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Review

REVIEW

Clinical valve thrombosis and subclinical leaflet thrombosis in transcatheter aortic heart valves: clinical manifestations, diagnosis, and treatment

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Abstract

During the last decade, transcatheter aortic valve replacement (TAVR) has rapidly expanded as an alternative to surgical aortic valve replacement (SAVR) in patients with symptomatic severe aortic valve stenosis (AS) and increased surgical risk. In TAVR, a bioprosthetic valve is positioned within the stenotic native aortic valve. Although favorable short- and medium-term outcomes have been reported, thrombosis of the transcatheter heart valve (THV) has occurred, with two different entities being described: clinical valve thrombosis and subclinical leaflet thrombosis. In clinical valve thrombosis, an increase in transvalvular gradient appears as a result of obstructive thrombus formation, which eventually leads to symptoms of heart failure. Subclinical leaflet thrombosis is an incidental finding, characterized by a thin layer of thrombus covering the aortic site of the leaflet—called hypo-attenuating leaflet thickening (HALT)—as described on and defined by 4-dimensional computed tomography (4DCT) imaging. This phenomenon may affect motion of the leaflets and is then classified as hypo-attenuation affecting motion (HAM). Even in the case of HAM, the transvalvular pressure gradient remains within the normal range. Clinical valve thrombosis requires treatment, whereas the clinical impact and need for intervention in subclinical leaflet thrombosis is uncertain. Anticoagulant therapy protects against and resolves both clinical valve thrombosis and subclinical leaflet thrombosis, but studies exploring different antithrombotic strategies after TAVR are ongoing. This review summarizes currently available literature within the field of THV thrombosis and provides recommendations for a patient-tailored approach in TAVR patients, although guidelines are still lacking.

Key words: TAVR; subclinical leaflet thrombosis; clinical valve thrombosis

Background

Transcatheter aortic valve replacement (TAVR) has become the standard treatment for patients with symptomatic severe aortic valve stenosis at increased surgical risk.[1–3] Indications for this minimalistic approach are expected to expand rapidly towards patients at lower surgical risk and younger age.[4,5] However, as experience with transcatheter valve replacement has grown, issues have emerged. Thrombosis of surgical heart valve

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prostheses is a well-known phenomenon but has now also been described in transcatheter heart valves (THV).

Reduced prosthetic leaflet motion was incidentally noted on 4-dimensional computed tomography (4DCT) imaging in a few patients after TAVR. This finding raised concern about possible THV thrombosis and prompted further investigation. This led to studies describing the phenomenon of subclinical leaflet thrombosis in all brands of transcatheter and surgical bioprosthetic aortic valves.[6–9] Since then, this phenomenon has been further investigated in several observational studies and registries.

In THV thrombosis, clinical valve thrombosis needs to be distinguished from subclinical leaflet thrombosis. Clinical valve thrombosis after TAVR typically presents with an increase of transvalvular gradient and symptoms of heart failure caused by obstructing thrombus in the THV. Subclinical leaflet thrombosis is an incidental finding on 4DCT imaging, which does not cause symptoms or elevated transvalvular pressure gradients outside the normal range (Fig. 1). This review summarizes the currently available literature within the field of THV thrombosis and provides recommendations for a personalized approach for patients, for which no guidelines are currently available.

Prevalence

Given that THV thrombosis has only recently been described, available data are relatively sparse. In two retrospective analyses, the prevalence of clinical valve thrombosis was reported to be 0.6% and 2.8% after TAVR,[10,11] whereas the prevalence of subclinical leaflet thrombosis has been reported to be as high as 13-38% in studies assessing this phenomenon by means of TEE and/or 4DCT cardiac imaging.[8,9,12]

After SAVR, the prevalence of clinical valve thrombosis has been reported to range between 0.1% and 5.0%,[10] whereas subclinical leaflet thrombosis has only been described in 4% of the largest cohort of surgical aortic bioprosthesis ($n = 138$) assessed by 4DCT imaging.[12] In this latter trial stented and stentless—but not sutureless—bioprosthetic valves were investigated after a median time of 63 (79–417) days. In a smaller study of 47 patients receiving a surgical sutureless bioprosthesis, which shows similarities with the design of THVs, prevalence of subclinical leaflet thrombosis, diagnosed by means of 4DCT, was as high as 38%, after a median time of 491 (36–1246) days after the procedure. There are not many data available on subclinical leaflet thrombosis after SAVR, but these two diverging results in prevalence could suggest that the design of the bioprosthesis also influences prevalence.[13] Also, timing of imaging after AVR might influence reported incidence. Subclinical leaflet thrombosis has been reported from as early as 5 days after AVR, up until months to even years after AVR, with some studies suggesting an increase of incidence over time.[6,14]

Risk factors

During SAVR, the native valve leaflets are surgically excised, whereas in TAVR the native leaflets remain present and are pushed aside into the sinuses of Valsalva when the THV is being deployed into the aortic root. These mechanical differences, leading to differences in valve geometry and flow dynamics between TAVR and SAVR could possibly explain the higher prevalence of subclinical leaflet thrombosis following TAVR.

Several risk factors have been suggested for THV thrombosis, including damage to the leaflet tissue by crimping the THV into the delivery system, lack of endothelialization during the first period after implantation, or blood flow stasis in the neosinuses of Valsalva outside the valve frame.

In one retrospective analysis, the use of antiplatelet therapy alone, balloon-expandable valves, valve-in-valve procedures, and obesity appeared to be predictive for clinical valve thrombosis.[11]

For subclinical leaflet thrombosis, a prospective study investigating 4DCT in balloon-expandable THVs, reported male sex, larger sinuses of Valsalva, and prosthesis size to be associated with an increased risk.[15] The potential role of fluid hemodynamics and valve geometry is also notified in a study reporting that regional underexpansion of the valve frame is associated with subclinical leaflet thrombosis, particularly for THV with an intra-annular—and not supra-annular—valve position.[16] The hypothesis is that, if the frame is not fully expanded, the leaflet may not completely unfold and be more prone to thrombus formation. Interestingly, both THV underexpansion of selfexpanding valves and subclinical leaflet thrombosis most often occur at the level of the native non- and right-coronary cusp. One other study has shown that intra-annular THVs and deeper implantation of supra-annular selfexpanding THVs both show a larger size of the neosinus, and are associated with higher risk for leaflet thrombosis.[17]Accordingly, in a recently published meta-analysis where data from seven observational studies were pooled, supra-annular THVs were associated with lower risk for leaflet thrombosis than were intra-annular designed THVs.[18]

A hypothesis was generated from some *in vitro* studies that post-dilatation might increase the risk for leaflet thrombosis because of histologically proven tissue damage to the leaflets. However, to date no clinical studies have shown this relation, and, the opposite effect of post-dilatation was suggested by Fuchs *et al.* In that study regional expansion was associated with elevated risk for leaflet thrombosis, which were both reduced by post-dilatation.[16]

Diagnosis

In case of clinical valve thrombosis, the functionality of the THV is affected by thrombus formation (Fig. 1), leading to heart failure symptoms such as dyspnea. Studies investigating clinical valve thrombosis have shown

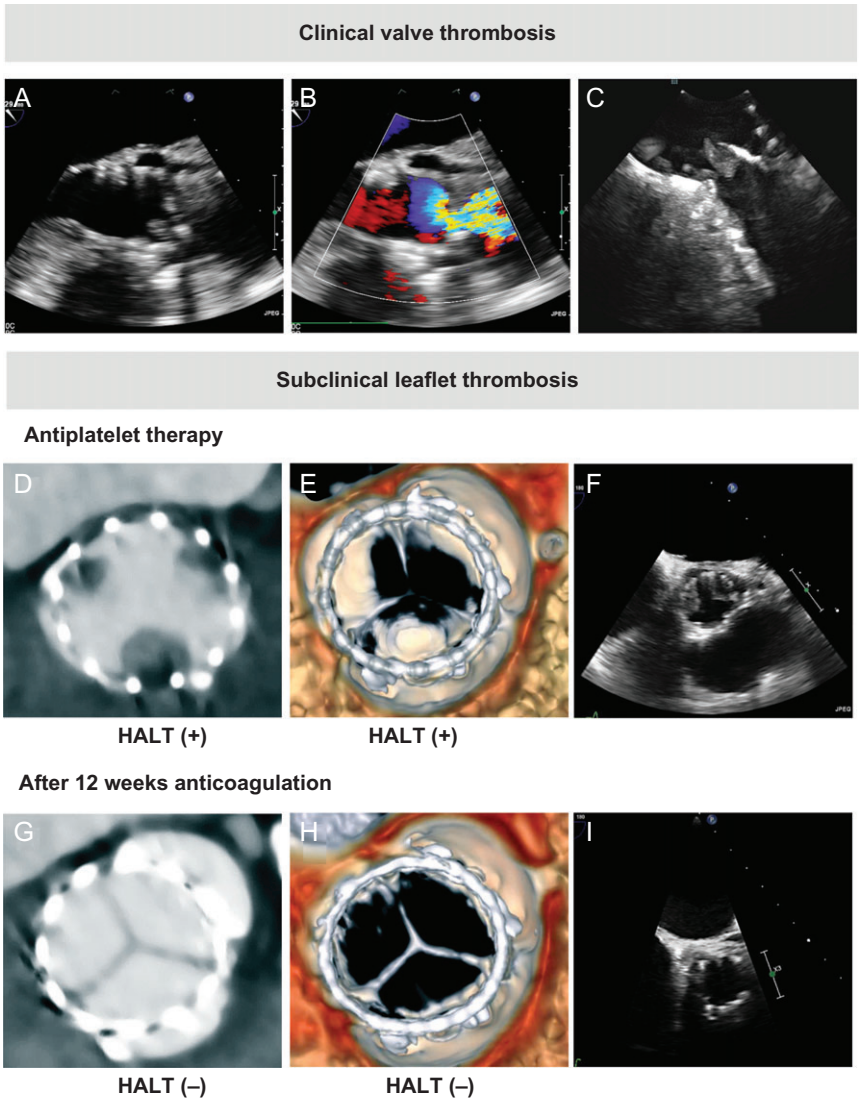

Figure 1. Clinical valve thrombosis and subclinical leaflet thrombosis. (A, B) Transesophageal echocardiography (TEE) showing valve thrombosis and turbulent color flow over the transcatheter aortic bioprosthesis in a patient presenting with an elevated mean transvalvular gradient at transthoracic echocardiography (TTE, 37 mmHg) and dyspnea NYHA class 3-4, a few years after TAVR. (C) Thrombotic mass at the aortic side of the prosthetic leaflets was confirmed by intracardiac echocardiography (ICE). (D, E) Incidental finding of hypoattenuating leaflet thickening (HALT) at the base of the transcatheter heart valve leaflets, with hypoattenuation affecting motion (HAM) visible in systole in the volume-rendered 4D computed tomography (4DCT) images; (F) this reduced leaflet motion of two leaflets was confirmed by TEE. (G, I) Resolution of the leaflet thickening and reduced leaflet motion following 3 months of anticoagulation treatment, as shown by 4DCT and TEE imaging.

significantly elevated transvalvular gradients, with more than 90% of patients having a mean transvalvular gradient of more than 20 mmHg.[10,11] Clearly, if a TAVR patient presents with symptoms of heart failure, first-line assessment should include transthoracic echocardiography (TTE) to examine for THV dysfunction.

For subclinical leaflet thrombosis, the diagnosis is not that obvious and often only made co-incidentally by cardiac (4D)CT scan, as part of a clinical study protocol. These patients are asymptomatic and changes in transvalvular gradient are more subtle and often still within the normal range.[8,12,19] In the combined SAVORY/RESOLVE registries, the mean aortic valve gradient in THV with hypo-attenuation affecting motion (HAM) was 13.8 ± 10.0 mmHg compared with 10.4 ± 6.3 mmHg in THV with normal leaflet motion.[12]

Currently, post-procedural 4DCT scanning is not recommended for use as a screening method for subclinical valve thrombosis, because of the additional exposure to radiation and contrast agent and, therefore, should not be performed outside clinical studies. Importantly, transesophageal echocardiography (TEE) has been shown to be equally sensitive for detection of thrombotic appositions, leaflet thickening, or restricted leaflet mobility of the THV compared with 4DCT imaging (Fig. 1).[8,11]

Clinical presentation and evolution

Clinical valve thrombosis becomes apparent either because of heart failure symptoms, or by a sudden increase of the transvalvular aortic gradient on echocardiography. In a study describing clinical valve thrombosis after TAVR in 26 patients, two out of three patients presented with dyspnea, while the remaining cases were detected on routine follow-up echocardiography.[10] In another study, a lower proportion of patients (38.9%) presented with symptoms of dyspnea, whereas NT-proBNP levels were significantly elevated.[11] Both studies also demonstrated that thrombosis can occur early or late after implantation, with a wide distribution over time after THV implantation [median time to diagnosis of valve thrombosis: 181 (IQR 45–313) days, and 181 (IQR 25–297) days].[10,11]

As mentioned above, patients with subclinical leaflet thrombosis are typically asymptomatic. However, there is a concern that this phenomenon may progress into clinical valve thrombosis, cause stroke or other thromboembolic events, and/or impair the durability of the THV.

Reports on a potential association between subclinical leaflet thrombosis and stroke/transient ischemic attack (TIA) have raised concerns. In the SAVORY and RESOLVE registries, subclinical leaflet thrombosis with reduced leaflet motion was associated with increased incidence of TIA.[12] In contrast, a prospective trial, investigating 4DCT or echocardiography in 434 patients that underwent TAVR, did not show any increase of the risk for stroke after 3 years of follow-up, in patients that had (possible) subclinical leaflet thrombosis.[20] One meta-analysis, although involving a limited number of retrospective studies, also reported an overall odds ratio of 3.38 (95% CI: 1.78–6.41, $P < 0.001$) for cerebrovascular events in case of HAM compared with HALT, thereby suggesting an impact of "thrombus burden" on the risk for neurological events.[21] However, it should be kept in mind that all these reports are based on retrospective data and often there is a very long temporal separation between the neurological event and the 4DCT scan showing subclinical leaflet thrombosis. Furthermore, it has been reported that natural history of subclinical leaflet thrombosis includes temporal dynamic changes between HAM, HALT, and normal status without changing the antithrombotic regimen.[14] Also, the observation that cerebrovascular rates at long-term follow-up in large randomized trials are not higher in TAVR populations compared with SAVR populations does not support the hypothesis that subclinical valve thrombosis would be an important source of thromboembolic events.[5,22,23]

Finally, some concerns have also been raised about the possible negative impact of subclinical leaflet thrombosis on long-term THV durability. Given that this phenomenon is a dynamic process that appears and disappears—and this may occur several times during the lifespan of the valve—it is difficult to investigate its possible impact on long-term durability. However, importantly, although subclinical leaflet thrombosis is more common after TAVR compared with SAVR, medium-term durability of THVs has been shown to be non-inferior to durability of surgical aortic bioprosthesis in several large randomized trials, with follow-up periods of up to 5 years.[5,22,24]

Prevention and treatment

In two retrospective studies reporting on clinical valve thrombosis after TAVR, the mean transvalvular gradient could be reduced from 34–42 mmHg to 16–17 mmHg following 2-6 weeks' treatment with oral vitamin K antagonists (VKA).[10,11] Interestingly, in one of the studies, two patients showed relapse after temporarily stopping VKA therapy, whereas no relapse was demonstrated among patients who were switched from VKA to non-VKA oral anticoagulants.[11]

Patients treated with anticoagulant therapy for subclinical leaflet thrombosis showed resolution of leaflet opacities and restoration of normal leaflet mobility in all patients.[12,16] However, relapse occurred in half of the patients when anticoagulant therapy was interrupted.[8] Furthermore, progression from HALT to HAM never occurred in patients on oral anticoagulation, whereas this HALT to HAM progression was reported in 13/60 patients (22%) on antiplatelet therapy.[14]

Anticoagulation seems to be preventive for development of both clinical valve thrombosis and subclinical leaflet thrombosis, whereas single or dual APT does not have this effect.[8,11,16] In accordance, treatment with anticoagulation seems to have—at least temporarily—beneficial effects on restoration of leaflet motion and transvalvular gradients in case of THV thrombosis.

European guidelines (ESC/EACTS) recommend 3-6 months of double antiplatelet therapy followed by single antiplatelet therapy, whereas the American association (AHA/ACC) recommends an initial period of 3 months with oral anticoagulation in patients at low bleeding risk (Class IIb, level of evidence C).[25,26] Given the limitations of only temporary effects of short-term anticoagulant therapy, and increased bleeding risks associated with long-term anticoagulant therapy, we would currently not recommend administering anticoagulant therapy as a standard regimen after TAVR for prevention of leaflet thrombosis. Multiple trials involving 4DCT imaging (NCT02675114, NCT02701283) and different antithrombotic regimens (ARTE NCT01559298, AUREA NCT01642134, POPULAR-TAVI NCT02247128, GALILEO NCT02556203, ATLANTIS NCT02664649, AVATAR NCT02735902), will provide more evidence to develop the best antithrombotic strategy after TAVR.[27] For the frail population of TAVR patients, a patient-tailored approach for antithrombotic treatment is needed, aiming at a balance between patient-specific thrombus and bleeding risk.

Discussion

Following the European Society of Cardiology guidelines, patients that receive bioprosthetic aortic valves should be assessed clinically and with echocardiography at baseline, 3 months, and 1 year after TAVR, and annually thereafter, or sooner if new cardiac symptoms occur.[25] Currently, prescription of double APT is recommended for 3-6 months, followed by life-long single APT after TAVR, in cases of no indication for anticoagulant therapy (Fig. 2A). However, the optimal antithrombotic regimen after TAVR is still being investigated in different ongoing trials.

In patients with new symptoms of heart failure and/or a sudden increase in transvalvular pressure gradient or new central aortic regurgitation on TTE, additional TEE should be performed to examine for clinical valve thrombosis or other signs of THV deterioration. 4DCT imaging should only be considered as an alternative when TEE is not readily available or has been insufficient for the further work-up. If diagnosis of clinical valve thrombosis is confirmed, anticoagulation therapy should be started, providing there are no contraindications. Also, if a TAVR patient presents with a thromboembolic event (stroke, TIA, or peripheral embolism), it is reasonable to consider additional investigation with TEE and/or 4DCT imaging and anticoagulation therapy (Fig. 2A). The optimal type and duration of anticoagulant therapy in these cases is still unclear but should at least be continued until the thrombus has resolved and valve function is restored.

Finally, routine post-procedural 4DCT is not recommended to screen for subclinical leaflet thrombosis, because of the exposure to additional contrast and radiation, as well as the lack of evidence on the impact of intervention with anticoagulation therapy. Current recommendations are also to keep the antithrombotic treatment unchanged, even where subclinical leaflet thrombosis is detected. Although few reports indicate

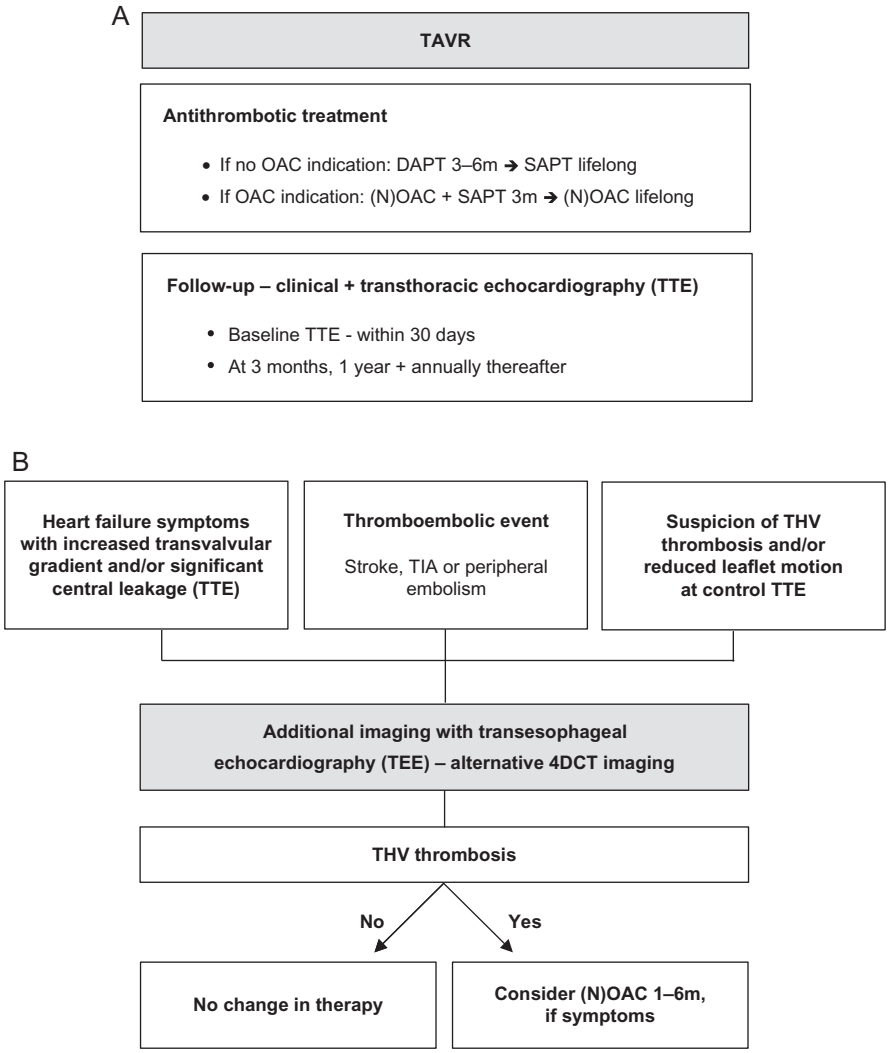

Figure 2. Algorithm for the follow-up of TAVR patients considering the risk for clinical valve thrombosis and subclinical leaflet thrombosis. 4DCT, 4-dimensional computed tomography; DAPT, double antiplatelet therapy; NOAC, novel oral anticoagulation; OAC, oral anticoagulation; SAPT, single antiplatelet therapy; TAVR, transcatheter aortic valve replacement; THV, transcatheter heart valve; TEE, transesophageal echocardiography; TIA, transient ischemic attack; TTE, transthoracic echocardiography.

that subclinical leaflet thrombosis can be resolved by anticoagulant therapy, it is uncertain whether short-term anticoagulation will benefit the long-term outcome. There is currently insufficient evidence linking this phenomenon of subclinical leaflet thrombosis with a worse outcome for the patient and initiation of anticoagulant therapy would expose these frail patients to a higher bleeding risk.

Conclusion

THV thrombosis after TAVR has recently been described and divided into two different entities: clinical valve thrombosis and subclinical leaflet thrombosis. Clinical valve thrombosis presents with heart failure symptoms and an increase in transvalvular gradient, whereas subclinical leaflet thrombosis is an incidental finding on post-procedural TEE or 4DCT imaging. Treatment with anticoagulation for clinical valve thrombosis is recommended, if no contraindication is present, although optimal type and duration of anticoagulant therapy is not clear. Whether or not subclinical leaflet thrombosis is associated with an increased risk for thromboembolic events or accelerated THV degeneration is unclear. However, based on currently available data, it is not recommended to start anticoagulation therapy in such cases, nor to screen systematically for this phenomenon with 4DCT imaging. Currently, several trials investigating different antithrombotic strategies following TAVR are ongoing, with some of these trials also studying subclinical leaflet thrombosis by 4DCT imaging. As evidence is lacking on the optimal antithrombotic strategy after TAVR and approach to patients with subclinical leaflet thrombosis or clinical valve thrombosis, we are obliged to apply an individually tailored strategy in this very specific population.

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