doi:10.1093/eurheartj/ehx473

Leaflet Thrombosis after TAVI

During the last decade, transcatheter aortic valve implantation (TAVI) has become an important alternative to surgical aortic valve replacement (SAVR) in patients with aortic valve stenosis and at intermediate- or high-surgical risk. Although TAVI has technically matured, guidelines on post-procedural antithrombotic therapy are scarce and no randomized trials have explored what the best strategy is. Extrapolation from surgical bioprosthetic aortic valves also has limitations as the level of evidence is low, as well as different bioprosthetic valves are used and patients are treated.

Recently, four-dimensional volume-rendered computed tomography (4DCT) has revealed the presence of subclinical leaflet thrombosis in a significant number of patients who received surgical or transcatheter bioprosthetic aortic valves, *Figure 1*.[1] Thus, among 890 patients from the RESOLVE and SAVORY registries it was reported that five of 138 patients (3.8%) with subclinical leaflet thrombosis after SAVR and 101 of 752 patients (13.4%) after TAVI.[2] This valve leaflet thickening and reduced leaflet motion have—with reference to their CT appearance—been referred to as hypo-attenuating leaflet thickening (HALT) and the more severe hypo-attenuation affecting motion (HAM), respectively. Observations suggest that HALT and HAM are two stages of the same phenomenon, with leaflet thickening affecting leaflet motion at a more advanced stage. Although HAM may be associated with a small increase in transvalvular gradient, this is within the normal range in bioprosthetic aortic valves and will not allow for detection of HAM on transthoracic echocardiography. However, transoesophageal echocardiography will often visualize the reduced leaflet motion.

Apart from absence of anticoagulant therapy, there is no consistency in the reported risk factors for subclinical leaflet thrombosis.[1–4] The crimping of the transcatheter heart valves into the delivery system and post-dilatation of the valve prostheses have also been mentioned to potentially cause damage to the leaflets with an increased risk of leaflet thrombosis. However, the relative low incidence of the phenomenon may contradict this hypothesis. Furthermore, post-procedural suboptimal antiplatelet therapy (in clopidogrel non-responders) or the existence of an underlying inherited thrombophilia cannot be fully excluded in a subset of patients. In a recent in-depth analysis of the SAVORY registry, it was demonstrated that regional stent frame under-expansion of self-expanding transcatheter heart valves may be associated with a significantly higher incidence of leaflet thrombosis.

It is still a source of speculation whether subclinical leaflet thrombosis will impact the post-procedural outcome, e.g. increase the risk of stroke, or lead to early structural valve deterioration (SVD). Registry data suggest that the phenomenon may be associated with a higher prevalence of transient ischaemic attack (TIA), but not stroke.[2] However, these findings must be interpreted with caution due to a temporal separation between the 4DCT and the clinical event and prospective clinical studies are warranted. Likewise, there are no data available about the potential negative impact of subclinical leaflet thrombosis on the durability of bioprosthetic aortic valves. However, it has been reported that absence of anti-coagulation therapy is an independent risk factor for SVD after TAVR, but without exploring the presence of leaflet thrombosis.[5] Furthermore, it is unknown whether leaflet thrombosis can progress from a subclinical to a clinical state with symptoms and increased transvalvular gradient. In general, clinical leaflet thrombosis is relatively rare after TAVI with an occurrence of 0.6–2.8% and may be resolved by anticoagulant therapy.[6,7]

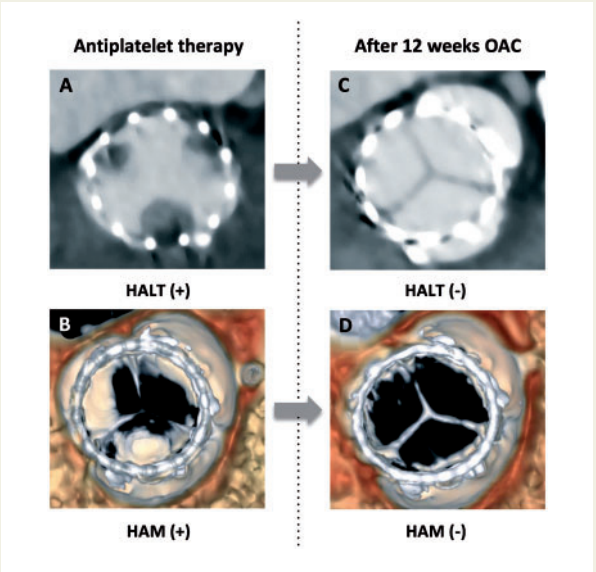

Figure 1 Four-dimensional, volume-rendered computed tomography showing hypo-attenuating leaflet thickening (HALT) with reduced leaflet motion [hypo-attenuation affecting motion (HAM)] in a transcatheter heart valve while under dual antiplatelet therapy (*A* and *B*). This leaflet thickening resolved after 12 weeks of effective (international normalized ratio 2–3) oral anticoagulant therapy (OAC) (*C* and *D*).

Guidelines/expert consensus statements typically recommend dual anti-platelet therapy for 1–6 months after TAVI followed by single anti-platelet therapy in patients without other indication for anti-coagulation. This relies mainly on the extrapolation of anti-thrombotic regimens following coronary artery stenting. However, despite the common presence of a metallic stent, coronary artery stenting and TAVI differ by a number of features that may influence thrombus formation, in particular, stent diameter, environment (atheromatic plaques vs. calcified annulus/leaflets), and the presence of prosthetic leaflets.

In the 2017 AHA/ACC focused update,[8] oral anti-coagulation therapy with a vitamin K antagonist is mentioned as a reasonable treatment option for at least 3 months after TAVI in all patients at low risk of bleeding (*Table 1*). For TAVI patients with other indications for oral anti-coagulation, a combination of anti-coagulation therapy plus aspirin or clopidogrel is commonly suggested. For surgical bioprosthetic aortic valves, oral anti-coagulation therapy was initially recommended during the first 3 months, which corresponds to the time for endothelialisation of the sutured ring. However, this rationale was challenged by series suggesting that anti-platelet therapy alone may have a better risk-benefit profile. This led to changes in the European and American guidelines stating that low-dose aspirin should be considered for the first 3 months after implantation of a bioprosthetic aortic valve with higher bleeding risk, *Table 1*.[8,9]

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Table 1 Antithrombotic therapy for bioprosthetic aortic valves

AHA/ACC guidelines	ESC/EACTS guidelines
Class I	**Class I**
	Oral anticoagulation is recommended lifelong for patients with bioprostheses who have other indications for anticoagulation. (*Level of Evidence: C*)
Class IIa	**Class IIa**
Aspirin 75–100 mg per day is reasonable in all patients with a bioprosthetic aortic valve. (*Level of Evidence: B*)	Low-dose aspirin should be considered for the first 3 months after implantation of an aortic bioprosthesis. (*Level of Evidence: C*)
Anticoagulation with a VKA to achieve an INR of 2.5 is reasonable for at least 3 months and for as long as 6 months after surgical bioprosthetic AVR in patients at low risk of bleeding. *(Level of Evidence: B)*	
Class IIb	**Class IIb**
Anticoagulation with a VKA to achieve an INR of 2.5 may be reasonable for at least 3 months after **TAVI** in patients at low risk of bleeding. *(Level of Evidence: B)*	
Clopidogrel 75 mg daily may be reasonable for the first 6 months after **TAVI** in addition to life-long aspirin 75-100 mg daily. (*Level of Evidence: C*)	Oral anticoagulation may be considered for the first 3 months after implantation of an aortic bioprosthesis. (*Level of Evidence: C*)
	Expert consensus
	Despite the lack of evidence, a combination of low-dose aspirin and a thienopyridine is used early after **TAVI**, followed by aspirin or a thienopyridine alone.
	In **TAVI** patients in AF, a combination of a VKA and aspirin or thienopyridine is generally used, but should be weighed against increased risk of bleeding.

TAVI-specific recommendations are indicated in grey shaded.
AF, atrial fibrillation; AVR, aortic valve replacement; INR, international normalized ratio; TAVI, transcatheter aortic valve replacement; VKA, vitamin K antagonist.

One highly relevant question is whether the clinical practice should be changed based on these new insights for subclinical leaflet thrombosis. Currently, routine 4DCT to evaluate for subclinical leaflet thrombosis should not be performed outside clinical studies, as this will expose patients to radiation and contrast without evidence that a positive silent finding may have any clinical impact. In addition, there is currently not sufficient evidence to change the general recommendations for anti-thrombotic therapy following TAVI. However, patients who after TAVI or SAVR present with a new stroke/TIA or an increased transvalvular gradient may be considered for 4DCT and oral anticoagulant therapy in case leaflet thrombosis is present.

Both vitamin-K antagonists and novel oral anti-coagulants seem to protect against this phenomenon.[2] However, it is not yet clear whether a short-term course or life-long therapy with these oral anticoagulants will be needed, as there may exist a temporal dynamic pattern of evolution of this phenomenon.[10] This means, that subclinical leaflet thrombosis may develop or regress early or late after valve replacement, even without change in anti-thrombotic regime. Thus, short-term anti-coagulation may not necessarily protect against leaflet thrombosis at a later stage. On-going randomized controlled trials exploring different anti-thrombotic regimes will provide important information to the field (NCT01559298; NCT01642134; NCT02247128; NCT02556203; NCT02664649; NCT02735902). An interesting sub-study to the GALILEO trial will explore the frequency of leaflet thrombosis following TAVI during novel oral anticoagulants and antiplatelet therapy (NCT02833948).

In conclusion, it is currently recommended not to change clinical practice with regards to the choice of a transcatheter or surgical bioprosthetic aortic valve. TAVI has become an important and life-saving treatment option for patients with severe aortic stenosis, and the current uncontrolled data do not justify a limitation to the further expansion of this therapy.

Although anti-coagulation therapy prevents leaflet thrombosis, this may be associated with higher risk of bleeding. Therefore, it is currently not recommended to use anti-coagulation as routine post-procedural anti-thrombotic management. Instead, it is recommended to await the on-going randomized clinical trials between TAVI and SAVR, where a subset of patients will undergo 4DCT imaging, as well as the above-mentioned trials investigating different anti-thrombotic regimes following TAVI.

Lars Sondergaard MD DMSc
Corresponding author:
Rigshospitalet, University of Copenhagen
Blegdamsvej 9,
2100 Copenhagen, Denmark
Phone: +45 35458693,
Fax +45 35452705,
email lars.00.soendergaard@rh.regionh.dk

Sigitas Cesna[1,2], Manik Chopra[1], Gintautas Bieliauskas[1], Ole De Backer[1]

[1]The Heart Center, Rigshospitalet, University of Copenhagen, Denmark; [2]Centre of Cardiology and Angiology, Vilnius University, Vilnius, Lithuania

Conflict of interest: none declared.

References

References are available as supplementary material at *European Heart Journal* online.

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