Transcatheter Heart Valve Thrombosis: Incidence, Predictors, and Clinical Outcomes

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Abstract
Since its initial approval, the number of transcatheter aortic valve replacement procedures performed has increased exponentially with evolving indications that now include patients at intermediate risk for perioperative mortality following surgery. Multiple studies and reports have observed the phenomenon of leaflet dysfunction and thrombosis on follow-up imaging that may be associated with serious adverse outcomes. This review provides an insight into the incidence, predictors, and management of transcatheter heart valve thrombosis.

Keywords
Transcatheter aortic valve replacement, transcatheter heart valve, leaflet thrombosis, hypoattenuated leaflet thickening, leaflet motion

Transcatheter aortic valve replacement (TAVR) is a recent innovation that has transformed the care of patients with symptomatic severe aortic stenosis. It has emerged as an alternative for surgical aortic valve replacement (SAVR) in prohibitive-, high-risk, and more recently, intermediate-risk surgical patients. More than 200,000 TAVRs have been performed in 65 countries around the world.1

As for surgical valves, transcatheter heart valve (THV) thrombosis is a rare, but serious, clinical adverse event with reported mortality rates reaching 30 %.2 Multiple reports and studies have shed light on the incidence of THV leaflet thrombosis. This article summarizes the current and evolving literature on the incidence, predictors, and clinical outcomes of THV thrombosis.

Transcatheter Heart Valve Thrombosis: Emerging Concerns
THV-reduced leaflet mobility was first described by Makkar et al. in patients enrolled in the Portico Re-sheathable Transcatheter Aortic Valve System US Investigational Device Exemption (PORTICO IDE) trial, and the Assessment of Transcatheter and Surgical Aortic Bioprosthetic Valve Thrombosis and Its Treatment with Anticoagulation (RESOLVE) and Subclinical Aortic Valve Bioprosthesis Thrombosis Assessed with Four-Dimensional Computed Tomography (SAVORY) registries.3 Patients underwent a dedicated 4D volume-rendered computed tomography (CT) scan at different time intervals post TAVR with reduced leaflet mobility ranging from 13 to 40 %. Although the study was underpowered for clinical outcomes, several important findings were described: (i) the incidence of stroke or transient ischemic attack (TIA) was higher in patients with reduced leaflet mobility (18 % versus 1 %; p=0.007); (ii) patients on therapeutic anticoagulation with warfarin had a lower incidence of reduced leaflet mobility compared with patients on dual antiplatelet therapy (0 % versus 51 %; p=0.007); and (iii) therapeutic anticoagulation completely resolved the CT finding of reduced leaflet mobility.

In a retrospective analysis of 4,266 consecutive patients who underwent TAVR with Edwards Sapien/Sapien XT (Edwards Lifesciences) and Medtronic CoreValve (Medtronic, Inc.) in 12 centers, Latib et al. reported 26 patients with valve thrombosis, defined as valve dysfunction in addition to either histopathology or an imaging modality demonstrating evidence for thrombosis, or an appropriate hemodynamic response to anticoagulation, restoring normal prosthetic valve function within 2 months of therapy.4 The incidence of clinically significant leaflet thrombosis was reported as 0.61 % in this large multicenter registry, with the majority of patients presenting with worsening dyspnea (65 %) and having increased transvalvular gradients (92 %).4

A recent report from The Manufacturer and User Facility Device Experience (MAUDE) database revealed 30 cases of structural valve dysfunction due to leaflet thrombosis (Edwards Sapien = 20; CoreValve = 10) out of the 5,691 TAVR-related adverse events.

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Clinical Versus Subclinical Transcatheter Heart Valve Thrombosis

Clinically significant THV thrombosis manifests as either heart failure or stroke or TIA, and has been associated with adverse clinical events, including cardiogenic shock in 6.7 % of cases and death in 10.7–30.0 % of cases.4,5

Subclinical THV thrombosis is diagnosed if there is either an increase in transaortic mean gradient on follow-up studies by 10 mmHg or direct visualization of thrombus on the leaflets; or a CT scan identifying reduced leaflet motility along with hypoattenuated leaflet thickening are documented on cardiovascular imaging in the absence of the aforementioned clinical manifestations, followed by resolution of imaging findings following a course of anticoagulation.1

Hypoattenuated Leaflet Thickening Versus Hypoattenuation Affecting Motion As Predictors of Thrombosis

An important distinction in the natural history of progression of THV leaflet thrombosis is the imaging characteristic of the valve, and its implication on prognosis and clinical outcomes. As noted in earlier studies, hypoattenuated leaflet thickening (HALT) observed on CT scans performed post implantation was not a rare finding, and was dependent on post-procedural antithrombotic therapy. In a study evaluating Edwards Sapien 3 transcatheter aortic valves on post-TAVR CT scans (from 890 patients) in RESOLVE and SAVORY registries identified subclinical THV thrombosis in 106 patients; normal leaflet motion was restored in 31 patients after initiation of anticoagulation.8

In their analysis from the SAVORY registry that included patients undergoing both TAVR (n=75) and SAVR (n=30), Søndergaard et al. identified HALT in 38.1 % and hypoattenuation affecting motion (HAM) in 20.2 %.9 Of these, progression was identified in 15.5 % of patients, and regression in 10.7 %. Progression was less likely in patients on vitamin-K antagonists (VKA) and other forms of oral anticoagulants (OR 0.014; P=0.036). The investigators postulated that subclinical leaflet thrombosis is a common finding after both TAVR and SAVR, and may progress from normal leaflet motion to HALT, to the more severe HAM, at variable intervals after valve implantation. Evaluating population-specific risk factors, Midha et al. analyzed data from patients in the RESOLVE registry, excluding patients on anticoagulation.10 The analysis concluded that: (i) Edwards Sapien 3 valves that were 10 % overexpanded (per diameter) had a higher propensity toward developing a thrombus; and (ii) CoreValve Evolut R valve implantation depth correlated with increased thrombus volume. In another analysis of a multicenter registry that included 1,521 patients, valve hemodynamic deterioration (VHD) was present in 4.5 % of the cohort during follow-up where multiple risk factors were identified to be independent predictors of VHD.11 These risk factors included: the absence of anticoagulant therapy at hospital discharge, a valve-in-valve (TAVR in a surgical valve) procedure, the use of a 23-mm valve, and a higher body mass index.

Management of Clinical and Subclinical Transcatheter Heart Valve Thrombosis

In the study by Latib et al., the vast majority of patients with subclinical THV thrombosis were treated conservatively with anticoagulation with improved transvalvular gradients on follow-up echocardiography.12 There was a reduction in transaortic mean gradient from 41.9 to 16.9 mmHg after a median of 39 days of therapeutic anticoagulation.

Similarly, for HALT and HAM that were identified on follow-up CT scans, there was regression of HAM and improved leaflet motion after anticoagulation in the study by Søndergaard et al. The initiation of anticoagulation (either warfarin or direct oral anticoagulants) was effective in restoration of normal leaflet function in 100 % in patients with HALT and HAM, where dual antiplatelet therapy failed to do so with progression or persistence of leaflet motion abnormality in the absence of anticoagulation.

The current European Society of Cardiology (ESC)/European Association of Cardio-Thoracic Surgery (EACTS) guidelines for the management of bioprosthetic valve thrombosis recommend treatment with a VKA and/or unfractionated heparin before reintervention.12

Valve Imaging Post Transcatheter Aortic Valve Replacement

There is no consensus with regard to imaging modality of choice and frequency for valve imaging post TAVR. The current ESC guidelines recommend imaging after TAVR or SAVR with a transthoracic echocardiogram to be routinely performed within 30 days to establish baseline valve function, another echocardiogram 1 year after implantation, and annually thereafter.12

HALT and HAM identified on CT imaging as primordial forms of leaflet thrombosis were associated with only mild increase in transvalvular gradients.13 Relying completely on echocardiography alone may therefore be a challenge. In cases reported from the MAUDE database, the occurrence of leaflet thrombosis was highest in the first year post implant, suggesting that a closer follow-up with advanced imaging at least in the first year post procedure may be of high clinical value.2

Conclusion

With expanding indications, TAVR will increasingly continue to require a practical, safe, and cost-effective follow-up strategy to ensure valve structure and function integrity. HAM and HALT incidences noted on follow-up imaging are not trivial, and are thought to be primordial to valve thrombosis as they can either progress or regress in accordance with medical therapy. With the inclusion of a broader patient population, early and timely diagnosis of leaflet dysfunction will be critical for delivering appropriate therapy and improving patient outcomes.

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