study, edoxaban monotherapy 60 mg once daily (or 30 mg once daily in the presence of creatinine clearance of 30-50 mL/min, low body weight <60 kg, or the use of certain P-glycoprotein inhibitors) was associated with a numerically lower incidence of SLT compared to dual antiplatelet therapy.[21]

The exact pathophysiologic mechanism of TAV thrombosis remains unclear, but one may speculate that a TAVR procedure fulfills all 3 components of Virchow's triad.[8,12,22-26] First, the degenerated native valve remains in situ for TAV anchoring and may act as a prothrombotic stimulus. Second, neo-sinus formation by the TAVR procedure may result in blood stasis which is associated with a hypercoagulable state. Third, it may induce focal vascular trauma which may enforce platelet aggregation.[26,27] Furthermore, TAV underexpansion and larger TAVs have also been correlated with more SLT.[10,14,27-29] Specifically for balloon-expandable valves, the degree of stent frame deformation may also predict SLT

ABBREVIATIONS AND ACRONYMS

CVT = clinical valve thrombosis
HALT = hypoattenuated leaflet thickening
MSCT = multislice computed tomography
NOAC = non-vitamin K oral anticoagulant
RLM = reduced leaflet motion
SAVR = surgical aortic valve replacement
SLT = subclinical leaflet thrombosis
TAV = transcatheter aortic valve
TAVR = transcatheter aortic valve replacement
VKA = vitamin K antagonist

FIGURE 1 Grading of HALT and RLM



(Upper panel) Hypoattenuated leaflet thickening (HALT) grading based on percentage of affected leaflet. (Lower panel) Stages of reduced leaflet motion (RLM). Severity of RLM is assessed by the amount of leaflet immobility which is best visualized during systole.

incidence.[30] It is unclear whether SLT is more frequent with TAVR than with SAVR, which precludes neo-sinus formation through excision of the degenerated calcific valve. Subanalyses of the 2 pivotal randomized low-risk trials found similar HALT frequencies with TAVR and with SAVR at 1 year.[8,9]

CVT is uncommon after TAVR with an overall incidence of 1.2%.[7] In the intermediate- and low-risk PARTNER-2 and PARTNER-3 trials using balloon-expandable valves, incidence was 0.2% and 2.5%, respectively.[31,32] Only 3 of 44 (6.8%) TAV failure cases in the PARTNER-2 trial were caused by CVT.[31] In the randomized intermediate-risk SURTAVI (Safety and Efficacy Study of the Medtronic CoreValve System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement) trial and the Evolut Low Risk trial, incidence of valve thrombosis was 0.5% at 5 years and 0.5% at 4 years, respectively.[33,34]

DIAGNOSIS

Most cases of SLT are incidental findings that are revealed by clinical surveillance or research MSCTs. The spatial resolution of transthoracic and transesophageal echocardiography is often inadequate to identify HALT (with or without RLM). The degree of HALT and RLM on MSCT may vary and is commonly graded in relation to the percentage of the affected leaflet(s) (Figure 1).

Timing in relation to the index procedure may help to differentiate CVT from structural valve deterioration without valve thrombosis. Most CVT cases have been reported within the first year and structural valve degeneration occurs predominantly more than 1 year after the index TAVR procedure. Contemporary European Society of Cardiology and American Heart Association/American College of Cardiology guidelines[1,2] recommend multimodality imaging that includes MSCT and (transesophageal) echocardiography for a comprehensive understanding of bioprosthetic valve leaflet morphology, mobility, function, and the presence of thrombus when CVT is suspected in the context of otherwise unexplained increase in transprosthetic gradient, heart failure, and/or neurologic symptoms. Systematic MSCT surveillance is not recommended in the absence of symptoms. It may be reasonable to initiate therapy for CVT to prevent further

complications in patients without increased bleeding risk before MSCT confirmation. In the presence of impaired kidney function, reduced contrast MSCTs using spectral image reconstruction techniques (eg, photon-counting MSCTs) may provide superior results while minimizing contrast loads.[35,36] Alternatively, cardiac magnetic resonance imaging may provide indirect measures of valve function such as insights into altered flow patterns or signs of valve regurgitation, although direct leaflet assessment is often hampered by metal stent artefacts.[36,37] Echocardiographic demonstration of normalizing transprosthetic gradients to the levels closely after the index TAVR procedure may suffice during the follow-up of CVT therapy.

CLINICAL SIGNIFICANCE

The clinical significance of SLT is unclear. By default, SLT causes no symptoms and has no meaningful impact on hemodynamic valve performance. However, SLT may be associated with marginal pressure gradient increase and has been linked to structural valve degeneration over time.[12,38] In addition, a meta-analysis has suggested a slightly increased incidence of neurological events including transient ischemic attacks.[5] Conflicting results exist regarding mortality, with SLT being linked to increased mortality in 1 study[39] but not in 2 others.[38,40] Moreover, RLM seems more impactful than HALT. An estimated 16% of patients may have a mean postprocedural aortic valve gradient >20 mm Hg and 15% may experience an increase of >10 mm Hg compared to measurements directly after TAVR.[12]

The PARTNER-3 CT substudy found a similar natural course for HALT and RLM, but one observational study has reported spontaneous resolution in 50% and 18% of HALT and RLM cases, respectively.[6,8]

TREATMENT OF SUBCLINICAL LEAFLET THROMBOSIS

The natural progression of SLT varies. HALT and RLM may resolve spontaneously, but oral anticoagulation expedites its resolution.[6,8,9] Studies have found that 35% to 54% of HALT cases at 30 days had resolved spontaneously at 1-year follow-up without change in the antithrombotic regimen.[8,9] Conversely, 15% of HALT progressed to RLM and 3% to 9% of HALT progressed to CVT with overt symptoms.[6-9] With this in mind, closer clinical and echocardiographic follow-up of patients with confirmed HALT is recommended. A follow-up MSCT scan to assess spontaneous HALT resolution is optional at 3 to 6 months (**Figure 2**).

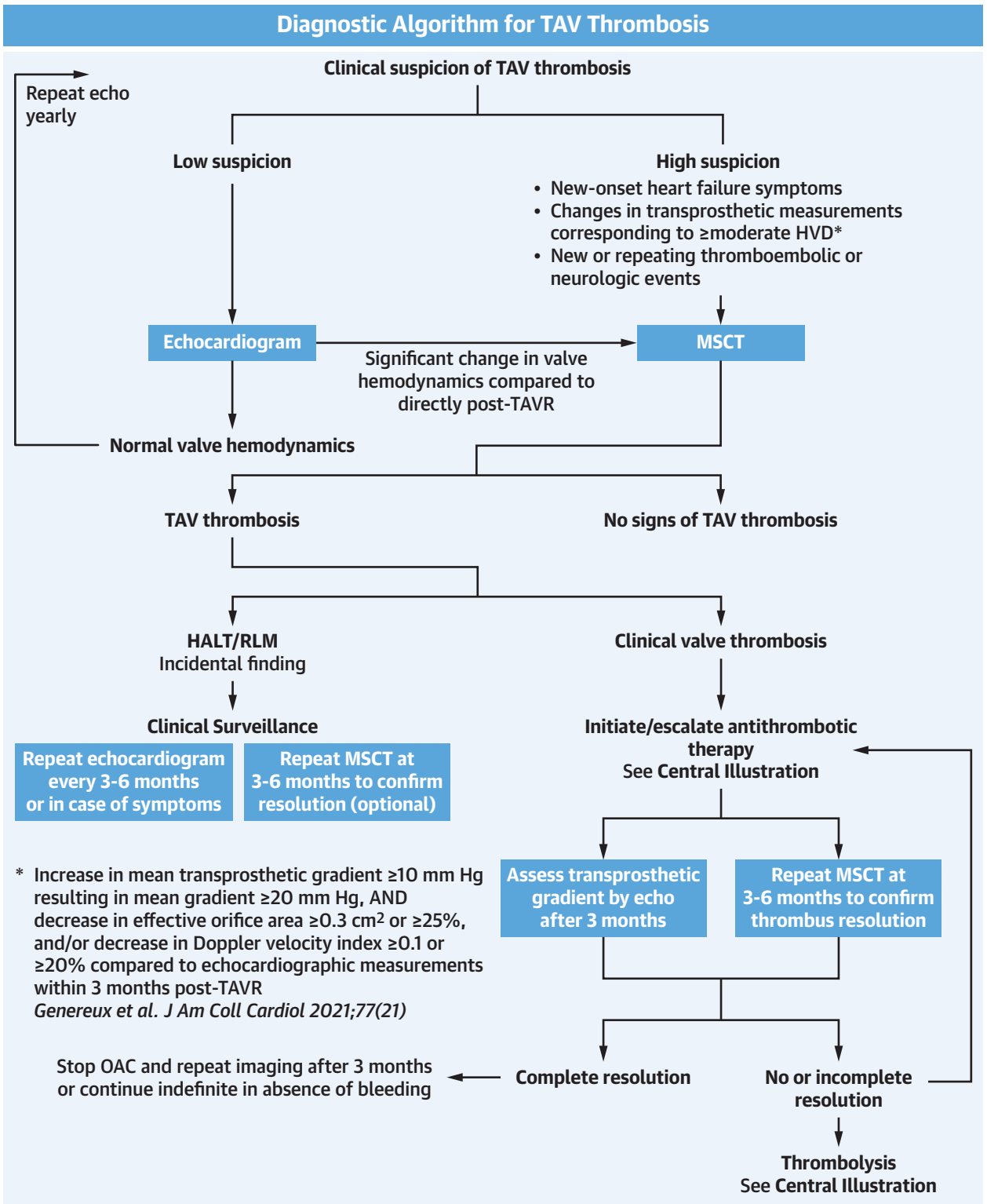
Observations that vitamin K antagonist (VKAs) and non–vitamin K oral anticoagulants (NOACs) were associated with a lower HALT/RLM incidence in substudies of randomized controlled trials and multiple MSCT registries lend credence to a switch from single or dual antiplatelets to a NOAC or VKA-based regimen to treat HALT and RLM.[12,14,17,19,20,41,42] VKA may be more potent than NOAC in this regard: in ATLANTIS stratum 1, patients on VKA had numerically lower incidence of grade 3 or 4 RLM or grade 3 or 4 HALT than patients on apixaban (5.55% vs. 9.5%; $P = 0.28$).[20]

Importantly, pre-emptive use of NOAC after TAVR in patients with no formal indication for (N)OAC is contraindicated since both the GALILEO and ATLANTIS trials found a signal of harm with NOAC combined with antiplatelet therapy instead of antiplatelet therapy alone, as shown by higher bleeding and all-cause death rates.[43,44] More research is required to distinguish the HALT and RLM phenotypes that are unlikely to resolve and may progress to CVT. The decision to modify the antithrombotic regimen in the context of SLT should be individualized and may be triggered by more pronounced RLM, incremental transprosthetic gradients, and equivocal clinical symptoms (eg, transient ischemic attack, atypical chest discomfort and fatigue).

TREATMENT OF CVT

CVT is a continuum from subtle clinical symptoms and mounting transprosthetic gradients to overt cardiogenic shock with severe aortic stenosis. Oral anticoagulation may be recommended in patients who developed CVT on antiplatelet therapy. In patients who developed CVT under NOAC, VKA may be recommended. There are no head-to-head comparisons of NOACs that may support a switch from NOAC to a different NOAC. Parenteral unfractionated or low-molecular-weight heparin is reasonable in CVT with more pronounced symptomatology until therapeutic international normalized ratio (INR) levels are reached. Current valvular guidelines do not elaborate on treatment strategies for bioprosthetic heart valve thrombosis but suggest valve-reintervention or thrombolysis in CVT with mechanical heart valves.[1,2] European Society of Cardiology guidelines recommend urgent or emergency valve replacement in critically ill patients with obstructive mechanical valve thrombosis without serious comorbidity, and thrombolysis when surgery is unavailable, when the patient is at very-high surgical risk, or when there is right-sided valve thrombosis. Surgery may be considered for large (>10 mm) nonobstructive thrombi complicated by embolism. The American Heart Association/

FIGURE 2 Algorithm for the Diagnosis and Follow-up of Suspected and Confirmed TAV Thrombosis



Diagnostic management based on clinical likelihood, echocardiographic measurements in relation to measurements directly post-TAVR, and observed treatment effect. HVD = hemodynamic valve deterioration; MSCT = multislice computed tomography; OAC = oral anticoagulation; TAV = transcatheter aortic valve; TAVR = transcatheter aortic valve replacement; other abbreviations as in Figure 1.

American College of Cardiology guidelines recommend slow-infusion, low-dose thrombolytics or emergency surgery for all patients with left-sided mechanical heart valve thrombosis and symptoms of valve obstruction. Empirical data underscore the rationale for slow-infusion, low-dose thrombolytics for TAV thrombosis.

Hereafter we present an overview of available literature (**Table 1**) and show common current dilemmas with 3 case vignettes (**Figure 3**).

VITAMIN K ANTAGONISTS. Ten heterogenic reports[12,14,17,41,42,45-49] described a total of 131 cases in which VKA was used to treat TAV thrombosis. In some series, SLT was identified by routine surveillance imaging that documented elevated transthoracic echo gradients, confirmed by evidence of HALT/RLM on MSCT or positive response to VKA or NOAC;[14,17,42,45-47] other series only included symptomatic patients and thus CVT.[41,48,49] Treatment strategies were: 1) VKA monotherapy (n = 68); 2) VKA therapy with concomitant antiplatelets (n = 38); or 3) initial therapy with heparin followed by VKA (n = 22). Target INR was 2.0 to 3.0. In patients who developed TAV thrombosis on VKA, target INR levels were increased to 2.5 to 3.5 without adding antiplatelet therapy (n = 3).[14]

TAV thrombosis resolved in 120 of 131 patients (91.6%) as was confirmed by repeat imaging and/or normalization of transvalvular gradients. In 1 patient, the transvalvular gradient improved but did not normalize. Three patients were lost to follow-up and 7 patients progressed to CVT with incremental heart failure symptoms. A decrease in transvalvular gradients was described as early as 14 days after initiation of anticoagulation,[17,41,49] and at 3 months, repeat MSCT confirmed thrombus resolution in >85% of cases.[12,14,45,47] None of the case series described serious bleeding events with VKA treatment for TAV thrombosis.

NOACs. Five reports with a total of only 16 patients described TAV thrombosis treatment with NOACs.[12,41,50,51] Rivaroxaban was used in 3 patients (in 2 patients with concomitant antiplatelet therapy), apixaban and aspirin in one. The type of NOAC was not specified in 12 patients. The definition of TAV thrombosis varied, but a common criterion was incremental mean transvalvular gradients.[41,50,51] NOAC use resulted in resolution of TAV thrombosis with normalization of transvalvular gradients in all patients within 3 to 4 months.

There was 1 major gastrointestinal bleeding event in a patient on rivaroxaban and clopidogrel that resolved by clopidogrel cessation.[51]

The largest report[12] on TAV thrombosis treatment with VKA or NOAC described 4 deaths and 4 strokes in 106 patients but did not elaborate on the antithrombotic regimen at the time of death or the time between diagnosis of TAV thrombosis and death.

VKA OR NOAC DURATION. After confirmation of resolution of TAV thrombosis by repeat MSCT and/or normalization of the mean transprosthetic gradient toward the gradient directly post-TAVR, interruption of the oral anticoagulation therapy may be considered. Two case series reported on the discontinuation of VKA or NOAC in 10 patients.[12,17] TAV thrombosis recurred in 6 of 10 patients who discontinued oral anticoagulation. Detailed information was known for 4 patients with a recurrence.[12] These patients discontinued oral anticoagulation after 3 months and confirmation of full restoration of leaflet motion per repeat MSCT. Median time to recurrence was 164 days.[12] Four patients switched from VKA to NOAC without TAV thrombosis recurrence during an average follow-up of 1.9 years.[17]

A larger study on anticoagulation for bioprosthetic valve thrombosis that included patients with surgical bioprosthetic valve thrombosis and TAV thrombosis reported a recurrence of valve thrombosis in 23% of patients after VKA or NOAC discontinuation with a median time to recurrence of 23 months (Q1-Q3: 11-39 months).[58] This high recurrence rate supports repeat MSCT at 6 months after interruption of anticoagulation and may justify indefinite therapy with VKA or NOAC after TAV thrombosis resolution in the absence of bleeding issues.

AORTIC VALVE REINTERVENTION. Reintervention was described in only 4 cases of TAV thrombosis.[49,55-57] TAVR explant surgery was performed in 3 patients and redo-TAVR in 1 patient. One patient developed pulmonary embolism and renal failure after explant surgery and the patient who underwent redo-TAVR died of noncardiac causes 16 days after the procedure.

Explant surgery in the context of TAV failure (which may include TAV thrombosis) is a high-risk procedure. The EXPLANT TAVR registry reported in-hospital life-threatening or major bleedings in 16% of patients. Mortality, stroke, and rehospitalization occurred at 30 days in 13.1%, 6%, and 14%, respectively.[59] The redo-TAVR registry suggested a lower 30-day complication rate for redo-TAVR for TAV failure (death: 2.9%, all-stroke: 1.4%, major bleeding: 11.3%).[60]

A nonrandomized comparison of both strategies confirmed the higher all-cause mortality with surgical TAVR explant than with redo-TAVR (at 30 days: 13.6% vs 3.4%, $P < 0.001$; and at 1 year: 32.4% vs 15.4%, $P = 0.001$). Stroke rates were similar between treatment strategies.[61]

TABLE 1 Overview of Case Series Reporting TAV Thrombosis

First Author, Year	Number of Patients Within Treatment Strategy	TAV Thrombosis Diagnosis Criteria	Treatment	Important Outcomes
Vitamin K antagonists				
Hansson et al,[14] 2016	26 of 28	MSCT evidence of thrombus.	Warfarin monotherapy (n = 6). Warfarin + antiplatelet therapy (n = 17). Increase of INR from 2.0-3.0 to 2.5-3.5 (n = 3).	Resolution of TAV thrombosis in 22 patients. Progression to obstructive thrombosis in 5 patients. Similar stroke rates at 12 months in TAV thrombosis patients as compared to patients without TAV thrombosis (12% vs 3%, $P = 0.15$), but low numbers.
Jose et al,[17] 2017	18 of 18	1) TAV dysfunction secondary to thrombosis diagnosed on response to anticoagulation therapy, echo or computed tomography, or histopathology findings; or 2) Evidence of mobile mass suspicious of thrombus in absence of infection.	Phenprocoumon monotherapy with target INR: 2.0-3.0 (n = 18).	Normalized echo transaortic mean gradient in 17 of 18 patients. Reduction but no normalization in 1 of 18 patients. Recurrence of thrombosis in 2 patients after temporary cessation of phenprocoumon. No recurrence in 4 patients switched to NOAC.
Franzone et al,[41] 2018	6 of 10	One of following: 1) mean transvalvular gradient ≥20 mm Hg at TTE, 2) increase of more than 50% of a transvalvular gradient, or 3) recent or new onset of symptoms or signs of heart failure and TEE or MSCT confirmation of thrombus.	Phenprocoumon monotherapy (target INR unknown) (n = 4) Phenprocoumon + aspirin (n = 2).	Resolution of symptoms occurred in a median of 4 weeks of starting treatment in all patients. Pressure gradients normalized in all patients receiving phenprocoumon. Up to 25 months, no patients experienced cerebrovascular events or thrombo-embolic complications, cardiac death or clinically significant bleeding.
Latib et al,[45] 2015	21 of 26	1) TAV dysfunction secondary to thrombosis diagnosed on response to anticoagulation therapy, echo or computed tomography, or histopathology findings; or 2) Evidence of mobile mass suspicious of thrombus in absence of infection.	Warfarin monotherapy, possibly preceded by bridging with unfractionated heparin or LMWH (n = 21).	Anticoagulation resulted in significant decrease of mean transvalvular gradient or disappearance of the thrombotic mass in all patients within a median of 2 months. 2 patients died despite effective treatment, one of which of cardiac cause (acute heart failure). No embolic events were reported.
Pache et al,[46] 2015	16 of 16	Presence of HALT on MSCT assessed by 2 radiologists.	Combination therapy of phenprocoumon with target INR of 2.5-3.5 and clopidogrel 75 mg/day.	Complete normalization of pressure gradients in all 13 patients with follow-up MSCT. One patient died of noncardiovascular cause at 8 months, 1 patient experienced exertional dyspnea symptoms (NYHA functional class II), all other patients were asymptomatic. No patients experienced stroke or bleeding complications.
Leetma et al,[47] 2015	4 of 5	MSCT evidence of thrombus, defined as low-attenuating mass attached to TAV cusps or diffuse thickening of ≥1 cusps.	Combination of warfarin and clopidogrel (n = 2). Combination of warfarin and aspirin (n = 1). Infusion of unfractionated heparin, followed by subcutaneous LMWH and combination of warfarin and heparin (n = 1).	Three of four patients were alive at 3 months with resolved thrombus and asymptomatic. The patient with initial unfractionated heparin infusion developed refractory heart failure and died at 93 days after thrombus diagnosis. No embolic events were recorded in all 5 patients.
Fan et al,[48] 2018	1	Progressive exertional dyspnea with imaging evidence of thrombus (echo, confirmed by MSCT).	Warfarin	Normalization of transvalvular gradient and resolution of symptoms.
De Marchena et al,[49] 2015	1	Elevated transvalvular gradients.	Warfarin	Resolution of elevated gradients occurred after initiation of warfarin therapy. Patient remained asymptomatic after TAVR, despite the elevated gradients.
Chakravarty et al,[12] 2017	24 of 36 patients with repeat MSCT scan (unknown number of TAVR/SAVR patients).	Reduced leaflet motion on MSCT.	Warfarin (n = 24)	Reduced leaflet motion resolved in all patients receiving warfarin for 3 months. Recurrence of RLM in 4 of 8 patients with discontinued OAC therapy (warfarin or NOAC)
Reardon et al,[42] 2019	14 of 16 patients (all LOTUS valves)	Elevated mean transvalvular gradient, MSCT confirmed in 12 of 16 cases.	Nonspecified OAC (n = 14)	Resolution of valve thrombosis in 12 patients, treatment effect in other 4 patients unknown. No death or strokes.

Continued on the next page

TABLE 1 Continued

First Author, Year	Number of Patients Within Treatment Strategy	TAV Thrombosis Diagnosis Criteria	Treatment	Important Outcomes
Direct oral anticoagulants				
Franzone et al,[41] 2018	2 of 10	1 or more of following: 1) mean transvalvular gradient ≥20 mm Hg at TTE; 2) increase of more than 50% of a transvalvular gradient; 3) recent or new onset of symptoms or signs of heart failure and TEE or MSCT confirmation of thrombus.	Combination of apixaban 5 mg bidaily and aspirin (n = 1). Combination of rivaroxaban 20 mg daily and aspirin (n = 1).	Resolution of symptoms occurred in a median of 4 weeks of starting treatment in all patients. Pressure gradients normalized in all patients receiving direct OACs. Up to 25 months, no patients experienced cerebrovascular events or thrombo-embolic complications, cardiac death or clinically significant bleeding.
Mathiassen et al,[50] 2017	1	Elevated mean transvalvular gradient and MSCT evidence of thrombosis.	Rivaroxaban 20 mg daily.	4 months of treatment reduced mean transvalvular gradient from 73 mm Hg to 10 mm Hg and resolved thrombus formation (MSCT). No bleeding complications occurred despite increased bleeding risk.
Liang et al,[51] 2021	1	Worsening heart failure symptoms, with elevated mean transvalvular gradients on echo and HALT and RLM on MSCT.	Combination of rivaroxaban and clopidogrel.	3 months of treatment reduced mean transvalvular gradient from 48 mm Hg to 17 mm Hg and caused relief of symptoms 5 months after initiation of OAC treatment, the patient experienced gastrointestinal bleeding requiring blood transfusion. After discontinuation of clopidogrel, patient persisted free of bleeding events.
Chakravarty et al,[12] 2017	12 of 36 patients with repeat MSCT scan (unknown number of TAVR/SAVR patients).	Reduced leaflet motion on MSCT.	Nonspecified direct OAC (n = 12).	RLM resolved in all patients receiving NOAC for 3 months. Recurrence of RLM in 4 of 8 patients with discontinued OAC therapy (warfarin or NOAC).

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TAV thrombosis represented 2.9% of patients with TAV failure. Safety and efficacy of redo-TAVR or TAVR explant for CVT therefore remain unsettled and further research is warranted.

THROMBOLYSIS. Thrombolytic agents convert plasminogen to plasmin that disintegrates fibrin to dissolve thrombus. Thrombolysis is recommended for patients with mechanical heart valve thrombosis who are unfit to undergo surgery or have right-sided thrombi. In the TROIA[52] (Comparison of Different Transesophageal Echocardiography Guided Thrombolytic Regimens for Prosthetic Valve Thrombosis) and the PROMETTEE[53] (Prosthetic Mechanical Valve Thrombosis and the Predictors of Outcome) trials, various thrombolytic strategies were evaluated. The ultraslow, low-dose infusion strategy with 25 mg alteplase over 25 hours had the highest success rates (90%) and was associated with few complications (1 death, 2 major ischemic events, and 2 major bleedings in 120 patients with mechanical heart valve thrombosis). In the nonrandomized multicenter HATTUSHA study,[62] a thrombolytic strategy was compared to repeat surgery in 158 patients with mechanical heart valve thrombosis. Thrombolysis was associated with lower mortality rates (2.4% vs 18.7%, respectively) and lower incidence of overall (12.0% vs 62.7%, respectively) and major complications (6.0% vs 41.3, respectively). However, treatment allocation was per physician's discretion and no formal statistical comparisons were performed.

Literature on thrombolysis for surgical bioprosthetic or TAV thrombosis is scarce and typically included older patients with higher bleeding risks. One report showed a favorable outcome in one patient with ultraslow, low-dose infusion strategy of 25 mg alteplase over 25 hours, which was repeated until resolution of the elevated transvalvular gradient.[54]

In **Figure 3**, we present 3 case vignettes of TAV thrombosis. One patient who developed TAV thrombosis under aspirin monotherapy was successfully treated with VKA. One patient developed TAV thrombosis while receiving rivaroxaban and was treated effectively by VKA. One patient who presented with acute heart failure and type 2 myocardial infarction under edoxaban was treated with repeated ultraslow, low-dose intravenous thrombolysis until symptom resolution and transprosthetic gradient normalization.

SUGGESTED TREATMENT ALGORITHM. A rational treatment algorithm for TAV thrombosis is shown in the **Central Illustration**. Prophylactic use of full-dose NOAC to prevent TAV thrombosis in patients after

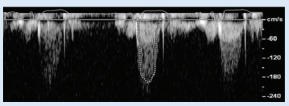
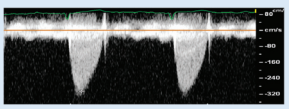
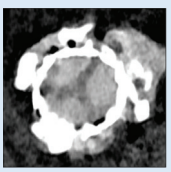
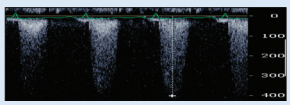
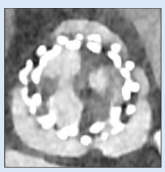
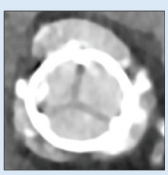
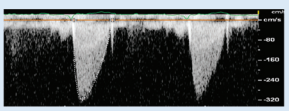
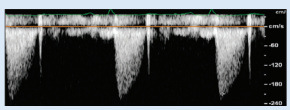
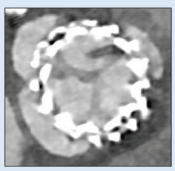
TABLE 1 Continued

First Author, Year	Number of Patients Within Treatment Strategy	TAV Thrombosis Diagnosis Criteria	Treatment	Important Outcomes
Thrombolysis				
TROIA trial from Özkan et al[52], 2013[a]	182 patients with 220 incidences of mechanical prosthetic valve thrombosis, between 1993 and 2009.	Confirmation of thrombus by TEE in patients with all following: 1) thromboembolism or persistently low INR for 3 months; and 2) prosthetic valve dysfunction or thrombus on transthoracic echocardiography.	1) 3-h infusion of 1.5 M units of streptokinase, repeat up to maximum dose 3 M units (n = 16; 1993-1997); 2) 24-h infusion of 1.5 M units of streptokinase, repeat up to maximum dose 3 M units (n = 41; 1997-2002); 3) 5-h infusion of 90 mg alteplase after 10 mg starting bolus, repeat up to maximum dose 200 mg (n = 10; 2001-2002); and 4) 6-h infusion of 50 mg alteplase, repeat up to maximum dose 150 mg (n = 27; 2002-2005) 5) 6-h infusion of 25 mg alteplase, repeat up to maximum dose 150 mg (n = 108; 2005-2009).	Treatment success (resolution of increased gradient, clinical improvement in symptoms and ≥75% reduction of thrombus size) was achieved in 68.8%, 85.4%, 75.0%, 81.5%, and 85.5% of episodes, respectively. Any complication of death, ischemic or hemorrhagic stroke, TIA, thromboembolism, or any bleed occurred in 41 episodes; was similar between groups 1 - 4, but significantly lower in group 5; mainly driven by absence of mortality in group 5.
The Ultra-slow PROMETTEE trial from Özkan et al,[53] 2015[a]	114 patients with 120 episodes of mechanical prosthetic valve thrombosis.	Confirmation of thrombus by TEE in patients with all following: 1) thromboembolism or persistently low INR for 3 months; and 2) prosthetic valve dysfunction or thrombus on transthoracic echocardiography.	Ultraslow infusion of 25 mg alteplase (n = 120).	Treatment success (resolution of increased gradient, clinical improvement in symptoms and ≥75% reduction of thrombus size) was achieved in 90% of episodes. 77.5% of patients required ≥2 rounds of alteplase infusion, median of 2 rounds and maximum of 8 rounds. Complications were death (n = 1), ischemic stroke (n = 1), peripheral embolism (n = 1), major bleeds (n = 2), and minor bleeds (n = 3).
Adrichem et al,[54] 2023	1	Heart failure symptoms, with elevated mean transvalvular gradients and MSCT evidence of HALT and RLM.	Four doses of ultraslow (25-h) infusion of 25 mg alteplase.	Reduction of mean transvalvular gradient and MSCT evidence of reduction in HALT and normalization of leaflet motion.
Aortic valve reintervention				
De Marchena et al,[49] 2015	1 of 4	Elevated mean transvalvular gradients, presumed to be because of pannus formation. At autopsy confirmed to be secondary to valve thrombosis.	Valve-in-valve TAVR.	Noncardiac death 16 days after redo-TAVR.
Trepels et al,[55] 2009	1	Exertional dyspnea and elevated mean transvalvular gradients, with evidence of thrombus at transesophageal echocardiography and aortic angiography.	TAVR explant and SAVR.	Successful reintervention. No clinical outcome data available.
Greason et al,[56] 2013	1	Exertional dyspnea with elevated mean transvalvular gradients and restricted motion of two of three valve cusps.	TAVR explant and SAVR.	Successful reintervention. In hospital pulmonary embolism, acute renal failure requiring temporary dialysis and atrial fibrillation. Upon discharge persistent low gradients up to 1+ month.
Lancellotti et al,[57] 2013	1	New-onset heart failure symptoms and elevated mean transvalvular gradients.	TAVR explant and SAVR.	Successful reintervention. Clinical recovery months after SAVR, good prosthesis function.

[a]These studies have included only patients with mechanical valve prostheses.

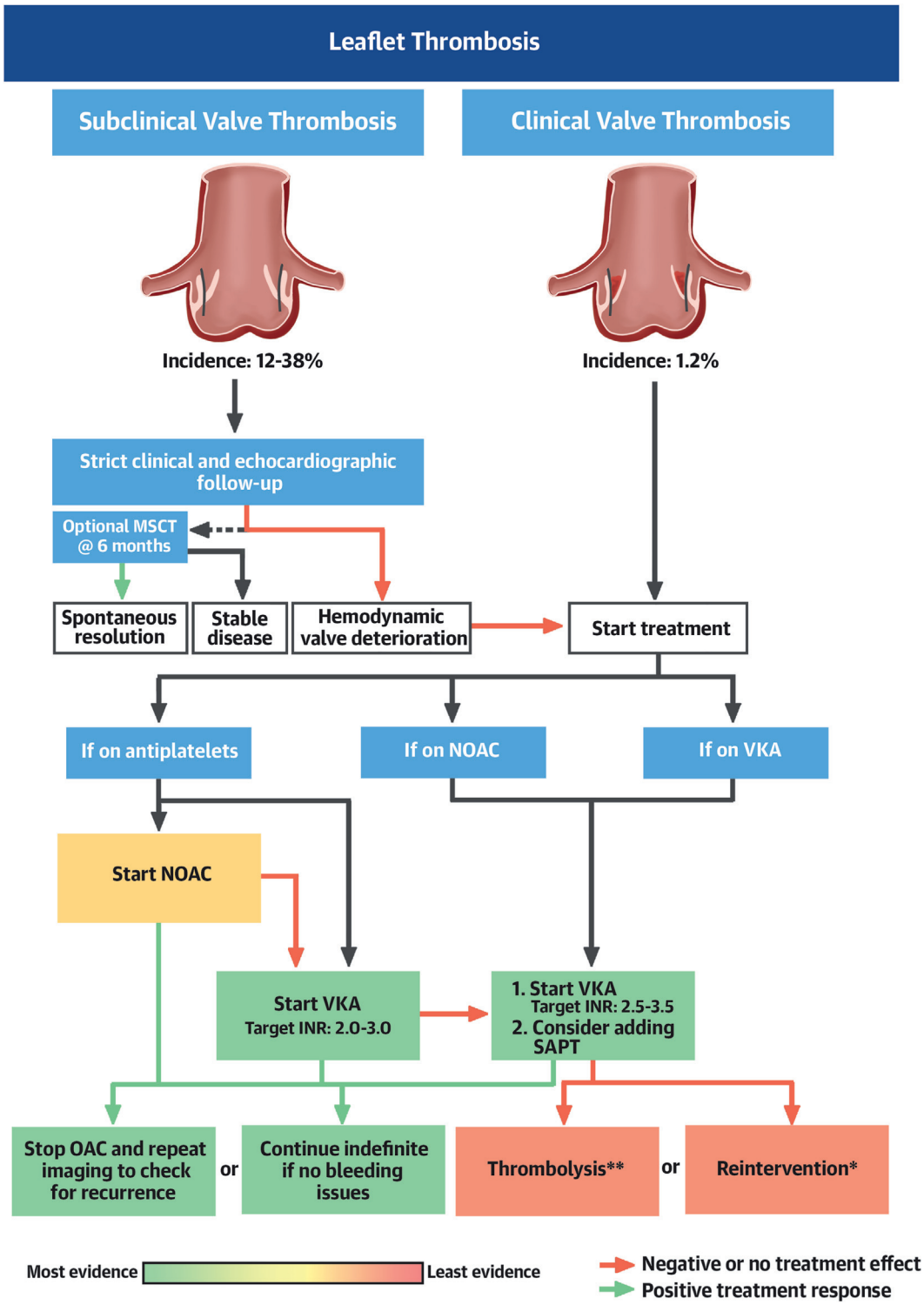
HALT = hypoattenuated leaflet thickening; INR = international normalized ratio; LMWH = low-molecular-weight heparin; MSCT = multislice computed tomography; NOAC = non-vitamin K oral anticoagulant; OAC = oral anticoagulant; PROMETTEE = Prosthetic Mechanical Valve Thrombosis and the Predictors of Outcome; RLM = reduced leaflet motion; SAVR = surgical aortic valve replacement; TAV = transcatheter aortic valve; TAVR = transcatheter aortic valve replacement; TEE = transesophageal echocardiogram; TROIA = Comparison of Different Transesophageal Echocardiography Guided Thrombolytic Regimens for Prosthetic Valve Thrombosis; TTE = transthoracic echocardiogram.

FIGURE 3 Clinical Case Vignettes

	Case 1: Valve thrombosis under aspirin resolved by VKA	Case 2: Valve thrombosis under NOAC resolved by VKA	Case 3: Valve thrombosis under NOAC resolved by ultraslow thrombolysis
Clinical Presentation	Male patient of 79 years of age History of CABG and a TAVR with a LOTUS valve Presents with 2-time recurrent non-ST-segment elevation MI 3 years after TAVR	Male patient of 82 years of age History of stroke and atrial fibrillation; directly after TAVR, increased transprosthetic gradients were present Presents 1 month after TAVR with progressive exertional dyspnea, NYHA functional class III	Male patient of 79 years of age History of atrial fibrillation, CABG, and previous homograft AVR and TAV-in-SAV intervention (Evolut R) and TAV-in-TAV (Sapien 3 ultra) Presents 19 months after last TAVR with acute heart failure and elevated cardiac enzymes
Current Antithrombotic Strategy	Aspirin 80 mg once daily, added ticagrelor after first non-ST-segment elevation myocardial infarction	Rivaroxaban 10 mg once daily	Edoxaban 60 mg once daily
Diagnostic Work-Up	TTE:  Low gradients, mean PG 10 mm Hg, peak V 2.0 m/s MSCT: Hypoattenuated leaflet thickening and reduced leaflet motion of the transcatheter heart valve  CAG: Small LIMA with patent LAD, patent venous graft after recent PCI and known CTO of RCA	TTE:  Increased gradients, mean PG 30 mm Hg, peak V 3.5 m/s. MSCT: Diffuse hypodense thickening of valve leaflets, suspect of possible valve thrombosis  CAG: Not repeated	TTE:  Increased gradients, peak V 4.0 m/s. MSCT: Hypoattenuated leaflet thickening of all valve leaflets Thickening of left leaflet suspect for thrombosis  CAG: Patent LIMA-LAD and venous graft on MOl MO2 and RDP Invasive mean gradient 68 mm Hg
Valve Thrombosis Treatment	Aspirin and ticagrelor were switched for acenocoumarol (target INR: 2.0-3.0) and clopidogrel 75 mg once daily	Rivaroxaban was switched for acenocoumarol (target INR: 2.0-3.0)	Edoxaban was discontinued and 2 cycles of ultraslow low-dose infusions of 25 mg alteplase were administered.
Outcome	TTE: Not repeated MSCT: Complete resolution of hypodensities on transcatheter heart valve Normal leaflet mobility  Clinical outcome: Patient was asymptomatic 6 weeks after initiation of acenocoumarol	TTE:  Reduction but not normalization of gradients Mean PG 22 mm Hg, peak V 3.2 m/s, 3 months afterVKA initiation MSCT: Not repeated Clinical outcome: Improvement in dyspnea symptoms; currently in NYHA functional class II	TTE:  Reduction of gradients to mean PG 9 mm Hg and peak V 2.4 m/s, 6 days after first alteplase infusion MSCT: Reduction of transcatheter heart valve thrombus and improved opening of valve leaflets; still, significant residual thrombus remains  Clinical outcome: Significant improvement in symptoms Patient was prescribed acenocoumarol with target INR 2.0-3.0 as maintenance therapy At 1 month, patient had some residual dyspnea symptoms (NYHA functional class II)

Various presentations and management options for valve thrombosis. AVR = aortic valve replacement; CABG = coronary artery bypass graft; CAG = coronary angiography; CTO = chronic total occlusion; INR = international normalized ratio; LAD = left anterior descending artery; LIMA = left internal mammary artery; MI = myocardial infarction; MO1/2 = marginal obtuse artery 1/2; MSCT = multislice computed tomography; NOAC = non-vitamin K oral anticoagulant; PCI = percutaneous coronary intervention; PG = pressure gradient; RCA = right coronary artery; RDP = ramus descendens posterior artery; V = velocity; SAV = surgical aortic valve; TTE = transthoracic echocardiography; VKA = vitamin K antagonist; other abbreviations as in Figure 2.

CENTRAL ILLUSTRATION Treatment Algorithm for Transcatheter Aortic Valve Thrombosis



Adrichem R, et al. J Am Coll Cardiol. 2024;84(9):848-861.

Suggested course of action for patients with confirmed subclinical leaflet thrombosis (SLT) or clinical valve thrombosis (CVT) based on clinical condition and current antithrombotic therapy. *To be repeated until CVT resolution. **Preference for ultraslow low-dose alteplase infusion over reintervention, unless high bleeding risk or failed previous thrombolysis. Preference for redo-TAVR over TAVR-explant because of high surgical risk associated with TAVR-explant. INR = international normalized ratio; NOAC = non-vitamin K oral anticoagulant; OAC = oral anticoagulation; SAPT = single antiplatelet therapy; TAVR = transcatheter aortic valve replacement; VKA = vitamin K antagonist.

TAVR with no clear indication for oral anticoagulation should be discouraged.[43,44] In stable TAVR patients on antiplatelet therapy who develop SLT with gradual increases in transvalvular gradients and/or equivocal symptoms, antiplatelets may be switched to VKA or NOAC. Dual antiplatelet therapy does not appear to be more beneficial than single antiplatelet therapy in the prevention of TAV thrombosis.[12,63] In stable TAVR patients who develop SLT with gradual increase in transvalvular gradients and/or equivocal symptoms under NOAC or VKA, NOAC should be switched to VKA and INR should be targeted to 2.5 to 3.5. An antiplatelet drug may be added in case of incomplete resolution (as determined by repeat MSCT or persistently elevated transprosthetic gradients). Typically, HALT resolution is expected within 1 to 3 months. If anticoagulation is interrupted, transthoracic echocardiography and repeat MSCT imaging is advised after 6 months (**Figure 2**). Anticoagulation may be continued if well tolerated and in the context of valve-in-valve, very high gradient at time of SLT, frame deformation, or large valve size.

TAVR patients with CVT should be treated with parenteral unfractionated or low-molecular-weight heparin in combination with VKA until target INR is reached. If the clinical picture does not improve, elevated transprosthetic gradients persist and TAV thrombosis does not resolve, an ultraslow, low-dose infusion strategy with 25 mg alteplase over 25 hours should be considered. Infusions should be repeated until symptoms and transvalvular gradients have improved. Reintervention with redo-TAVR or explant surgery should only be considered in patients who cannot tolerate pharmacotherapy. Reintervention strategy selection should be patient-tailored and based on clinical and anatomical features. After CVT resolution, we recommend indefinite continuation of VKA or NOAC in the absence of high bleeding risk features.

CONCLUSIONS

TAV thrombosis covers a continuum from SLT to CVT. Pharmacotherapy with oral anticoagulation and thrombolytics is the treatment of first choice and is driven by symptomatology. Further research is required to determine the optimal antithrombotic regimen after TAVR, unravel the clinical implications of SLT and define the best treatment algorithms of CVT.

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