Subclinical Leaflet Thrombosis in Transcatheter Aortic Valve Replacement Detected by Multidetector Computed Tomography — A Review of Current Evidence —

Hashrul N. Rashid; Adam J. Brown, PhD; Liam M. McCormick, MD; Ameera S. Amiruddin; Kim K. Be; James D. Cameron, MD; Arthur Nasis, MD, PhD; Robert P. Gooley, PhD

Subclinical leaflet thrombosis (SLT) following transcatheter aortic valve replacement (TAVR) has been increasingly recognized. SLT has the hallmark features of hypo-attenuated leaflet thickening (HALT) on multidetector computed tomography (MDCT), which may result in hypoattenuation affecting motion (HAM). The actual prevalence of this condition is uncertain, with limited observational registries. SLT has caught the attention of the cardiovascular community because of concerns regarding its clinical sequelae, specifically the potential increased incidence of cerebrovascular events. There are available, albeit sparse, data to suggest that when left untreated, SLT may lead to valve deterioration with potential hemodynamic compromise and potentially clinically overt prostheses thrombosis. Some clinicians have opted to treat patients with SLT with anticoagulation. Although anticoagulation may be a rational treatment option, little data exist on the safety and efficacy of this treatment. This is particularly important considering TAVR patients also have higher bleeding risk than the standard population. In this review, we aim to summarize the current evidence on SLT, explore its pathophysiological mechanism, discuss the current treatment options and future trials that may clarify the optimal antithrombotic strategies of SLT.

Key Words: Aortic stenosis; Transcatheter aortic valve replacement/implantation; Thrombosis

Transcatheter aortic valve replacement (TAVR) is an established treatment in the management of patients with symptomatic severe aortic stenosis who are at high or extreme surgical risk.1-4 TAVR has also been used in the treatment of patients at intermediate surgical risk, with recent evidence demonstrating at least equivalent efficacy when compared with surgical aortic valve replacement (SAVR).2,3 Multidetector computed tomography (MDCT) has become the gold-standard in pre-TAVR assessment for prosthesis sizing,6-7 and recent data have emerged regarding its role in postprocedural assessment of leaflet morphology and integrity.5,6 MDCT provides high-spatial resolution images, low intra-operator variability and is non-invasive when compared with transesophageal echocardiography (TEE), making it a practical imaging modality to assess leaflet morphology.

Subclinical leaflet thrombosis (SLT) detected with MDCT has been recently described in the setting of TAVR and to a limited extent, following bioprosthetic SAVR.8,9 SLT represents one end of a spectrum of leaflet thrombosis (LT). Subjects with SLT have MDCT detected HALT, but are asymptomatic with transvalvular gradient measurements within the normal range. This is in contrast to overt clinical LT (CLT) that can lead to symptoms of heart failure associated with overt valve dysfunction.10 Most patients with MDCT-defined LT in observational studies have been classified as SLT and were asymptomatic at diagnosis.9

With TAVR use expanding into lower surgical risk cohorts, understanding the mechanism of SLT and its clinical consequences will become of even greater significance. As younger patients in the future might undergo TAVR and survive longer with these implants, there are valid concerns about the effects of SLT on prosthesis longevity and integrity. This review describes our current understanding on SLT in TAVR; specifically, its epidemiology, pathophysiology, clinical sequelae and existing gaps in knowledge.

Definitions and Computed Tomography (CT) Features
The hallmark feature of SLT on MDCT is hypoattenuation on the surface of bioprosthetic valve leaflets and leaflet...
Leaflet immobility is graded as normal (no RELM), mild (<50% RELM), moderate (50–70% RELM), severe (>70% RELM) or immobile (100% RELM). The authors describe a new entity, hypootenuation affecting motion (HAM), which is defined as moderate or greater leaflet immobility. Confusingly, this definition is similar to Makkar et al’s initial definition of significant RELM, though the term HAM has already been adopted in the current literature. In situations where HAM or RELM is not clearly defined on MDCT, TEE is used to assist in diagnosis.

A recent publication presented a novel method to quantify thrombus burden through 3D volumetric assessment. The stent frame and thrombus was reconstructed using imaging software that allows an accurate assessment of thrombus volume. Among the main limitations to that study were the single-observer quantification of thrombus (the intra- and interobserver variability of this technique was unclear) and the lack of standardization in the timing of MDCT post-TAVR. Even so, this novel technique would allow MDCT operators to accurately diagnose SLT, report weighted thrombus volume according to valve size and may be a future tool to monitor thrombus regression with treatment.

Transcatheter echocardiography (TEE) or TEE may accurately assess leaflet function and valvular gradient. The European Society of Cardiology/European Society of Cardio-Thoracic Surgery (ESC/EACTS) recommends a baseline TTE between 6 and 12 weeks following implantation of bioprosthetic valves, and the American Heart Association/American College of Cardiology (AHA/ACC) suggests initial echocardiography in the ‘postoperative period’. No definition of SLT is provided in either set of guidelines. Makkar et al found RELM features on 4D volume-rendered MDCT were similar to those on TEE imaging, but their study was limited to a small number of patients. Though valvular hemodynamic deterioration on echocardiography (an increase of bioprosthetic peak transvalvular gradient by 10mmHg from baseline) has been suggested to correlate with LT, there are other potential causes, such as pannus formation and structural leaflet dysfunction. Thus, MDCT has become the preferred imaging modality to diagnose SLT in TAVR prostheses.

**Epidemiology**

The prevalence of SLT varies according to the MDCT-based registry, likely because of different lengths of follow-up and types of TAVR prostheses. The prevalence of SLT was found to be approximately 13% in the largest reported TAVR registry to date, with similar prevalence in 2 other published registries. Overall, the prevalence of SLT ranges from 7% to 40%, with the latter prevalence derived from...
Subclinical Leaflet Thrombosis in TAVR

Recent analysis of the SAVORY registry demonstrated that SLT could progress and regress variably with repeat MDCT imaging. A total of 84 patients with SLT were analyzed by MDCT at 2 time points, at a mean of 140 and 298 days. Prosthesis SLT was classified into 3 subgroups depending on the presence of HALT and/or HAM and its severity described in the following ascending order: [HALT (−), HAM (−)], [HALT (+), HAM (−)] and [HALT (+), HAM (+)]. Progression (increase in severity at the second MDCT scan) was reported in 15.5%, regression (reduction of severity) in 10.7% and stability (unchanged severity) was reported in most prostheses (73.8%). Patients on oral anticoagulants did not experience progression of SLT (vs. patients on antiplatelet therapy).

Potential Mechanisms Underlying SLT

Virchow’s triad describes the importance of 3 factors in the pathogenesis of thrombosis: (1) surface damage (or leaflet damage in this SLT), (2) hemodynamic flow alteration and (3) hypercoagulable state.

Surface (Leaflet) Damage

Transcatheter prosthetic leaflets undergo significant stress and micro-trauma during both delivery and deployment of the valve system. Firstly, the TAVR prosthesis undergoes crimping to allow its delivery through a small arterial sheath. Valve crimping may lead to irregular leaflet surfaces, microfilamentous damage and reduced integrity of the pericardial leaflets (Figure 3). Additionally, valve leaflets are exposed to further damage during initial deployment, especially in balloon-expandable valves, through direct

Figure 2. Natural progression and/or regression of leaflet thrombosis (LT) in transcatheter heart valves (THV): most THV do not develop LT. The development of hypo-attenuated leaflet thickening (HALT) occurs in the early stages of LT, mainly in asymptomatic patients (subclinical LT [SLT]). This may progress to reduced leaflet motion (RELM) in patients with a large HALT area. When left untreated, this may lead to clinically overt LT, leading to deterioration of valve function and a potential increase in the risk of cerebrovascular events.
Hemodynamic Flow Alteration

Low-flow severe aortic stenosis is defined as an aortic valve area >1.0 cm² (0.6 cm²/m²) with reduced stroke volume, from either reduced left ventricular ejection fraction or a small left ventricular cavity caused by left ventricular remodeling, resulting in insufficient flow to generate a transvalvular gradient of greater than 40 mmHg. Though traditionally excluded from initial TAVR trials, the clinical application of TAVR has extended into this cohort. A low cardiac output state leads to reduced transprosthetic flow, which promotes hypercoagulability by disrupting the balance of activated clotting factors and inhibitors on the leaflet surface (blood stasis leads to a greater increase in clotting factors over inhibitors). Over time, this increases the risk of developing LT, with some studies demonstrating a trend towards a higher incidence of SLT in patients with low cardiac output. Aside from this, other factors such as valve malapposition (leading to delayed prosthesis endothelialization), malexpansion of the inflow portion of the valve (which leads to valve leaflet folding and altered perivalvular flow) and residual native valve calcium nodules (disrupting laminar flow and causing paravalvular regurgitation) may contribute to the pathogenesis of SLT.

A recent study demonstrated the role of the neo-sinus in the development of SLT. The deployment of the TAVR
prosthesis creates 2 separate periprosthetic spaces: the native aortic sinus and the neo-sinus. The neo-sinus is the space from the prosthesis frame and the prosthesis leaflets. Intra-annular valves are shown to have larger neo-sinuses and flow stagnation zones when compared with supra-annular valves using the in vitro flow model. These stagnation zones are greatest at the base of the prosthesis leaflets, where SLT usually arises. Furthermore, retrospective clinical analysis has revealed a strong correlation between deeper implant depth, which results in a larger neo-sinus, and SLT in supra-annular valves. Subannular neo-sinuses are also more likely to develop a larger thrombus burden. Though such novel findings allude to the role of fluid hemodynamics in the pathogenesis of SLT, this hypothesis needs to be further validated in a larger, more diverse cohort.

**Hypercoagulable State**

Certain patient comorbidities such as advanced age, cancer, chronic kidney disease, diabetes and inflammatory conditions are associated with the development of thromboembolism because of the propensity to developing hypercoagulability with these conditions. Hypercoagulability is likely caused by an increase in circulating thrombogenic factors (e.g., tissue factor) either from increased production or reduced clearance. Some studies have suggested an association between the development of SLT with certain patient comorbidities such as chronic kidney disease and diabetes, though this has not been consistently reported throughout the literature.

Degenerated, calcified aortic valves demonstrate increased endothelial surface expression of tissue factors and activated factor XI, which may result in increased thrombogenicity. These factors promote thrombin generation and activation of the coagulation cascade. In surgical valve replacements, the native calcified aortic valve is excised to accommodate the prosthesis, and this may at least partially explain the reduced incidence of SLT in conventional surgical bioprostheses when compared with TAVR.

Conversely, the use of an anticoagulation agent post-procedurally has been shown to reduce the risk of developing SLT when compared with conventional antiplatelet regimens. Agents such as vitamin K antagonist (VKA) and direct oral anticoagulants (DOAC) reduce the incidence of LT, with the former being a Class I indication for treatment in mechanical prosthetic valves. Furthermore, commencement of anticoagulation with a VKA has been shown to result in regression, and even resolution of DOAC in this setting is not yet established.

**Clinical Implications**

Though it is clear that CLT with aortic valve replacement can lead to serious adverse events such as stroke and death, the clinical sequelae of SLT are less certain. The landmark study by Makkar et al reported a concerning increase in rates of cerebrovascular events (CVE) in the SLT cohort, driven primarily by transient ischemic attacks (TIA). These findings were further confirmed with an updated SAVORY-RESOLVE registry in a larger cohort. A plausible explanation for increased CVE could be embolic migration of leaflet thrombus or de novo thrombus formation from severe leaflet immobility. Even so, other studies have not reported increased rates of CVE with SLT, and even Makkar et al’s seminal paper failed to demonstrate this within the PORTICO IDE cohort.

A recent systematic review and meta-analysis of observational studies consisting of 1,704 patients with transcatheter and surgical aortic bioprosthetic valves, revealed a strong relationship between LT and CVE. This was driven primarily by TIA, although the rate of stroke almost reached clinical significance. Furthermore, the MDCT features of RELM were more strongly associated with CVE, when compared with HALT alone. Though this study was limited by its observational nature, both TIA and stroke outcomes showed a similar signal, which may suggest a similar underlying pathophysiological process in patients with LT.

Justified concerns exist regarding the effect of SLT on long-term leaflet integrity and valve function. The proliferation of thrombus formation over a period of time could lead to HAM and an increased transvalvular gradient (which itself might accelerate leaflet degeneration). One study demonstrated a reduction in aortic valve area and mean aortic valve gradient in the SLT cohort when compared with the non-SLT cohort at 6 months. These differences were not significant at 3 years, but that could be from attrition bias (the majority of the patients were lost to follow-up) or the commencement of treatment (it was unclear if SLT patients were treated with anticoagulation during the follow-up of the study).

These inconsistent findings suggest larger trials are needed to systematically detect SLT through routine MDCT and evaluate its potential clinical effect. Both the PARTNER 3 (Sapien 3) and Corevalve Low Risk (Corevalve Evolut R) trials will have MDCT substudies to evaluate LT, which may provide further insight into the clinical implications of this condition.

**Gaps in Knowledge and Future Trials**

The uncertainty surrounding the clinical sequelae of SLT has led to ambiguity in its management. Some cardiologists have opted to treat SLT with anticoagulation, albeit with little evidence or guideline support for this. Even so, routine anticoagulation can be hazardous because TAVR recipients have multiple comorbidities that could increase their bleeding risk, such as advanced age, renal impairment, hypertension and frailty. The therapeutic window of anticoagulation becomes narrower because of the high bleeding risk; therefore, careful consideration needs to be taken when managing these patients.

With regards to the ideal antithrombotic therapy post-TAVR, both the ESC/EACTS and AHA/ACC guidelines recommend dual-antiplatelet therapy with clopidogrel and aspirin for 3–6 months, followed by aspirin alone, though these recommendations are based on regimens used in initial TAVR trials (Table 1). The recent AHA/ACC guidelines have acknowledged the role of anticoagulation in the prevention of SLT. Though VKA may be considered in patients with low bleeding risk to prevent SLT, with a target international normalized ratio of 2.5 for the first 3 months, though the evidence behind this is still sparse (Class IIb, level of evidence C). Though both guidelines advise anticoagulation in clinically overt LT, neither has provided advice surrounding the management of cases of subclinical LT with normal valve hemodynamics, because of the previous uncertainty surrounding the clinical sequelae of this condition. Even so, the clinical inclination has been
to start anticoagulation, usually with VKAs, and results have demonstrated regression or resolution of SLT. \(^4^6\) There are currently no recommendations for antithrombotic therapy in patients with a recent stent and SLT. In such cases, clinical acumen is recommended in this evidence-free zone.

One randomized trial, the ARTE trial, demonstrated that aspirin alone reduced the risk of major bleeding without the expense of myocardial infarction or stroke when compared with dual-antiplatelet therapy. \(^3^5\) Even so, this was a small study and did not evaluate for SLT. A similarly designed trial with a larger cohort, the Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation (POPULAR-TAVI [NCT02247128]), will compare clopidogrel and aspirin alone after 3 months of dual-antiplatelet therapy in non-atrial fibrillation patients (Cohort A), with results expected in 2019.

A recent study\(^3^6\) compared the safety and efficacy of 2 different anticoagulants (VKA and apixaban) post-TAVR. Of the 617 patients in the trial, 272 with atrial fibrillation were randomized to VKA or apixaban 5 mg daily for 12 months, with aspirin therapy only indicated for 1 month (triple antithrombotic therapy was indicated if a Lotus valve system was implanted). The primary endpoint was the early safety endpoint at 1 month (composite outcomes and bleeding complications). Apixaban had lower rates of the primary safety endpoint and life-threatening bleeding when compared with VKA at 1 month, but routine imaging to detect SLT was not performed.

A few major randomized trials will further address the role of DOAC as an antithrombotic agent post-TAVR.

### Table 1. Current AHA/ACC and ESC/EACTS Guidelines on Antithrombotic Therapy With Transcatheter Aortic Valve Replacement

<table>
<thead>
<tr>
<th>Year</th>
<th>AHA/ACC</th>
<th>ESC/EACTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>Clopidogrel 75 mg daily may be reasonable for the first 6 months in addition to lifelong aspirin 75–100 mg daily (Class IIb, LOE C)</td>
<td>Dual-antiplatelet is recommended for 3–6 months then lifelong single-antiplatelet therapy (Class IIA, LOE C) Single-antiplatelet may be considered in patients with high bleeding risk (Class IIb, LOE C)</td>
</tr>
</tbody>
</table>

### Table 2. List of Current Anticoagulation Trials With Transcatheter Aortic Valve Replacement

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of patients</th>
<th>Duration, months</th>
<th>First arm</th>
<th>Second arm</th>
<th>Primary outcomes</th>
<th>Results or expected completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARTE</td>
<td>222</td>
<td>3</td>
<td>Aspirin 100 mg</td>
<td>Aspirin 100 mg and clopidogrel 75 mg</td>
<td>MACCE</td>
<td>Completed. Aspirin arm had less MACCE</td>
</tr>
<tr>
<td>Seeger et al (AF cohort)</td>
<td>617 (272 in AF cohort)</td>
<td>1</td>
<td>Apixaban 5 mg twice daily (additional aspirin 100 mg if Lotus Valve)</td>
<td>VKA (additional aspirin 100 mg if Lotus Valve)</td>
<td>VARC2 early safety endpoint (MACCE, life-threatening bleed, major vascular complication, acute kidney injury and valve dysfunction)</td>
<td>Completed. Apixaban had better early safety endpoint</td>
</tr>
<tr>
<td>AUREA</td>
<td>124</td>
<td>3</td>
<td>VKA</td>
<td>Aspirin 100 mg and clopidogrel 75 mg</td>
<td>Cerebral thromboembolism on magnetic resonance imaging</td>
<td>December 2017</td>
</tr>
<tr>
<td>GALILEO</td>
<td>1,520</td>
<td>25</td>
<td>Rivaroxaban 10 mg and aspirin 100 mg for 3 months, then rivaroxaban alone</td>
<td>Clopidogrel 75 mg and aspirin 100 mg for 3 months, then aspirin alone</td>
<td>MACCE, TE and valve thrombosis</td>
<td>November 2018</td>
</tr>
<tr>
<td>ATLANTIS</td>
<td>1,510</td>
<td>13</td>
<td>Apixaban 5 mg twice daily</td>
<td>VKA or antiplatelet therapy</td>
<td>MACCE, TE, intracardiac thrombus and valve thrombosis</td>
<td>April 2019</td>
</tr>
<tr>
<td>POPULAR-TAVI (cohort A – no OAC indication)</td>
<td>684</td>
<td>12</td>
<td>Aspirin 100 mg</td>
<td>Aspirin 100 mg and clopidogrel 75 mg for 3 months, then aspirin alone</td>
<td>All-bleeding complications</td>
<td>September 2019</td>
</tr>
<tr>
<td>POPULAR-TAVI (cohort B – OAC indication)</td>
<td>316</td>
<td>12</td>
<td>VKA</td>
<td>VKA and clopidogrel 75 mg for 3 months, then OAC alone</td>
<td>All-bleeding complications</td>
<td>September 2019</td>
</tr>
<tr>
<td>AVATAR</td>
<td>170</td>
<td>12</td>
<td>VKA</td>
<td>VKA and aspirin 75–100 mg</td>
<td>MACCE, major bleed and valve thrombosis</td>
<td>April 2020</td>
</tr>
<tr>
<td>ENVISAGE-TAVI AF</td>
<td>1,400</td>
<td>36</td>
<td>VKA</td>
<td>Edoxaban</td>
<td>MACCE, major bleed and valve thrombosis</td>
<td>November 2020</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; MACCE, major adverse cardiovascular and cerebrovascular outcomes (all-cause death, myocardial infarction, stroke and transient ischemic attack); OAC, oral anticoagulant (either vitamin K antagonist or direct acting oral anticoagulant); TE, thromboembolism (pulmonary embolism, deep vein thrombosis and non-central nervous system embolic events); VKA, vitamin K antagonist.
The Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis (ATLANTIS) trial [NCT02664649] will randomize successful TAVR patients to apixaban, dual-antiplatelet therapy or VKA in a 2:1:1 fashion with 13 months of follow-up. The Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-Based Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes (GALILEO) trial [NCT02556203] will randomize patients in an equal fashion to a rivaroxaban arm (rivaroxaban 10 mg daily with aspirin 100 mg, followed by rivaroxaban alone after 3 months) or the standard dual-antiplatelet therapy arm (clopidogrel 75 mg with aspirin 100 mg, followed by aspirin alone after 3 months) with a longer follow-up of 25 months. Both have a primary outcome of death, myocardial infarction, stroke, venous thromboembolic events, bleeding and LT.

With regards to patients with atrial fibrillation, the POPULAR-TAVI study also has a second cohort of atrial fibrillation patients (Cohort B), comparing VKA monotherapy against VKA with clopidogrel 75 mg daily for 3 months. The primary outcome is non-procedural-related bleeding at 1 year. The Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation (ENVISAGE-TAVI AF) trial [NCT02943785] compares separate anticoagulation strategies, by randomizing patients to either VKA or edoxaban (the use of antiplatelet therapy at the discretion of the treating physician). A list of randomized TAVR trials on antithrombotic therapy is summarized in Table 2.

The role of surveillance using MDCT in TAVR patients for LT is also unclear. Though large registries have performed systematic MDCT on patients following TAVR, this practice has certain practical limitations and potentially harmful effects for patients. Mandatory MDCT on all patients would provide significant logistical constraints in less-equipped centers and the cost of routine MDCT imaging is not negligible. Routine MDCT may impose harmful effects on patients from radiation exposure (particularly as we move towards treating younger patients) and a nephrotoxic effect of iodinated contrast media. Certain patient effects on patients from radiation exposure (particularly as we move towards treating younger patients) and a nephrotoxic effect of iodinated contrast media. Certain patient...


