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EDITORIAL COMMENT

Subclinical Thrombosis of Bioprosthetic Aortic Valves*

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Transcatheter aortic valve replacement (TAVR) is now a safe, effective, and durable treatment strategy for symptomatic patients with severe aortic stenosis (AS), across the entire spectrum of surgical risk (1). Since its inception, concerns regarding the thrombogenicity of transcatheter bioprosthetic valves coupled with weak supporting evidence have led to significant uncertainty and variability in the use of antithrombotic therapies after TAVR (2). Initial clinical practice guidelines recommended the use of dual antiplatelet therapy for a period of 3 to 6 months post-TAVR based on extrapolations from the experience with metallic coronary stent and histopathology studies suggesting that the time frame of bioprosthetic valve neoendothelialization occurs during this time period (2). In parallel, emerging data suggested that a significant proportion of patients post-TAVR have findings on computed tomography (CT) imaging compatible with leaflet thrombosis, which appeared to be associated with increased risk of thromboembolic events and were reversed or prevented by oral anticoagulation (OAC), but not by antiplatelet therapy (3,4). In response to these findings and with the expansion of TAVR to younger patients with severe AS, the U.S. Food and Drug Administration mandated CT ancillary studies to be incorporated into the TAVR trials of patients at low surgical risk to understand the natural history of subclinical leaflet thrombosis of transcatheter and surgical bioprosthetic valves and its association with valve hemodynamics and clinical outcomes (5).

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In this issue of the *Journal*, Makkar et al. (6) present the results of the 4-dimensional CT ancillary study from the PARTNER (Placement of AoRTic TraNscathetER Valve Trial) 3 trial, which randomized patients with severe AS at low risk for surgery to TAVR using the Sapien 3 (Edwards Lifescience, Irvine, California) device versus surgical aortic valve replacement (SAVR) with a bioprosthetic valve. Patients were eligible for inclusion in this study if they had no pre-existing indication for anticoagulation and no contraindication to undergo a CT scan with contrast at sites with the ability to perform high-quality multiphasic, electrocardiogram (ECG)-gated 4D-CT acquisitions. Patients underwent cardiac 4D-CT at 30 days and 1 year after TAVR or SAVR. All 4D-CTs were analyzed by an independent core laboratory blinded to patient information, with 1-year CTs analyzed independently of the 30-day CT findings. Also, the treating investigators were blinded to the results of the CT scans. Primary imaging endpoints of interest were the percent of hypoattenuated leaflet thickening (HALT) and reduced leaflet motion (RLM) at 30 days and 1 year after randomization. HALT was defined as an increased leaflet thickness with meniscal appearance on long-axis views at the time of leaflet coaptation (in diastole). In the event of

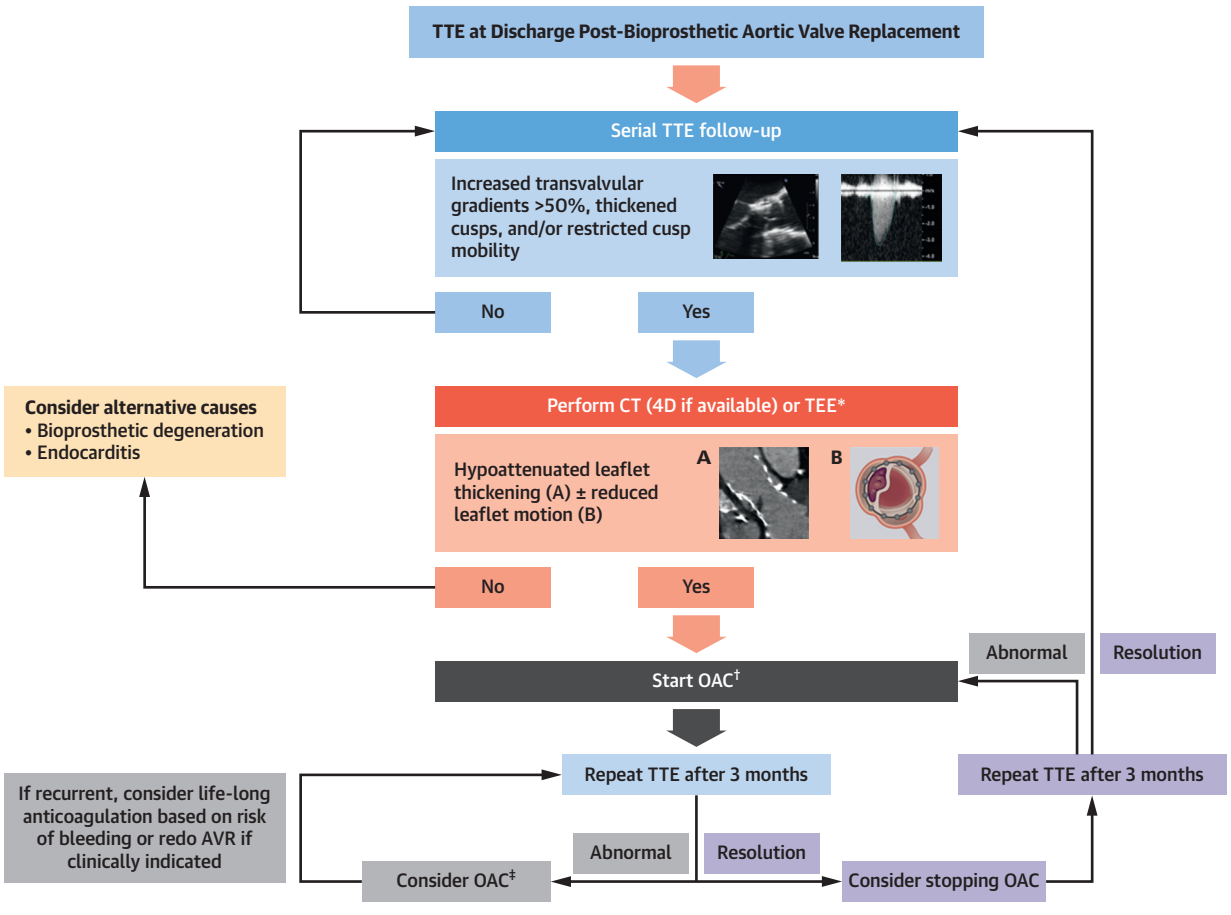
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FIGURE 1 Clinical Decision-Making Algorithm for the Detection and Treatment of Bioprosthetic Aortic Valve Thrombosis



*If CT is contraindicated. †With a vitamin-K antagonist or a direct oral anticoagulant. ‡Consider changing type of anticoagulant if persistent. 4D = 4-dimensional; AVR = aortic valve replacement; CT = computed tomography; OAC = oral anticoagulation; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

patients with HALT, the presence of RLM was evaluated as normal leaflet motion, partially restricted, and immobile. A total of 435 patients at 48 sites were randomly assigned to undergo either TAVR (221 patients) or SAVR (214 patients), of whom 4.7% and 21.0% were discharged on anticoagulation in the TAVR and SAVR groups, respectively. The authors found that HALT was significantly more frequent after TAVR than after SAVR at 30 days (13% vs. 5%). However, at 1 year there were no significant differences in HALT between TAVR and SAVR (28% vs. 20%). The prevalence of HALT fluctuated over time, such as that among the patients with HALT at 30 days, spontaneous resolution was observed at 1 year in 56% of cases in the absence of anticoagulation. Conversely, among patients without HALT at 30 days, new HALT was observed at 1 year in 21% of patients. Of note, patients who were on OAC at the time of 4D-CT were less likely to have HALT and RLM at both 30 days and 1 year. In terms of transthoracic echocardiography (TTE) findings, there were modest but not statistically significant differences at 30 days in mean transvalvular gradient in patients with HALT compared with those without HALT (13.2 ± 0.81 mm Hg vs. 11.7 ± 0.24 mm Hg); however, there was a graded relationship between greater degrees of HALT burden and mean transvalvular gradient, ≈5 mm Hg higher in those with more extensive or persistent HALT. Overall, the rates of clinical endpoints at 1 year were low; however, HALT at any

timepoint (30 days or 1 year) was associated with higher rates of stroke, transient ischemic attack, or thromboembolic complications as well as clinical valve thrombosis.

This study has several strengths. This is the first randomized comparison between TAVR using a current-generation balloon-expandable device and SAVR to evaluate the incidence of subclinical leaflet thrombosis, and therefore, it adds to prior observational studies (3,4). The treating physicians were blinded to the results of the 4D-CT to not alter the natural history of this phenomenon by prescription of OAC. However, nearly 5 times more patients were prescribed OAC in the SAVR group at the time of discharge (most likely for new-onset atrial fibrillation) compared with the TAVR group, which, at least in part, could explain the differences in the frequency of HALT at 30 days.

These results need to be placed into perspective with the recently completed GALILEO (Global Study Comparing a rivAroxaban-based Antithrombotic Strategy to an antipLatelet-based Strategy After Transcatheter aortIc vaLve rEplacement to Optimize Clinical Outcomes) trial, which was the first randomized controlled trial investigating the efficacy and safety of OAC with the factor Xa-inhibitor rivaroxaban after successful TAVR in patients without an established indication for OAC. In the main GALILEO trial, which included 1,644 patients with a mean age of ≈80 years, a 10-mg rivaroxaban-based antithrombotic strategy was associated with a higher risk of death or thromboembolic complications and a higher risk of bleeding than an antiplatelet-based strategy (7). Of note, the rates of clinical valve thrombosis were low (≈0.6 per 100 person-years at a median follow-up time of 17 months) but numerically reduced with the use of a rivaroxaban-based antithrombotic strategy (0.4 vs. 0.9 per 100 person-years) (7). In the ancillary GALILEO 4D-CT study, the rivaroxaban-based strategy was more effective than the antiplatelet-based strategy in reducing HALT (12.4% vs. 32.4%) and RLM (12.4% vs. 31.7%) (8); however, these effects did not translate into significant improvement in valve hemodynamics evaluated with TTE or in reductions of thromboembolic events (8). Therefore, based on these results, a strategy of routine anticoagulation after TAVR appears to have an unfavorable risk-benefit balance in this patient population.

After SAVR with bioprosthetic valves, a short course of OAC is recommended to reduce the risk of thromboembolism while endothelialization of the bioprosthetic valve is ongoing (2). However, although this approach has been used in clinical practice for more than 50 years, it is not supported by solid evidence (2). The possible sequelae of subclinical leaflet thrombosis include thromboembolism, early bioprosthetic valve degeneration, and progression toward clinical valve thrombosis (2). The relatively short follow-up of this study precludes evaluating the impact of early HALT/RLM on long-term durability and rates of degenerative bioprosthetic valve dysfunction at the present time. Whether a strategy of routine short-term anticoagulation is associated with a favorable risk-benefit balance in younger patients with less comorbidities warrants further evaluation with both transcatheter and surgical bioprosthetic valves.

After more than a decade of investigations, TAVR has been demonstrated to improve quality of life and prolong survival in appropriately selected patients with severe AS (1). However, the clinical significance of subclinical bioprosthetic valve thrombosis, as detected by advanced imaging, remains uncertain. The fluctuating nature of this phenomenon, its resolution even in the absence of OAC, and the unclear benefits of preventing it with OAC question the utility of a routine CT imaging follow-up. In addition, a 4D-CT imaging modality may not be available in real-world settings, and not all patients can undergo CT imaging with contrast (e.g., patients with renal dysfunction). Therefore, monitoring of patients post-TAVR should focus on a comprehensive clinical assessment and standardized TTE evaluation of bioprosthetic valve function. The use of CT should be triggered by alarming TTE findings followed by the use of therapeutic anticoagulation to reverse thrombosis-related bioprosthetic valve dysfunction. If CT is contraindicated or inconclusive, transesophageal echocardiography may be used for the evaluation of leaflet thickness and motion. A clinical decision-making algorithm for the detection and treatment of bioprosthetic aortic valve thrombosis integrating these concepts is provided in **Figure 1**.

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