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VIEWPOINT

Subclinical leaflet thrombosis: should we be concerned?

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Since the first transcatheter aortic valve implantation (TAVI) on 16 April 2002, by the late Alain Cribier, as a percutaneous treatment for aortic stenosis, multiple studies have demonstrated the efficacy and safety of this approach. Over the last decade, with a refinement in imaging techniques and broad use of TAVI bioprostheses, subclinical leaflet thrombosis (SLT), quantified via four-dimensional computed tomography angiography (4D-CTA) and the imaging correlates, hypoattenuated leaflet thickening (HALT) and reduced leaflet motion have been identified as early complications after TAVI. In the clinical reality of patients without an indication for oral anticoagulation, core lab rates of HALT at 30 days and 1 year have been described at 24.5% and 32.0%, respectively[1]. Additionally, HALT does fluctuate regardless of medical therapy: most of the patients who had it at 1 month were not the same as those who had it at 1 year.

The impact of SLT on cardiovascular outcomes and early degeneration of TAVI bioprostheses remains poorly understood, with conflicting results reported in the literature. Hence, as controversy surrounds the clinical relevance of SLT, we should be considering several aspects.

Does subclinical leaflet thrombosis matter with regard to cardiovascular outcomes?

Whilst an increased risk for short-term adverse cardiovascular events (most commonly, thromboembolic cerebral events) was described in the initial studies that characterised SLT, this association has been inconsistent in more contemporary datasets. A recent meta-analysis of 25 studies described an increased rate of cerebral events in individuals with SLT; however, this was mainly driven by transient ischaemic attacks[2]. Interestingly, in the Evaluation of Cerebral Thromboembolism After TAVR (EARTH-TAVR) study, an associated substudy of the GALILEO (Global Study Comparing a rivAroxaban-based Antithrombotic Strategy to an antipLatelet-based Strategy After Transcatheter aortIc vaLve rEplacement to Optimize Clinical Outcomes) trial, the investigators were able to showcase that even when using magnetic resonance imaging, the presence of SLT was not correlated with the new thromboembolic lesions on serial imaging[3]. In addition, no differences in haemodynamic parameters, including orifice area and mean pressure gradients of the newly implanted valves, were noted in this study, nor in other registry-based reports with longer-term follow-up. Hence, it is to be debated whether SLT represents a finding with major immediate clinical impact, or an imaging observation with limited short-term and unknown long-term consequences. On the other hand, its relevance to future pannus formation and bioprosthetic valve degeneration appears plausible and remains worrisome.

Does a pharmacological treatment benefit the affected patient?

Furthermore, because of the increased recognition of SLT, numerous studies have investigated the impact of antithrombotic strategies in the treatment of this entity. As the first large-scale trial in this space, the GALILEO study investigated the impact of an antithrombotic approach centred around intermediate-dose rivaroxaban (10 mg daily) compared to a dual antiplatelet strategy in TAVI patients. Whilst rivaroxaban treatment showed greater efficacy in averting impaired leaflet motion in the imaging substudy, it was linked to a surprisingly elevated likelihood of mortality, as well as an expected increased risk of bleeding[4]. Subsequent randomised studies (e.g., full-dose apixaban in the ATLANTIS trial) documented similar results, again in patients without any indication for chronic oral anticoagulation. However, these trials were restricted to mostly short to intermediate follow-up, limiting the clinical relevance of those findings. Although the indication for TAVI is continuously being expanded to the lower-risk population, a relevant proportion of individuals undergoing TAVI still have comorbidities and are, therefore, more vulnerable to bleeding events. Here, the use of non-vitamin K antagonist oral anticoagulants

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(NOACs) in the absence of any other indication for oral anticoagulation should be debated critically, especially in frail and elderly patients. In reaction to this uncertainty, the 2021 European Society of Cardiology and the European Association for Cardio-Thoracic Surgery Guidelines for the management of valvular heart disease endorse the selected use of oral anticoagulants in patients with computed tomographic findings of SLT in parallel with elevated gradients as a Class IIa, Level of Evidence B recommendation, at least until an improvement in imaging findings is noted[5]. On the other hand, the lessons from the 4D-CTA studies can be very helpful once significant HALT is documented in patients with an elevated transvalvular gradient (after TAVI or surgically implantation); an intermediate dose of rivaroxaban, full dose of apixaban or appropriately adjusted dose of edoxaban or warfarin (for a target international normalised ratio [INR] of 2-3) may be utilised for a short term. Subsequent echocardiographic and 4D-CTA imaging can monitor their success and guide their potential continuation or interruption/modification.

Should routine screening be carried out?

The use of 4D-CTA has become the gold standard for the detection of SLT, since the noted changes are mostly undetectable via transthoracic or transoesophageal echocardiography. Currently, a routine 4D-CTA imaging screening after TAVI is not recommended. Also, since it is still unclear which patients are most likely to (a) develop SLT and (b) suffer an SLT-associated adverse event, including early valve degeneration, a clinically pertinent algorithm on valve imaging during the follow-up period remains to be established. Transthoracic echocardiography to track the transvalvular gradients is still the most popular and easiest imaging method.

Hence, the question remains: does SLT matter? Given the context of the currently available data, this cannot be answered with certainty. As discussed, the use of TAVI globally is growing continuously and is being expanded to younger patients. In these individuals with extended life expectancy, SLT and its potential long-term sequelae could be of greater importance than in the previously investigated rather elderly populations (with significant comorbidities). These younger patients could represent the population in whom SLT truly does matter, and concern by their treating cardiologists with regard to adverse outcomes and potential valve degeneration is warranted. Therefore, further clinical investigation on the optimal pharmacological treatment in patients without a definite indication for oral anticoagulation should continue. Finally, studies concerning both the natural history of SLT in this growing patient population and the efficacy, as well as safety, of treatment approaches using intensified antithrombotic regimens need to be carried out to substantiate this hypothesis with randomised trial data.

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Conflict of interest statement

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