

EDITORIAL COMMENT

# Hypoattenuated Leaflet Thickening in Transcatheter and Surgical Aortic Valves\*



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In 2015, Makkar et al. (1) detected a reduced leaflet motion (RLM) by 4-dimensional computed tomography (CT) in a patient included in the PORTICO IDE (The Portico Re-sheathable Transcatheter Aortic Valve System U.S. Investigational Device Exemption [PORTICO IDE] study: a prospective clinical trial to evaluate TAVR with either a Portico valve [St. Jude Medical] or a commercially available valve) study who had had a stroke after transcatheter aortic valve replacement (TAVR). It was the beginning of the story of possible subclinical leaflet thrombosis in bioprosthetic valves, a phenomena referred to as hypoattenuating leaflet thickening (HALT), with reference to their CT appearance (2). Questions raised by these observations were (3):

1. What is the incidence of HALT and RLM?
2. Is it restricted to TAVR or is it observed after surgical aortic valve replacement (SAVR)?
3. Is it device-specific or is it distributed equally among all bioprosthetic models?
4. What is the natural course of these abnormalities?
5. Is thrombus the causal mechanism?
6. What is the clinical significance of RLM and HALT, especially in terms of stroke and structural valve deterioration?
7. What therapeutic strategy should be adopted?

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Several registries analyzed the possible subclinical leaflet thrombosis among high-risk patients who underwent TAVR. Because of the rapid clinical adoption of TAVR in low-risk patients, the interest of the report by Blanke et al. (4), now published in this issue of the *Journal*, is to provide additional elements of response to these questions in a cohort of low-risk patients randomly allocated to undergo either TAVR or SAVR.

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Among the 1,403 patients randomized in the Evolut Low Risk trial (5), which showed the noninferiority of TAVR versus SAVR in low-risk patients, 318 patients without anticoagulants had an evaluable CT scan performed at 30 days (179 in the TAVR arm and 139 in the SAVR group).

The incidence of HALT was 16.9% at 30 days without a significant difference between TAVR and SAVR (17.3% vs. 16.5%;  $p = 0.85$ ). The frequency of RLM was also similar between TAVR and SAVR (14.6% vs. 14.3%;  $p = 0.48$ ). The repeated CT investigation at 1 year showed an increased rate of HALT (30.9% vs. 28.4%;  $p = 0.66$ ) and RLM (31% vs. 27%;  $p = 0.48$ ). The investigators found that HALT was dynamic in the first year after the procedure, with some spontaneous resolution between the 30-day and 1-year examination, whereas others without HALT at 30 days developed it at 1 year. This dynamic natural course of HALT could explain the large range of incidence (4% to 40%) reported in other series, depending on the timing of the CT scan. Unlike the results of the SAVORY (Subclinical Aortic Valve Bioprosthesis Thrombosis Assessed with Four-Dimensional Computed Tomography) registry and a recent meta-analysis on observational studies (6,7), which suggested a higher rate of HALT among transcatheter than surgical valves (13% vs. 4% and 13.2% vs. 3.6%, respectively), the paper by Blanke et al. (4) reported a

similar incidence in both type of devices in a randomized study, at both 30-day and 1-year follow-up. This was the first prospective randomized study to use a strict definition of HALT as detected by CT scan with a standardized data acquisition, analyzed by a core laboratory. The robustness of the methodology used in the current study made me more confident in these results than in those of previous registries or observational studies. If there was only 1 design (supra-annular self-expanding) of transcatheter valve evaluated, the investigators compared different types of surgical bioprostheses and showed that HALT was significantly more frequent with sutureless valves (25% at 30 days; 37% at 1 year) compared with stented valves (11.3% and 20.9% at 30 days and 1 year, respectively). These observations are in line with the study by Dalen et al. (8) who reported 38% of HALT at 491 days after Perceval (LivaNova PLC, London, United Kingdom) sutureless implantation. Moreover, Blanke et al. (4) detected predicting factors for HALT that were different for transcatheter than for surgical valves. Major predictors of HALT at 30 days were identified as female sex and small aortic annulus for TAVR, while it was a sutureless valve in the surgical arm. More important information provided by the study by Blanke et al. (4) was that the use of oral anticoagulants (OACs) was not a predictor of HALT in both groups. The investigators reported that only 50% of patients had sustained HALT between 30-day and 1-year CT and that many patients experienced a spontaneous resolution at 1 year without the use of OACs. Unlike the GALILEO (Global Study Comparing a Rivaroxaban-Based Antithrombotic Strategy to an Antiplatelet-Based Strategy after Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes) study (9), which reported a lower incidence of subclinical leaflet motion abnormalities using a low dose of rivaroxaban rather than antiplatelet therapy or other smaller series that reported the reduction of leaflet thickening observed under OAC and not under antiplatelet therapy, Blanke et al. (4) suggested that HALT was a dynamic phenomenon and not completely predictable by using OAC. One of the main limitations that supported this statement was that inclusion criteria were the absence of OACs at the time of 30-day CT, but some of these patients received OACs at the 1-year CT investigation (13% in the TAVR group and 17.2% in the SAVR group). Several observations reported a gradient normalization in parallel of the disappearance of HALT under OACs, which was confirmed in only 1 case of the

current study, where >75% leaflet thickening and 2 affected leaflets were detected by CT.

Despite all these observations by CT, the echocardiographic transvalvular gradients remained low in both groups at all times, regardless of HALT or RLM. This could be related to the low percentage of >1 observed thickened leaflet in the current study. These results conflicted with those of SAVORY and the RESOLVE (Assessment of Transcatheter and Surgical Aortic Bioprosthetic Valve Thrombosis and Its Treatment with Anticoagulation) registry or other smaller series, which reported a higher rate of moderate structural valve deterioration in cases of subclinical valve thrombosis. The potential residual empty spaces at low velocities between the stent frame and the native calcium in case of suboptimal implantation could favor thrombus deposit that might change over time due to endothelialization and/or continued expansion of the stent frame modifying the stent geometry. These technical elements could explain the discrepancies between the studies in which CT scan was performed at different post-procedural periods. The design of the prosthesis could have an impact as well; some data suggest a higher rate of HALT in annular design versus supra-annular design or in new generation versus past generation of balloon-expandable valves. However, there was no randomized study that provided a head-to-head comparison of transcatheter valves that focused on the rate of thrombosis.

Regarding clinical consequences, Blanke et al. (4) reassured that there was no association between HALT and stroke, transient ischemic attack, or death up to 1 year, whereas an increase of transient ischemic attack but not of stroke was described in observational studies.

To conclude, the paper of Blanke et al. (4) provides a reliable response to the 3 first questions: the rate of HALT; the equality between surgical bioprostheses and self-expanding supra-annular transcatheter valves implanted in low-risk patients; and the risk factor of using sutureless bioprosthesis.

Regarding the impact of HALT on valve hemodynamics and on the clinical outcome, currently, doubt persists due to conflicting results between studies and the low rate of events in the study by Blanke et al. (4). The question of the optimal approach remains open: should we adopt systematic anticoagulation? No, according to the results of the GALILEO study. Does the use of OAC have no impact? I am not convinced by the study by Blanke et al. (4). Additional studies are needed to prospectively investigate

the impact of OACs on subclinical leaflet thrombosis and its relationship with structural valve deterioration and thromboembolic events. The dosage, the type, and the duration of medication should be evaluated in addition to the type of patients with the greatest benefit, guided by well-identified risk factors that are probably different for transcatheter valves than surgical valves.

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**KEY WORDS** aortic valve, hypoattenuated leaflet thickening, leaflet thrombosis