



# 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

**T**ranscatheter 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.<sup>1–5</sup> 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).<sup>2,3</sup>

Multidetector computed tomography (MDCT) has become the gold-standard in pre-TAVR assessment for prosthesis sizing,<sup>6,7</sup> and recent data have emerged regarding its role in postprocedural assessment of leaflet morphology and integrity.<sup>3,5</sup> 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.<sup>8,9</sup> 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.<sup>10</sup> Most patients with MDCT-defined LT in observational studies have been classified as SLT and were asymptomatic at diagnosis.<sup>9</sup>

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

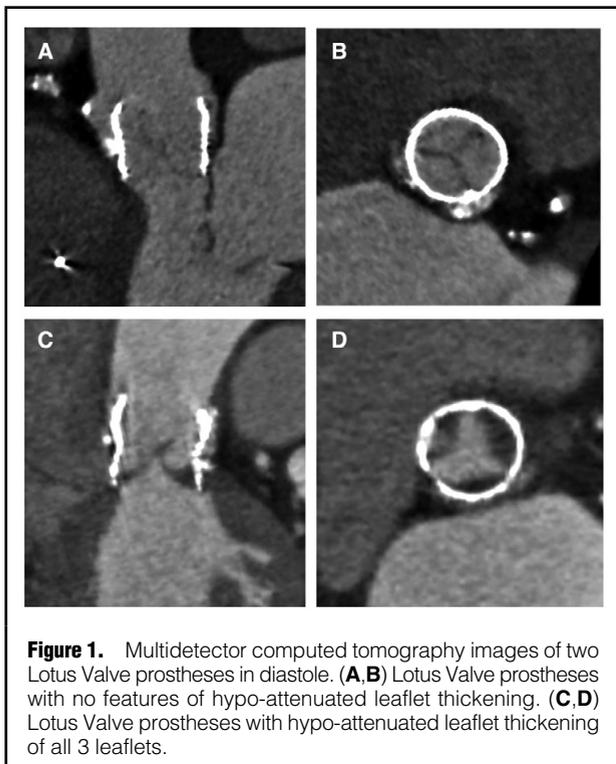
The hallmark feature of SLT on MDCT is hypoattenuation on the surface of bioprosthetic valve leaflets and leaflet

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Monash Cardiovascular Research Centre, Monash University and MonashHeart, Monash Health, Clayton, Victoria, Australia  
A.N. and R.P.G. are Joint senior author.

Mailing address: Robert P. Gooley, MBBS, PhD, Monash Cardiovascular Research Centre and MonashHeart, Monash Health, Melbourne, Victoria, Australia. E-mail: robert.gooley@monashhealth.org

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thickening.<sup>8,11</sup> This is frequently defined as hypoattenuated leaflet thickening (HALT) which is located on the leaflet surface when assessed on multiplanar reconstruction images obtained by MDCT<sup>1</sup> (Figure 1). These hypo-attenuating lesions are found on the aortic surface of the leaflet. The area of hypoattenuation almost invariably begins at the area of leaflet attachment and may extend, to a varying degree, along the transcatheter valve leaflet. Some studies have quantified the area of HALT by determining the largest area of HALT when examined on axial images (with en-face view of the valve) or the depth of leaflet thickness (in coronal view).<sup>9</sup> Interestingly, this has been shown to correlate with the degree of leaflet immobility.<sup>8</sup>

Leaflet immobility with MDCT was first described in the seminal paper by Makkar et al.<sup>12</sup> Through assessment with volume-rendered 4D MDCT, the mobility of bioprosthesis leaflets were assessed in 3 cohorts: a randomized trial (PORTICE IDE) and 2 large single-center registries [Sub-Clinical Aortic Valve Bioprosthesis Thrombosis Assessed with Four-Dimensional Computed Tomography (SAVORY) and Assessment of Transcatheter and Surgical Aortic Bioprosthetic Valve Thrombosis and Its Treatment with Anti-coagulation (RESOLVE)]. The authors defined significantly reduced leaflet motion (RELM) as moderate or greater leaflet immobility ( $\geq 50\%$  reduction). Findings from these 2 registries were further examined in a subsequent, larger sized analysis, which confirmed all cases with RELM had features of HALT, suggesting a temporal relationship between these conditions.<sup>10</sup>

A recently published article aimed to standardize the definition of SLT by describing a systematic Core-lab methodology to assess SLT with MDCT.<sup>5</sup> The initial step involved the assessment of HALT on transcatheter valve leaflets, which is performed during the diastolic phase in which the leaflets coapt. Prostheses with hypo-attenuating

lesion(s) detected on the leaflet surface were defined as HALT-positive leaflets. The presence of HALT can be further quantified by its maximal leaflet thickness (usually at the leaflet insertion point) and the total hypoattenuation area (HALT area) to determine the thrombus burden.

Prostheses that are HALT-positive are then assessed for RELM. The degree of RELM, assessed during systole at maximal leaflet opening, is calculated with the following equation:

$$\text{Degree of RELM (\%)} = \frac{\text{Width of HALT affected leaflet}}{\frac{1}{2} \times \text{Valve Diameter}} \times 100\%$$

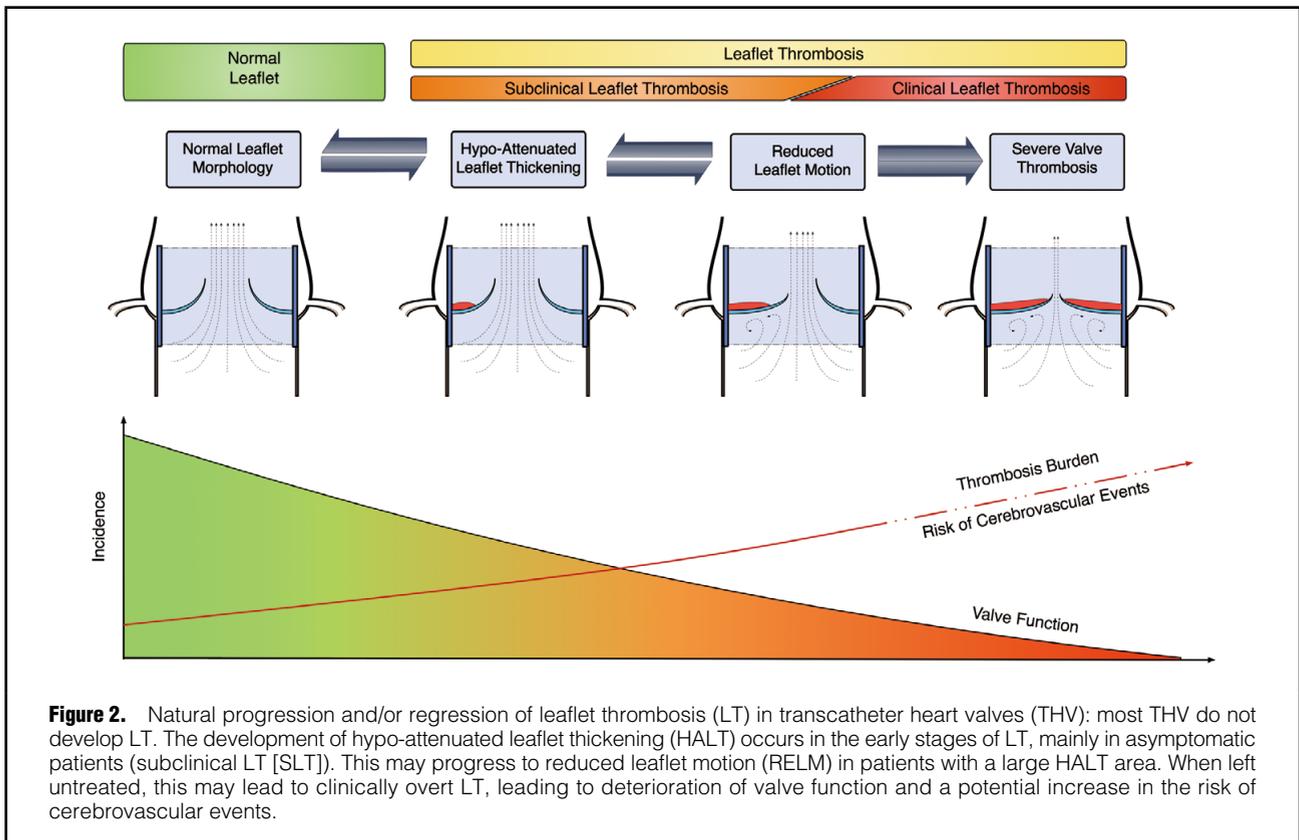
Leaflet immobility is graded as normal (no RELM), mild ( $< 50\%$  RELM), moderate (50–70% RELM), severe ( $> 70\%$  RELM) or immobile (100% RELM). The authors describe a new entity, hypoattenuation affecting motion (HAM), which is defined as moderate or greater leaflet immobility. Confusingly, this definition is similar to Makkar et al's initial definition of significant RELM,<sup>12–15</sup> though the term HAM has already been adopted in the current literature.<sup>9</sup> In situations where HALT 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.<sup>9</sup> The stent frame and thrombus were 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.

Transthoracic echocardiography (TTE) 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'.<sup>16</sup> 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.<sup>4,6</sup> 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.<sup>4</sup> 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.<sup>17</sup> Overall, the prevalence of SLT ranges from 7% to 40%, with the latter prevalence derived from



the PORTICO IDE trial that involved the self-expanding Portico valve (St. Jude Medical, Saint Paul, MN, USA).<sup>18</sup> This suggests the overall prevalence is highly variable and likely valve-specific.

Though mechanical surgical aortic valve thrombosis is a well-known phenomenon, little is known about SLT in bioprosthetic SAVR. In the same large registry of bioprosthetic valves, the prevalence of SLT with sutured or conventional surgical aortic valves was 4% (5 of 138 cases) and was less common when compared with transcatheter valves (13% or 101 of 752 cases) which was an independent risk factor for SLT on multivariate analysis.<sup>3</sup> However, a contemporary registry of a frequently used sutureless surgical bioprosthetic valve, the Perceval valve (LivaNova PLC, London, UK) revealed a much higher prevalence of SLT, with 38% of patients developing HALT.<sup>3,5,10</sup> Sutureless bioprosthetic valves are designed similarly to transcatheter valves, with a stent frame that anchors the valve to the aortic annulus and are deployed differently to sutured surgical bioprosthetic valves, which could explain the disparity in prevalence between the different type of surgical bioprostheses.

The onset and natural history of SLT are not well understood. Some studies report SLT occurring as early as 5 days post-implant on routine CT analysis,<sup>5</sup> while others have reported this phenomenon occurring much later (months to years).<sup>1</sup> Sequential CT studies have shown that the incidence of SLT slightly increases with time post-implantation.<sup>6,8</sup> It is hypothesized that when left untreated, SLT might lead to reduced effective orifice area and valve dysfunction, potentially converting to CLT.<sup>10</sup>

The severity of SLT may vary over time (**Figure 2**). A

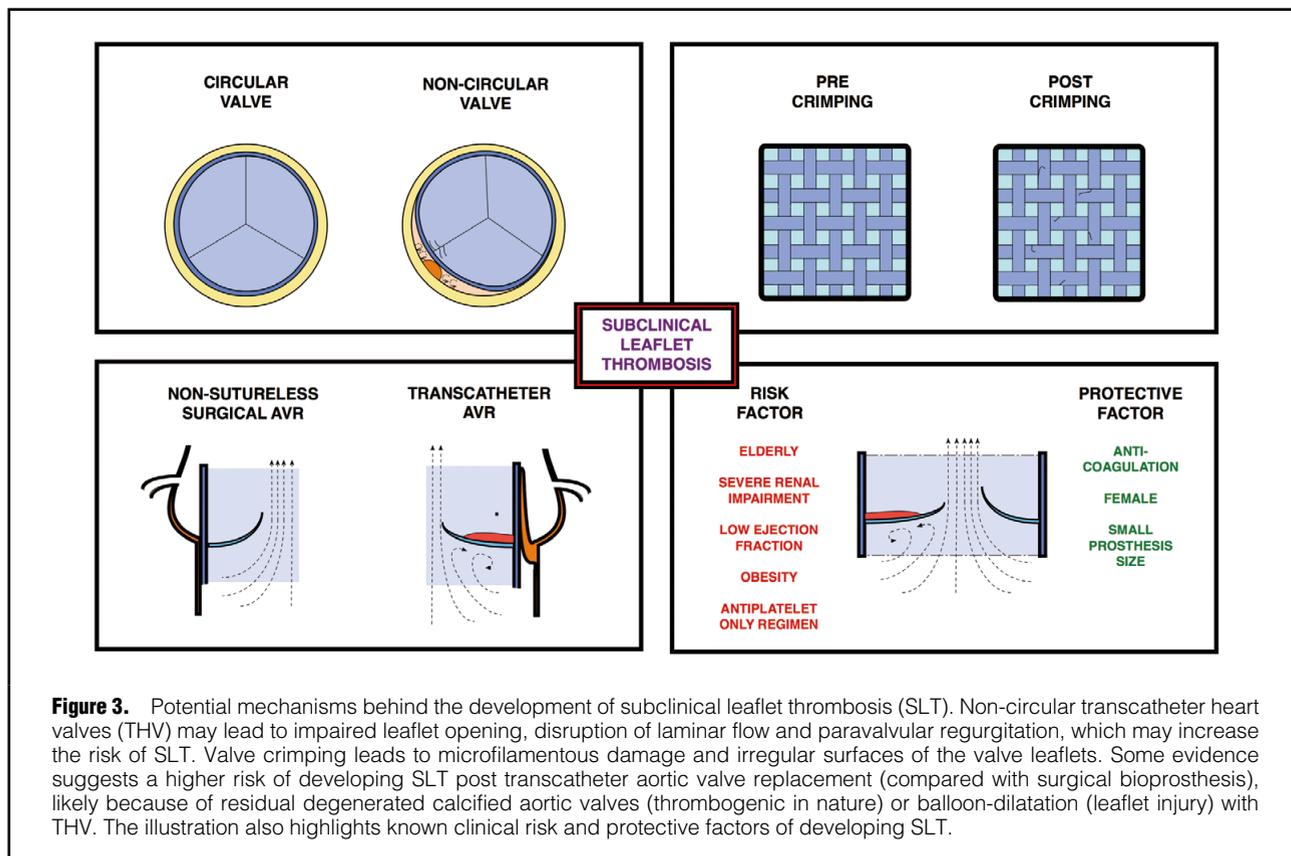
recent analysis of the SAVORY registry demonstrated that SLT could progress and regress variably with repeat MDCT imaging.<sup>6</sup> A total of 84 patients with SLT were analyzed by MDCT at 2 time points, at a mean of 140 and 298 days. Prosthesis SLT was classified into 3 subgroups depending on the 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 anti-coagulants 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<sup>19</sup> (**Figure 3**). Additionally, valve leaflets are exposed to further damage during initial deployment, especially in balloon-expandable valves, through direct



**Figure 3.** Potential mechanisms behind the development of subclinical leaflet thrombosis (SLT). Non-circular transcatheter heart valves (THV) may lead to impaired leaflet opening, disruption of laminar flow and paravalvular regurgitation, which may increase the risk of SLT. Valve crimping leads to microfilamentous damage and irregular surfaces of the valve leaflets. Some evidence suggests a higher risk of developing SLT post transcatheter aortic valve replacement (compared with surgical bioprosthesis), likely because of residual degenerated calcified aortic valves (thrombogenic in nature) or balloon-dilatation (leaflet injury) with THV. The illustration also highlights known clinical risk and protective factors of developing SLT.

trauma from forceful valve expansion.<sup>20</sup> Damage to the leaflet is further amplified during post-dilatation in under-expanded valves.<sup>21</sup> Lastly, the process of recapturing and resheathing in repositionable valves may also lead to surface leaflet abrasions and further leaflet damage.

Most of the demonstrated leaflet injury occurs at a microscopic level, with scanning electron microscopy revealing disruption of the collagen bundles and microfibrils of the leaflets.<sup>22</sup> Exposed collagen, in addition to a variegated leaflet surface, leads to increased surface thrombogenicity and subsequently, platelet activation. In vitro studies simulating crimped leaflets have demonstrated increased platelet and red blood cell clusters adhering to the surface of crimped, damaged fibrous layers.<sup>23</sup> The leaflet surface becomes a nidus for de novo thrombus formation, as has been observed on explanted transcatheter valves.<sup>24</sup>

The leaflet material could also contribute to its thrombogenicity, albeit to a lesser extent than the factors just discussed. Bioprosthetic surgical aortic valves with porcine pericardial leaflets have been shown to be an independent predictor of LT, as compared with bovine pericardial leaflets.<sup>25</sup> Though a similar association has not been conclusively demonstrated in transcatheter valves, it is an interesting finding because the Corevalve system (Medtronic, Minneapolis, MN, USA) consists of porcine leaflets whereas other valve systems such as the Edwards Sapien (Edwards Lifesciences, Irvine, CA, USA) and Lotus (Boston Scientific Inc., Malborough, MA, USA) valves consist of bovine leaflets.<sup>26</sup> We must be cautious in interpreting this in the context of transcatheter valves as TAVR prostheses have different structural designs than surgically implanted valves.

### Hemodynamic Flow Alteration

Low-flow severe aortic stenosis is defined as an aortic valve area  $>1.0\text{ cm}^2$  ( $0.6\text{ cm}^2/\text{m}^2$ ) 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  $40\text{ mmHg}$ .<sup>27</sup> 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).<sup>9</sup> 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.<sup>3,5</sup>

Local flow disturbance and turbulence at the level of the leaflet surface might promote platelet adhesion and activation. Large prosthesis size<sup>5,8</sup> and valve-in-valve deployment<sup>10</sup> have been shown to be predictors in the development of LT, likely because of alteration in flow patterns across the prosthesis,<sup>5</sup> but other studies have not reported similar findings.<sup>17</sup> 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.<sup>13-15</sup>

A recent study demonstrated the role of the neo-sinus in the development of SLT.<sup>9</sup> 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,<sup>1,5</sup> though this has not been consistently reported throughout the literature.<sup>3,8</sup>

Degenerated, calcified aortic valves demonstrate increased endothelial surface expression of tissue factors and activated factor XI, which may result in increased thrombogenicity.<sup>28</sup> 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.<sup>29</sup>

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.<sup>1,5</sup> 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.<sup>30,31</sup> Furthermore, commencement of anticoagulation with a VKA has been shown to result in regression,<sup>4</sup> and even resolution of SLT<sup>6</sup> in TAVR, but the role 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,<sup>32</sup> 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).<sup>12</sup> These findings were further confirmed with an updated SAVORY-RESOLVE registry in a larger cohort.<sup>3</sup> 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,<sup>5,7,8</sup>

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.<sup>16</sup> 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).<sup>1,6</sup> 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.<sup>1</sup> 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).<sup>1</sup>

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,<sup>33</sup> 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,<sup>30,31</sup> 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.<sup>34</sup> 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).<sup>34</sup> 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.<sup>31,34</sup> Even so, the clinical inclination has been

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

	AHA/ACC	ESC/EACTS
Year	2017	2017
Antiplatelet recommendation	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)	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)
Anticoagulation recommendation	Anticoagulation with VKA to achieve an INR of 2.5 may be reasonable for at least 3 months in patients with low bleeding risk (Class IIb, LOE C)	Oral anticoagulation is recommended lifelong in patients with other indications for anticoagulation (Class I, LOE C)

AHA, American Heart Association; ACC, American College of Cardiology; EACTS, European Association for Cardio-Thoracic Surgery; ESC, European Society of Cardiology; INR, international normalized ratio; LOE, level of evidence; VKA, vitamin K antagonist.

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

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

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.

to start anticoagulation, usually with VKAs, and results have demonstrated regression or resolution of SLT.<sup>4,6</sup> 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.<sup>35</sup> 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<sup>36</sup> 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 of all-cause death, ischemic stroke, major vascular complications 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.

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 factors such as renal impairment, inability to breath-hold or poorly controlled atrial fibrillation might limit the applicability and diagnostic accuracy of MDCT. Better patient selection through identifying patients at high risk of developing SLT and exclusion of patients with low diagnostic yield (poorly controlled atrial fibrillation and severe airways disease) might provide a systematic and practical method of screening patients with MDCT.

## Conclusions

SLT is a relatively common condition after TAVR. With TAVR being increasingly used worldwide in progressively lower risk patient cohorts, it is important to be aware of the presence, mechanisms, clinical sequelae and management options of SLT. Although much uncertainty still exists in this field, future studies have been planned to address key clinical questions, including predictors of this phenomenon, strategies for prevention and optimal treatment regimens.

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## Conflict of Interest Statement

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