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Subclinical Valve Thrombosis in Sutureless Bioprosthetic Valves

Bobby Yanagawa, MD, PhD; Subodh Verma, MD, PhD; C. David Mazer, MD, FRCPC

In the current issue of *JAHA*, Dalén et al[1] report the results of a single-center prospective observational study of 47 patients with implantation of the Perceval sutureless bioprosthesis (LivaNova, Milan, Italy). Cardiac computed tomography (CT) performed at a median of 491 days (range 36–1247 days) found hypo-attenuated leaflet thickening (HALT) in 18 (38%) and reduced leaflet motion (RLM) in 13 (28%) patients. HALT affected a single leaflet in 10 (56%), 2 leaflets in 6 (33%), and all leaflets in 2 patients (11%). The mean HALT leaflet thickening was 3 mm. For RLM, 1 leaflet was affected in 11 and 2 leaflets in 2 patients. Surprisingly, 5 of 18 patients with HALT (28%) and 3 of 13 patients with RLM (23%) were receiving anticoagulants at the time of CT. In fact, there was no significant difference in warfarin use between HALT and no HALT groups (22% versus 14%, P=0.45), but there was a trend towards reduced novel oral anticoagulant use in patients with HALT (6% versus 28%, P=0.06). Clinically, there were 3 strokes and 1 transient ischemic attack but no association with presence of HALT and RLM.

Makkar et al[2] first alerted the cardiovascular community to the existence of a significant and previously unrecognized risk of prosthetic leaflet motion reduction following transcatheter aortic valve replacement (TAVR) and bioprosthetic surgical aortic valve replacement (SAVR) in the absence of formal anticoagulation. It was hypothesized that this reduced leaflet motion was caused by subclinical leaflet thrombosis, which may trigger premature structural valve deterioration and constitute a nidus for cerebral thromboembolic events. The measures of valve thrombosis are HALT and RLM. The clinical consequences of such phenomena, and the role of anticoagulation for prevention and treatment are uncertain. This report by Dalén et al[1] adds important data to the overall literature of HALT and RLM and is the first report of protocol-driven CT focusing on sutureless SAVR.

Subclinical valve thrombosis is a newly recognized clinical entity that has been described in a variety of surgical and transcatheter bioprostheses.[3–10] These patients may present with early significant increases in transvalvular gradients and even overt thrombosis. Del Trigo et al[8] reviewed 1521 patients who underwent TAVI to find that 4.5% experienced clinical premature valve hemodynamic deterioration and an independent risk factor was no anticoagulation, suggesting that the mechanism was thrombosis related. Egbe et al[9] examined explanted bioprostheses at the Mayo Clinic (mean 24 months) and found that overt thrombosis (11% in the aortic position) was associated with HALT and RLM. The importance of this issue of subclinical valve thrombosis is underscored by the fact that the seminal study prompted the Food and Drug Administration to state that, “if reduced leaflet motion is detected by imaging, treatment options should be discussed with the team of physicians responsible for the patient’s care.”[11] Full anticoagulation with warfarin is currently the only treatment shown to reverse leaflet motion reduction in observational studies, although high-quality data in this regard are lacking.

Sutureless valves are bioprosthetic valves that are implanted in an open surgical procedure but require few or no sutures, thus allowing for significantly shortened cardiopulmonary bypass and cross-clamp times.[12,13] Sutureless valves are particularly useful for redo aortic procedures with calcified annuli that do not allow for conventional annular suturing, multiple valve procedures to reduce surgical times, and to facilitate minimally invasive procedures. There has previously been a single case report of early valve thrombosis with a size S sutureless SAVR.[14] Given that HALT and RLM have been reported with conventional SAVR and TAVR, it is not surprising that they also occur with sutureless SAVR.

What is surprising from this study is that the incidence of HALT and RLM was higher than that in the published literature for SAVR and even for TAVR.[2,10] In a recent report from the Assessment of TRanscathetEr and Surgical Aortic

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From the Division of Cardiac Surgery (B.Y., S.V.) and Department of Anesthesia (C.D.M.), Li Ka Shing Knowledge Institute of St Michael’s Hospital, University of Toronto, Ontario, Canada.

Correspondence to: C. David Mazer, MD, FRCPC, Department of Anesthesia, St. Michael’s Hospital, University of Toronto, 30 Bond St, Toronto, Ontario, Canada M5B 1W8. E-mail: mazerd@smh.ca

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BiOprosthetic VaLVe Thrombosis and Its TrEatment With Anticoagulation (RESOLVE) and the Subclinical Aortic Valve Bioprosthesis Thrombosis Assessed with Four-Dimensional Computed Tomography (SAVORY) registries, 12% of 890 patients undergoing SAVR and TAVR had subclinical leaflet thrombosis: 4% for SAVR and 13% for TAVR.[10] As Dalén et al have correctly explained, sutureless SAVR and some TAVR devices share the presence of a stent, the need for leaflet crimping or collapsing, and the need for balloon dilation (Medtronic Corevalve is self-expandable), all of which may contribute to thrombogenic potential. Also, all patients in this study were treated with low-dose aspirin or warfarin/novel oral anticoagulant alone. This is consistent with routine medical management post-SAVR.[15] However, whether the metallic stent of the sutureless SAVR is thrombogenic remains to be determined. If so, there may be an advantage to the use of more potent antithrombotic therapy with sutureless SAVR. On the other hand, unlike TAVR, in which the native valve is left in situ, for sutureless SAVR, the diseased leaflets and any large annular calcific deposits are removed, thus theoretically optimizing aortic root blood flow. Furthermore, there is less risk of suboptimal device implantation as the sutureless valve is placed under direct vision and an improperly implanted valve can easily be recognized, removed, and reimplanted. Finally, as a possible explanation of the increased incidence of HALT and RLM, the time point for CT in this study was considerably longer than in previous studies of early valve thrombosis.[3–10] More information about the incidence of RLM in sutureless and stentless aortic valves will be provided from the upcoming BELIEVE (Behavior of Valve Leaflets) study (NCT03200574).

Contrary to published studies, HALT and RLM were seen in patients receiving oral anticoagulation, and there was no significant difference in the use of warfarin or novel oral anticoagulant in patients with subclinical thrombosis compared with those without.[1] In the RESOLVE and SAVORY registries, subclinical leaflet thrombosis was seen less frequently among patients receiving anticoagulants and, in patients not already on anticoagulants, leaflet thrombosis completely resolved with initiation of anticoagulation.[2,10] It is possible that differences in warfarin management including the involvement of a thrombosis clinic or the use of home international normalized ratio monitoring may account, in part, for the variability in the observed incidence of subclinical thrombosis.

Also, in this study, there were few cerebral embolic events reported and no association with stroke was identified, but HALT and RLM were associated with increased rates of transient ischemic attacks. Early reports of subclinical thrombosis suggested a possible association with cerebral embolism,[1] but more recent studies have not found this link.[16,17] Further studies with protocol-driven cerebral imaging will be needed to better understand the cerebral embolic risk. Other important questions to address include whether subclinical valve leaflet thrombosis occurs in bioprostheses implanted in the mitral, tricuspid, or pulmonic positions, and what the natural history of this phenomenon is for all valve positions.

Given the uncertain but potentially adverse clinical consequences, there is an urgent and unaddressed need to study early postoperative valve structure and function, and evaluate the safety and efficacy of oral anticoagulation approaches for all prostheses. There are discordant positions in current clinical practice guidelines regarding short-term oral anticoagulation post-SAVR and no specific guidelines regarding the use of antiplatelet agents and anticoagulation for sutureless SAVR.[18–20] In the www.clinicaltrials.gov database, several recently posted randomized controlled trials are comparing standard of care versus anticoagulation following TAVR and SAVR with HALT and RLM as an outcome: (1) 1 small single-center, pilot trial at the Cleveland Clinic (Frequency of Reduced Leaflet Motion After Surgical Aortic Valve Replacement and Transcatheter Aortic Valve Replacement; NCT02696226); (2) a 300-patient randomized controlled trial comparing aspirin versus rivaroxaban postbioprosthetic SAVR (Comparison of a Rivaroxaban-based Strategy With an Antiplatelet-based Strategy Following Successful TAVR for the Prevention of Leaflet Thickening and Reduced Leaflet Motion as Evaluated by Four-dimensional, Volume-rendered Computed Tomography [4DCT] [GALILEO-4D]; NCT02833948); (3) a 200-patient randomized controlled trial comparing anticoagulation versus standard of care for thrombosis post-TAVR: RETORIC (Rule Out Transcatheter Aortic Valve Thrombosis With Post Implantation Computed Tomography; NCT02826200); and (4) a 1000-patient randomized controlled trial comparing aspirin versus rivaroxaban postbioprosthetic SAVR (NCT02974920). In the RESOLVE (NCT02318342), 1000 patients with early bioprosthetic valve thrombosis will be treated with warfarin for 3 months and resolution will be assessed by CT. These prospective studies along with the BELIEVE study will introduce high-quality evidence regarding the incidence of subclinical thrombosis and the optimal antithrombotic therapy for the subacute period following TAVR and bioprosthetic SAVR. The results of these studies may provide data supporting a possible change in current recommendations and practice patterns, and may lead to a larger end-point trial of major adverse cardiovascular events. The work by Dalén et al is an important early step in this journey.

Disclosures

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