Editorial

Valve thrombosis after transcatheter aortic valve replacement—cause for concern?

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Submitted Mar 05, 2020. Accepted for publication Mar 20, 2020.
doi: 10.21037/acs.2020.04.04
View this article at: http://dx.doi.org/10.21037/acs.2020.04.04

Bioprosthetic aortic heart valves

In patients with severe, symptomatic aortic stenosis, there has been a gradual shift from mechanical to bioprosthetic valves used in surgical aortic valve replacement (SAVR). This has partly been driven by a desire to avoid oral anti-coagulation therapy (OAC), as well as the perception that degenerated surgical bioprosthetic valves can be treated with implantation of a transcatheter heart valve (THV). In addition, several randomized clinical trials have provided the evidence for a paradigm shift towards transcatheter aortic valve replacement (TAVR), particularly in elderly patients with aortic stenosis. However, the bioprosthetic valves have limited longevity when compared to mechanical heart valves with a constant risk of structural valve deterioration (SVD), including valve thrombosis.

Thrombosis on bioprosthetic aortic heart valves

Although bioprosthetic valves are less thrombogenic than their mechanical counterparts, valve thrombosis is an important issue. Clinical valve thrombosis is defined as prosthetic valve dysfunction with the typical finding of a thrombus on the valve accompanied with an elevated transvalvular pressure gradient and often symptoms of heart failure or left-sided thromboembolic events. Clinical valve thrombosis has been reported to be relatively rare after TAVR with an incidence of 0.6–2.8%, and OAC may resolve the thrombosis and elevated gradient as well as clinical symptoms (1,2).

A more common finding in both transcatheter and surgical bioprosthetic aortic valves is subclinical leaflet thrombosis, with a thin layer of thrombosis on the aortic side of one or more of the bioprosthetic leaflets. This phenomenon is best visualized on four-dimensional volume-rendered computed tomography (4DCT) as Hypo-Attenuating Leaflet Thickening (HALT), which in some cases will affect the leaflet motion and is therefore termed Hypo-attenuation Affecting Motion (HAM) (3-6). Risk factors for subclinical leaflet thrombosis have not been fully identified, but it has been proposed that under-expansion of the stent frame is associated with an increased rate of subclinical leaflet thrombosis, whereas post-dilatation of self-expanding THV reduces the risk (7). The clinical relevance of subclinical leaflet thrombosis is also still unclear in terms of association with thrombo-embolic events and SVD. Although, a previous observational study has shown an association between subclinical leaflet thrombosis and cerebrovascular events. One important limitation of this observation is a long temporal separation between the clinical event and the 4DCT (6). Furthermore, even though subclinical leaflet thrombosis can be resolved by OAC, it is also a temporal dynamic phenomenon which can spontaneously progress from normal leaflet over HALT to the more severe HAM, and similar regression at different time stages (8). In a recent 4DCT sub-study of the PARTNER 3 trial, half of the leaflets with HALT detected at 30 days after TAVR were without thrombosis one year post-procedure even without OAC, whereas HALT appeared in 20% of patients at one year despite normal leaflet at 30 days (Makkar RR *et al.* TCT 2019). Based on the dynamic nature of subclinical leaflet thrombosis, it is

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difficult to link this thrombosis to cerebrovascular events.

Impact of anti-thrombotic therapy on subclinical leaflet thrombosis

OAC, including direct oral anticoagulants (DOAC), seem to both prevent and resolve subclinical leaflet thrombosis as compared to single or dual antiplatelet therapy (6). These preliminary findings complicate recommendations for optimal anti-thrombotic therapy after TAVR or SAVR, since life-long (D)OAC treatment is associated with an increased bleeding risk in elderly patients. While the indication for TAVR relies on randomized clinical trials, the antithrombotic strategy after TAVR has until now mostly been based on expert consensus. However, the GALILEO trial provided new insights for considering optimal anti-thrombotic therapy after TAVR. A total of 1,644 patients were randomized to: (I) rivaroxaban 10 mg daily plus aspirin 75–100 mg daily for 3 months, followed by rivaroxaban 10 mg daily as monotherapy, versus; (II) aspirin 75–100 mg daily plus clopidogrel 75 mg daily for 3 months, followed by aspirin 75–100 mg daily as monotherapy. The primary outcome of the study was a composite endpoint of major, disabling, or life-threatening bleeding or death. The GALILEO trial revealed that DOAC was associated with a higher risk of death or thrombo-embolic complications and a higher risk of bleeding than an antiplatelet-based strategy in this elderly patient cohort (9). On the other hand, in the GALILEO-4D sub-study, a total of 231 patients after TAVR were evaluated with 4DCT at 90 days after randomization (10). In this analysis, the rivaroxaban group showed lower rates of subclinical leaflet thrombosis of at least one leaflet (12.4%) than the antiplatelet group (32.4%). Furthermore, the rate of HAM was also lower in the rivaroxaban group (2.1%) than in the antiplatelet group (10.9%), suggesting that the rivaroxaban-based strategy was more effective in preventing subclinical leaflet thrombosis, despite the rivaroxaban group being associated with higher risk of bleeding and death. Other ongoing randomized clinical trials between different anti-thrombotic regimes may provide further evidence in this field (AUREA NCT01642134, POPULAR-TAVI NCT02247128, ATLANTIS NCT02664649, AVATAR NCT02735902).

Current recommendations regarding subclinical leaflet thrombosis

How should we act with regard to subclinical leaflet thrombosis at the present time? First of all, despite the fact that DOAC treatment after TAVR is effective in reducing subclinical leaflet thrombosis, anticoagulation cannot be recommended as routine therapy after TAVR for patients without any previous indication due to a higher incidence of death/life-threatening events without providing substantial benefits to the patients. Potential links between subclinical leaflet thrombosis and cerebrovascular events or early SVD need to be investigated in prospective trials in order to determine whether this phenomenon is a cause of concern.

For the time being, routine 4DCT to evaluate for subclinical leaflet thrombosis should not be performed outside of clinical studies, as this will expose the patients to radiation and contrast without any evidence that a positive silent finding indicates OAC therapy. On the other hand, patients who, after TAVR or SAVR, present with a new stroke/TIA or an increased transvalvular gradient may be considered for 4DCT and anticoagulation therapy in case of valve thrombosis.

Acknowledgments

Funding: MF is supported by a research grant from Japan Heart Foundation/Bayer Yakuhin Research Grant Abroad.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Sibilitz KL, Fukutomi M, Sondergaard L. Valve thrombosis after transcatheter aortic valve replacement—cause for concern? Ann Cardiothorac Surg 2020;9(6):505-507. doi: 10.21037/acs.2020.04.04

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