Journal of the American Heart Association

EDITORIAL

Putting a Halt to HALT: Does Anticoagulation Matter?

Abe DeAnda Jr, MD; Hani Jneid, MD

A temporary set-back to the then rapidly emerging field of transcatheter aortic valve replacement (TAVR) occurred in September of 2014, when St. Jude Medical temporarily halted implantation of their transcatheter valve. As part of PORTICO IDE (Portico Re-sheathable Transcatheter Aortic Valve System US IDE Trial), a subgroup of enrolled patients underwent postimplant imaging with multidetector computed tomography (MDCT) assessment of the stent frame of the implanted valve. In one patient who had experienced a cerebral embolic event, the MDCT had identified decreased leaflet motion consistent with thrombosis. Subsequent analysis of other patients as well as later data from 2 registries (the RESOLVE [Assessment of Transcatheter and Surgical Aortic Bioprosthetic Valve Thrombosis and Its Treatment With Anticoagulation] registry and the SAVORY [Subclinical Aortic Valve Bioprosthesis Thrombosis Assessed With Four-Dimensional Computed Tomography] registry) confirmed the low but real rate of either hypoattenuated leaflet thickening (HALT) or reduced leaflet motion, both presumably secondary to leaflet thrombosis.[1] In most cases, patients with HALT or reduced leaflet motion were asymptomatic or had subclinical findings.

See Article by Imaeda et al.

The Food and Drug Administration (FDA) weighed in, requesting computed tomographic evaluation as part of all future studies. Significantly, while the FDA recognized the presence of HALT, they also noted that the significance of this finding was unknown.[2] As data from the registries as well as other studies,[3] including a subgroup analysis of the PARTNER (Placement of Aortic Transcatheter Valves) 3 trial,[4] demonstrated a not insignificant occurrence of subclinical valve thrombosis, it became apparent that PORTICO IDE was not alone with this finding, and the study recommenced with eventual FDA approval.

As transcatheter aortic valve replacement expands into younger and lower surgical risk patients, continued concern remains of structural valve failure/dysfunction, including valve thrombosis. These concerns are not limited to TAVR only, as similar findings of HALT and reduced leaflet motion have been shown with surgically implanted tissue valves, with varying degrees of incidence and significance and various types of TAVR platforms.[1,3–7]

In the current study in this issue of the *Journal of the American Heart Association* (*JAHA*), Imaeda et al have retrospectively reviewed patients who had implantation of the Edwards Sapien XT TAVR, performed during October 2013 to December 2015.[8] Their analysis of MDCT data included the presence or absence of HALT at 1 year, and further reviewed outcomes out to a median follow-up period of 4.7 years. Valve function was assessed with transthoracic echocardiography and included indexed effective orifice area, mean pressure gradient, and indexed stroke volume. The primary outcome was a composite of all-cause mortality, heart

Key Words: Editorials ■ anticoagulants ■ TAVI

Correspondence to: Abe DeAnda, MD, Division of Cardiothoracic Surgery, UTMB-Galveston, 301 University Boulevard, Galveston, TX 77551.
Email: abdeanda@utmb.edu

For Disclosures, see page 2.

JAHA is available at: www.ahajournals.org/journal/jaha

failure readmission, and ischemic stroke. There was no surgical valve comparison. This study focused on the clinical outcomes of patients with and without HALT. The authors found an incidence of HALT at 1 year of 21.8% (27 of 124 patients), which was similar to the incidence of 24% seen in the PARTNER 3 trial. When comparing the two groups over the median time period of 4.7 years, there was no significant difference in the primary outcome or in the secondary outcomes of all-cause mortality, cardiovascular death, heart failure readmission, or ischemic stroke. Of the valve function measurements from transthoracic echocardiography, only indexed effective orifice area decreased significantly in the HALT group over the 5-year period.

The anticoagulation strategy used by Imaeda et al consisted of dual antiplatelet therapy for 6 months, followed by indefinite therapy with either aspirin or clopidogrel.[8] Significantly, if HALT was detected, the therapy was not altered or expanded. In the current study, this approach did not alter the incidence of either the composite primary outcome or ischemic stroke. One weakness was the specification of ischemic stroke as it pertains to a neurological event, ie, this did not include transient ischemic attacks or reversible ischemic neurological deficits. The incidence of either of these entities is unknown, as is the significance. In an evaluation of the RESOLVE/SAVORY registries, HALT was associated with an increased risk of transient ischemic attack (5% versus 1%, P=0.002).[5]

HALT is a dynamic process with still unknown significance in the long term. The finding of HALT at any time point does not extrapolate to worsening valve function or adverse clinical outcomes, at least in the short term. In both the SAVORY registry[9] and the PARTNER 3 trial[4] there were instances of resolution of HALT as well as new findings of HALT after an earlier MDCT, which did not detect the leaflet findings.

The authors conclude that anticoagulation may not be critical for the management of HALT, especially in the elderly cohort, of which their patients were. They go further in questioning whether monitoring with MDCT is necessary especially when the treatment will not change based on the results because there was no difference in adverse outcomes between patients with and without HALT. However, as TAVR moves into the realm of younger patients and as valve-in-valve procedures become more frequent, both which conceptually increase the risk of developing leaflet dysfunction, it would be important to not accept the results of Imaeda et al as pertinent to all patients with TAVR. Instead, it would be prudent to heed the original concern of the FDA when the PORTICO IDE was being evaluated—"Whether reduced leaflet motion is clinically meaningful or represents a subclinical advanced-imaging phenomenon, the loss of leaflet mobility renders the valve dysfunctional and demands additional investigation."

ARTICLE INFORMATION

Affiliations

Division of Cardiovascular and Thoracic Surgery (A.D.) and Division of Cardiovascular Medicine, UTMB-Galveston, Galveston, TX (H.J.).

Disclosures

None.

REFERENCES

1. Makkar RR, Fontana G, Jilaihawi H, Chakravarty T, Kofoed KF, De Backer O, Asch FM, Ruiz CE, Olsen NT, Trento A, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med*. 2015;373:2015–2024. doi: 10.1056/NEJMoa1509233
2. Laschinger JC, Wu C, Ibrahim NG, Shuren JE. Reduced leaflet motion in bioprosthetic aortic valves – The FDA perspective. *N Engl J Med*. 2015;373:1996–1998. doi: 10.1056/NEJMp1512264
3. Leetmaa T, Hansson NC, Leipsic J, Jensen K, Poulsen SH, Andersen HR, Jensen JM, Webb J, Blanke P, Tang M, et al. Early aortic transcatheter heart valve thrombosis: diagnostic value of contrast-enhanced multidetector computer tomography. *Circ Cardiovasc Interv*. 2015;8:e001596. doi: 10.1161/CIRCINTERVENTIONS.114.001596
4. Makkar RR, Blanke P, Leipsic J, Thourani V, Chakravarty T, Brown D, Trento A, Guyton R, Babaliaros V, Williams M, et al. Subclinical leaflet thrombosis in transcatheter and surgical bioprosthetic valves. PARTNER 3 cardiac computed tomography substudy. *J Am Coll Cardiol*. 2020;75:3003–3015. doi: 10.1016/j.jacc.2020.04.043
5. Chakravarty T, Sondergaard L, Friedman J, De Backer O, Berman D, Kofoed KF, Jilaihawi H, Shiota T, Abranowitz Y, Jorgensen TH, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet*. 2017;389:2059–2069. doi: 10.1016/S0140-6736(17)30757-2
6. Ruile P, Minners J, Breitbart P, Schoechlin S, Gick M, Pache G, Neumann FJ, Hein M. Medium-term follow-up of early leaflet thrombosis after transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. 2018;11:1164–1171. doi: 10.1016/j.jcin.2018.04.006
7. Yanagisawa R, Tanaka M, Yashima F, Arai T, Jinzaki M, Shimizu H, Fukuda K, Watanabe Y, Naganuma T, Higashimori A, et al. Early and late leaflet thrombosis after transcatheter aortic valve replacement. *Circ Cardiovasc Interv*. 2019;12:e007349. doi: 10.1161/CIRCINTERVENTIONS.118.007349
8. Imaeda S, Inohara T, Yoshijima N, Kobari Y, Myojin S, Ryuzaki T, Hattori O, Shinada K, Tsuruta H, Takahashi T, et al. Natural history of leaflet thrombosis after transcatheter aortic valve replacement: a 5-year follow-up study. *J Am Heart Assoc*. 2022. doi: 10.1161/JAHA.122.026334
9. Sondergaard L, De Backer O, Kofoed KF, Jilaihawi H, Fuchs A, Chakravarty T, Kashif M, Kazuno Y, Kawamori H, Maeno Y, et al. Natural history of subclinical leaflet thrombosis affecting motion in bioprosthetic aortic valves. *Eur Heart J*. 2017;38:2201–2207. doi: 10.1093/eurheartj/ehx369