EDITORIAL COMMENT

Shedding More Light on Valve Thrombosis After Transcatheter Aortic Valve Replacement*

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Based on strong evidence from randomized clinical trials and large registries, transcatheter aortic valve replacement (TAVR) has been enthusiastically embraced as a lifesaving and life-changing therapy for older, frail patients with severe aortic stenosis who are either inoperable or at high risk for conventional surgical aortic valve replacement (SAVR). Currently more than 200,000 patients worldwide have received such a valve, including >50,000 patients in U.S. pivotal trials with 1 of the 3 valves commercially approved by the Food and Drug Administration (FDA). These valves, Sapien XT and Sapien 3 (Edwards Lifesciences, Irvine, California) and CoreValve Evolut R (Medtronic, Inc., Minneapolis, Minnesota), have shown no significant clinical signal of early structural valve deterioration or valve thrombosis with follow-up to 5 years (1,2).

Recently, however, several reports of structural leaflet abnormalities have surfaced in both TAVR and SAVR, thus indicating that presumptive bioprosthetic valve leaflet thrombosis may be a more important issue than previously realized (3–6). The issue has been further addressed by 2 editorials including 1 by regulators from the FDA (7,8). In addition to abnormal findings noted at the time of clinical events (which may or may not have been related), the abnormalities have been detected in 2 ways: 1) by leaflet immobility, with or without thrombus, detected using sophisticated imaging, either 4-dimensional computed tomography (4D CT) or transesophageal echocardiography (TEE); or 2) by an abnormal interval increase in transvalvular gradients detected by continuous-wave Doppler imaging on transthoracic echocardiography (TTE) that is believed to indicate valve hemodynamic deterioration (VHD) (9).

The paper by Del Trigo et al. (10) in this issue of the Journal sheds further light on this condition that has, until recently, likely been underdiagnosed. In a series of 1,521 patients in a multicenter registry from 10 centers in 4 countries who had at least 2 TTE examinations post-TAVR, the investigators evaluated the incidence of VHD, defined as a ≥10 mm Hg increase in mean gradient during the follow-up period compared with discharge assessment, and early VHD, defined as the same increase occurring within the first year after TAVR. Using annualized changes in transvalvular mean gradients after TAVR on TTE, these investigators found a 4.5% incidence of VHD at a mean follow-up of 20 months. Independent predictors of the finding were the absence of anticoagulation, use of a valve-in-valve procedure, use of a 23-mm valve, and a greater body mass index.

Therefore, a natural question to ask is this: With such a strong evidence base in randomized trials and 8 years of commercial experience, why is this issue just now coming to light? First, the pivotal studies for approval performed only pooled analyses for hemodynamic changes over time that are unlikely to detect significant changes in a small percentage of individual patients. Pooled analyses of mean gradients could mask a low, but important, incidence of

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individual changes in mean gradients, as has been detected in this study. Second, the analyses could be subject to survivorship bias in that only alive patients could be evaluated at each time point for hemodynamic changes. Third, the findings of leaflet immobility or thrombus, or both, are detectable only on 4D CT and TEE; until recently, these imaging techniques were not used for surveillance. Fourth, in part because the valve abnormalities have not been previously noted, they are poorly correlated with clinical events, which have been the focus of most studies to date.

What are the takeaways from this study and the other recently published papers that have preceded it? And what are the critical issues now facing the burgeoning TAVR field?

1. The relationships among the abnormalities seen with imaging, the hemodynamic changes seen with TTE, and clinical events remain unclear, and clarification of these relationships is critical.

2. We do not know the incidence of these findings, either individually or in aggregate. Consecutive patient surveillance studies using 4D CT and TEE, as well as hemodynamic studies with follow-up TTE, should begin immediately. These studies should use standard definitions to allow comparison and then be merged with clinical, patient-specific data.

3. A wealth of unmined data currently exists in trial databases and registries. These data should be reviewed for hemodynamic changes occurring in individual patients, as well as in patients who have experienced adverse clinical events, including death, stroke, and heart failure. These data sources include the pivotal trial data from commercially approved devices, as well as the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry.

4. All patients undergoing TAVR should be monitored for incremental increases in transvalvular mean gradient by TTE. If a pre-specified but somewhat arbitrary gradient increase of ≈10 mm Hg is seen, more sophisticated imaging should be performed. Although the present report used a definition of VHD of ≈10 mm Hg, this cutpoint needs to be validated in larger series, including imaging data correlated with clinical outcomes.

5. If an interval increase in transvalvular mean gradient is detected, there should be consideration of anticoagulation, on the basis of a clinical evaluation of risk versus benefit in that individual patient.

6. It is unknown whether VHD is a specific device effect or a class finding. All TAVR valves and bioprosthetic SAVR valves should be carefully scrutinized.

7. Clinicians should be vigilant regarding possible VHD in patients undergoing TAVR or SAVR who experience clinical events. These patients should undergo 4D CT scanning or TEE as well as the more routine TTE.

8. Patients with possible risk factors for valve thrombosis or premature structural valve deterioration should be closely scrutinized through appropriate follow-up surveillance programs with more frequent screening.

9. If VHDF or a leaflet abnormality is detected, a trial of anticoagulation before repeat valve replacement should be strongly considered if bleeding risks for the individual patient allow it.

10. Anticoagulation should be considered in the first 3 months in those patients at highest risk for valve thrombosis, including patients who have had a valve-in-valve procedure, those with a high body mass index, or patients who receive smaller 23-mm valves and, therefore, may be more likely to have a patient-prosthesis mismatch.

11. Proposed and ongoing randomized trials evaluating the role of anticoagulation including novel oral anticoagulant and antiplatelet therapies should be strongly supported and expeditiously enrolled. Such trials include GALILEO (the Global Study Comparing a rivArOXaban-based Anti-thrombotic Strategy to an antiPlatelet-based Strategy After Transcatheter aortic vaLve rEplacement to Optimize Clinical Outcomes), which evaluated rivaroxaban versus dual antiplatelet therapy, and CLOE (Clopidogrel to Lower advErse ischemic events after transcatheter aortic valve) (aspirin vs. dual antiplatelet therapy).

12. Any new trial for further label expansion of TAVR use should include routine imaging surveillance, with findings correlated with possible predisposing clinical factors and association or causation with clinical events.

TAVR has undeniably benefited thousands of patients with severe aortic stenosis. However, as with any new therapy, adverse events and limitations—many unanticipated—may gradually become known as usage and experience expand. Over the past 2 years, light has been shed on the issue of subclinical valve thrombosis and VHD. It has become clear that the harder one looks, the more one finds. More light needs to be shed on this issue, including determining
the true incidence, clinical significance, predisposing factors, prevention, and treatment of valve thrombosis after TAVR. Expeditious answers to these questions are critical as this field continues to expand.

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