TAVR Thrombosis: A Systematic Review

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ABSTRACT

Introduction: Over the past decade, Transcatheter Aortic Valve Replacement (TAVR) has become the standard technique for treatment of severe symptomatic aortic stenosis in patients at high or intermediate surgical risk and more recently in low-surgical-risk patients. Although, it is not without potential complications and failure modes, such as endocarditis, structural failure, late embolization, or thrombosis.

Thrombosis can occur as early as within 30 days after valve implantation, and which has led to increased concerns of stroke and long-term valve durability. Clinical thrombosis may have clinical manifestations with recurrence of symptoms and/or increase in trans-prosthetic gradients.

It can also be asymptomatic without trans-prosthetic gradient elevation as revealed by cardiac CT scan showing a thickening of the valvular leaflets or cusp thrombosis, with potential impairment of the valve opening. This greatly underestimated complication has a 10% to 15% incidence.

Aim: Biomechanical factors, intrinsic patient-related predisposition as well as post-TAVR anti-thrombotic treatment have all been incriminated in the occurrence of TAVR thrombosis.

While anticoagulation effectively resolves the prosthetic thrombosis, routine use remains controversial and their benefit in the treatment of infraclinical thrombosis has not been clearly established.

Conclusion: We review the pathology, prevalence, diagnosis, hemodynamics, risk factors, prognosis, and treatment of Leaflet Thrombosis (LT), and suggest future directions in this field.

Keywords: Thrombosis; Prothesis; Antithrombotic; Cardiac computed tomograph

INTRODUCTION

Transcatheter Aortic Valve Replacement (TAVR) is an established therapy for patients with severe symptomatic Aortic Stenosis (AS) at increased risk for surgical aortic valve replacement (SAVR) as currently recommended by the European Society of Cardiology; [1] The recent positive results of TAVI in randomized trials expected to expand to patients across lower surgical risk categories.[2]

Prosthesis thrombosis is one of the post TAVI complications and occurs in approximately 10% of patients after transcatheter aortic valve replacement.[3] The post TAVI antithrombotic treatment aims at preventing the occurrence of this complication.

Two entities of post TAVI thrombosis must be distinguished: clinical thrombosis and subclinical thrombosis, whose definitions, symptomatic manifestations, clinical consequences, and therapeutic implications are quite different.[4]

This review aims to summarize and discuss the currently available data on clinical and subclinical valve thrombosis in post TAVI.

DEFINITION AND INCIDENCE

It is well known that mechanical heart valve implantation requires effective long-term anticoagulation with anti-vitamin K (AVK) because of an increased risk of thrombosis. this risk is much less recognized in bioprosthetic heart valves which the use of single platelet anti-aggregation is sufficient.[1,5]

However, despite the less thrombogenic profile of these valves, recent studies also show the occurrence of valve or valve leaflet thrombosis during the placement of a bioprosthesis whether a percutaneous or surgical approach. The use of cardiac CT after TAVI has revealed more frequent prosthesis thrombosis than might have been thought and has fueled a growing literature and clinical trials concerning the prevention of such thrombosis.

In practice, it is important to make the difference between two entities concerning TAVI thrombosis: clinical post TAVI thrombosis, and subclinical post TAVI thrombosis.[4]

Clinical post TAVI thrombosis is defined as valve dysfunction with a typical finding of a moving mass or thrombus involving part or all the TAVI leaflets visualized by echocardiography or cardiac CT.

Valvular dysfunction is often secondary to a decrease in valve clearance leading to stenosing, and much more rarely to a valve coaptation defect responsible for a valve leak.

Subclinical thrombosis after TAVI is frequently discovered by chance, following a scan done for other reasons, which reveals a hypodense image of the valve, better known by the acronym "HALT" for Hypo-Attenuating Leaflet Thickening. It is not accompanied by any clinical symptomology or elevation of trans-valvular gradients. The incidence of subclinical thrombosis appears to be much higher, ranging from 10 to 15% and occurring very often in the first months.

However, this hypodensity or HALT can be accompanied by a valve opening defect called "HAM" for Hypo-Attenuation Affecting Motion.

Following surgical aortic valve replacement (SAVR) with a bioprosthesis, the incidence of clinical valve thrombosis has been reported to range between 0.3 and 6.0%.[6,7]

DIAGNOSIS

European guidelines recommend echocardiography, including measurement of transprosthetic gradient, at baseline (within 30 days), at 1 year after valve implantation and annually thereafter, and earlier if any new symptom occurs.[8] TAVI thrombosis should be considered when mean trans-prosthetic pressure gradient is over 20 mmHg, or when a >50% increase from baseline is observed.

Thickening of the valve leaflets of more than 2 mm with a decrease in valve mobility are highly suggestive of TAVI thrombosis.[9]

Therefore, additional TEE imaging is recommended in case of clinical suspicion of prosthetic valve dysfunction. In practice, it is difficult to assess valve mobility on echocardiography. Any decrease in the mobility of the valve leaflets does not correspond to a valve thrombosis and is not always accompanied by an increase in trans-valvular gradients.

The CT scan also provides arguments to differentiate valve thrombosis from differential diagnoses, including structural degeneration often associated with the presence of calcification and valve coaptation defects responsible for valve leakage, or pannus with denser circular imaging localized at the base of the ventricular valve leaflets.

Finally, TAVI thrombosis is suspected on clinical and ultrasound grounds, but to refine the diagnosis, the use of a cardiac CT scan injected on the TAVI valve remains the technique of choice to make the diagnosis.

When the valve motion is decreased by more than 50%, the diagnosis of HAM (hypoattenuation affecting motion) is made (10) (Figure 1). In the case of valve thrombosis, the CT scan shows a hypodense image without contrast appended to the valve, which impedes the most often the valve clearance and responsible for the elevation of the trans-valvular gradients.

PREDISPOSING FACTORS AND PATHOPHYSIOLOGY

Thrombus on TAVI was observed to initiate at the base of the valve leaflet, a region known as the neo-sinus. The native aortic sinus is a region around the valve that accommodates the native leaflet motion and flow into the coronaries.[11] However, after TAVI the native sinus is divided into two distinct regions—the reduced native sinus and a new space between the prosthetic leaflets and native leaflets and the stent complex. The fluid dynamics associated with this non-physiological region and its inter- action with the stent and biological milieu has been the focus of many studies in the recent past.

Little is known about the rather complex pathophysiology of bioprosthetic thrombosis, and most explanations are based on CT findings. The difference in incidence of prosthetic valve thrombosis for surgical and transcatheter aortic bioprosthesis also suggests the involvement of multiple and divergent pathophysiological mechanisms, including device and host variables, and antithrombotic therapy.

During surgical AVR, the native valve leaflets are surgically excised, whereas in TAVI the native valve leaflets remain present and are pushed on the sides into the sinuses of Valsalva. This creates hemodynamic flow constraints that may explain the higher prevalence of subclinical thrombosis after TAVI.

The presence of microtrauma during valve crimping and release, the presence of a metal frame, poor valve-to-wall fit, delayed or lack of endothelialization, and residual aldehydes (a substance contained in the storage fluid of bioprostheses) may also contribute to leaflet thrombosis in the event of inadequate cleaning.

In addition, it has been suggested that bicuspid valves may be associated with a higher risk for leaflet thrombosis, as prothesis end up more often non-circular, under expanded, and bicuspid anatomies are sometimes linked with a larger sinus of Valsalva. However, evidence confirming this theoretical link is still missing.

Patient variability can potentially predict and partially explain biologic valve thrombosis. Others patient-specific comorbidities are known to cause a prothrombotic state: advanced age, renal failure, dialysis, diabetes mellitus, heart failure, atrial fibrillation, chronic anemia, and smoking.

The combination of these factors potentiates the probability of prosthesis thrombosis, especially since the more these factors are present, the more the patient will be referred to a percutaneous TAVI procedure, possibly explaining the higher incidence of clinical and subclinical thrombosis with this technique compared to a surgical method.

Finally, the antithrombotic strategy chosen after TAVI would have a major influence on the development of clinical and subclinical valve thrombosis. In two retrospective trials, a significantly lower rate of clinical valve thrombosis was reported in post TAVI patients on anticoagulant therapy compared to patients on antiplatelet agents.[12,13] Other studies have shown a significantly lower rate of subclinical thrombosis in patients on anticoagulants, whereas there appears to be no difference in incidence with dual or single platelet antiaggregation.

CLINICAL CONSEQUENCES

Clinical thrombosis after TAVI often manifests itself by a worsening or reappearance of dyspnea, leading to acute heart failure, rarely of sudden onset.

The thrombus that impedes the proper functioning of the TAVI valve mimics in practice the symptoms of a valvular stenosis, more rarely a valvular regurgitation or a combination of both. Another apparent risk in case of clinical valve thrombosis is the risk for thromboembolic events, which can present as a transient ischemic attack (TIA), stroke, or peripheral embolism.[14]

However, there is a theoretical concern that HALT/HAM may progress to clinical valve thrombosis with a risk of thromboembolic events or accelerated valve degeneration, thus decreasing the durability of the valve.[13]

Regarding thromboembolic events, studies have raised some concerns the association of subclinical thrombosis and stroke/TIA. In the SAVORY/RESOLVE registry, the presence of subclinical thrombosis affecting valve motion (HAM) was associated with an increased incidence of TIA.[13] However, these results should be interpreted with caution because the valve status (presence of HALT/HAM/normal CT scan) was not known at the time of TIA, with sometimes a long delay between the embolic event and the CT scan.

In contrast, a prospective trial including 434 TAVI patients studied by CT or echocardiography showed no increased risk of stroke at 3-year follow-up in patients with HALT or HAM.[15] The overall stroke rate in the latter study was 3.2% at 3 years, but none of the strokes were related to subclinical leaflet thrombosis.

Regarding the possible negative impact of subclinical leaflet thrombosis on the long-term durability of the TAVI valve. There are no solid data to evaluate this hypothesis. The fact that this phenomenon is a dynamic process makes it difficult to study its impact on the long-term durability of TAVI valves. This assumption is not supported by mid-term data demonstrating thrombosis durability to be non-inferior as compared to surgical

bioprosthetic valves, although subclinical leaflet thrombosis occurs more frequent after TAVR than after SAVR.
[16,17]

ANTITHROMBOTIC TREATMENT

The latest European Society of Cardiology (ESC) 2021 guidelines on the management of valve disease recommends treatment with simple antiplatelet aggregation aspirin post TAVI, in the absence of indication for long-term oral anticoagulation.[18]

However, US guidelines allow for the possibility of oral anticoagulation for the first 3 months after TAVI implantation, provided that patients are at low risk of bleeding (class IIb, level of evidence C).[19]

In case of obstructive valve thrombosis with life-threatening clinical condition, emergency treatment should be initiated. Valve replacement surgery is preferred if the patient's clinical condition allows it, thrombolysis remains a second-line therapeutic option, associated with negligible complication rates (bleeding, stroke, peripheral emboli, death).

In the case of clinical valve thrombosis, two studies have reported a beneficial evolution of trans-prosthetic gradients after VKA treatment (8,18). There are very few data on the treatment of clinical valve thrombosis with direct oral anticoagulants, but their use seems possible. Treatment with anticoagulants should be continued at least until the thrombus has disappeared and the valve function has been restored; on average, 14 days are needed to reduce the trans-valvular gradient.[20]

Regarding subclinical valve thrombosis (HALT and HAM), two studies have shown that the use of oral anticoagulation allowed complete resolution of the images of contrast hypoattenuation with normal restoration of the movement of the valve leaflets.[21,22]

While progression from HALT to HAM never occurred in patients on effective oral anticoagulation, it was reported in 22% of patients on antiplatelet therapy.[13]

Ruil et al.[23] followed the evolution of HALT by CT scan in 51 patients according to the antithrombotic regimen in place (29 patients on anti-aggregants and 22 patients on anticoagulants). After a median of 86 days, regression of HALT images was observed in 100% of patients treated with oral anticoagulation, whereas 38% of patients on antiplatelet agents (11 of 29 patients) had progression of cusp thickening. After a median of 91 days after stopping anticoagulant therapy, a CT scan performed in 10 patients revealed a significant increase in the restriction and thickness of the valve leaflets, concluding that the treatment of HALT may be challenging.

Given the asymptomatic nature and the uncertain evolution of subclinical thrombosis, no study has specifically addressed their management. The only data available to us are the results of sub-studies of the GALILEO and ATLANTIS trials.

In a subgroup analysis of the GALILEO study involving 231 patients after TAVI and assessed by CT scan at 90 ± 15 days after randomization, the Rivaroxaban group was associated with a lower risk of alteration of kinetics and valve thickness compared with the antiplatelet group alone. Recall that GALILEO is a multicenter clinical trial comparing Rivaroxaban 10 mg twice daily with single or dual antiplatelet therapy in post TAVI patients without indication for anticoagulation. This study was prematurely stopped at an interim analysis due to an increase in all-cause mortality, thromboembolic events and bleeding in patients treated with Rivaroxaban.[7,24]

ATLANTIS 4D-CT is a sub-study of the ATLANTIS study with 762 patients with operable CT scans with the objective of evaluating the incidence of prosthesis thrombosis at 3 months after TAVI and randomized in two arms between standard treatment versus Apixaban according to the existence (Apixaban vs. VKA) or not (Apixaban vs. anti-platelet aggregation) of an indication for prolonged anticoagulation.[25] Apixaban reduced the incidence of subclinical thrombosis in patients without an indication for long-term anticoagulation (apixaban vs. anti-platelet aggregation arm, OR=0.51, 95%CI 0.30 to 0.86). In patients with an indication for long-term VKA anticoagulation, the rate of TAVI bioprosthesis thrombosis was higher in the apixaban vs VKA group, but without significant difference. No clinical benefit was observed in the reduction of subclinical thrombosis after TAVI.

CONCLUSION

Bioprosthetic valve thrombosis encompasses two different entities: clinical valve thrombosis and subclinical leaflet thrombosis. Patients with clinical valve thrombosis often present with heart failure symptoms and an increase in transprosthetic gradient, while subclinical leaflet thrombosis is an incidental finding on post-procedural TEE and/or MDCT imaging.

Treatment with OAC is recommended for clinical valve thrombosis, although the optimal medical treatment and duration is not clear yet. Whether subclinical leaflet thrombosis is associated with an increased risk for thromboembolism or accelerated valve degeneration is still a matter of speculation. Based on current evidence, it is not recommended to perform routine TEE to screen for subclinical leaflet thrombosis, nor to treat with OAC in detected cases. However, it is recommended to shorten the echocardiographic follow-up interval in case of subclinical leaflet thrombosis. Given the significance and prevalence of TAVI thrombosis, potential areas of future research may focus on addressing scientific concerns specifically relating to the following issues.

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