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Bioprosthetic Aortic Valve Leaflet Thickening in the Evolut Low Risk Sub-Study

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ABSTRACT

BACKGROUND Subclinical leaflet thrombosis has been reported after bioprosthetic aortic valve replacement, characterized using 4-dimensional computed tomographic imaging by hypoattenuated leaflet thickening (HALT) and reduced leaflet motion (RLM). The incidence and clinical implications of these findings remain unclear.

OBJECTIVES The aim of this study was to determine the frequency, predictors, and hemodynamic and clinical correlates of HALT and RLM after aortic bioprosthetic replacement.

METHODS A prospective subset of patients not on oral anticoagulation enrolled in the Evolut Low Risk randomized trial underwent computed tomographic imaging 30 days and 1 year after transcatheter aortic valve replacement (TAVR) or surgery. The primary endpoint was the frequency of HALT at 30 days and 1 year, analyzed by an independent core laboratory using standardized definitions. Secondary endpoints included RLM, mean aortic gradient, and clinical events at 30 days and 1 year.

RESULTS At 30 days, the frequency of HALT was 31 of 179 (17.3%) for TAVR and 23 of 139 (16.5%) for surgery; the frequency of RLM was 23 of 157 (14.6%) for TAVR and 19 of 133 (14.3%) for surgery. At 1 year, the frequency of HALT was 47 of 152 (30.9%) for TAVR and 33 of 116 (28.4%) for surgery; the frequency of RLM was 45 of 145 (31.0%) for TAVR and 30 of 111 (27.0%) for surgery. Aortic valve hemodynamic status was not influenced by the presence or severity of HALT or RLM at either time point. The rates of HALT and RLM were similar after the implantation of supra-annular, self-expanding transcatheter, or surgical bioprostheses.

CONCLUSIONS The presence of computed tomographic imaging abnormalities of aortic bioprostheses were frequent but dynamic in the first year after self-expanding transcatheter and surgical aortic valve replacement, but these findings did not correlate with aortic valve hemodynamic status after aortic valve replacement in patients at low risk for surgery. (Medtronic Evolut Transcatheter Aortic Valve Replacement in Low Risk Patients; NCT02701283)
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The presence of possible subclinical leaflet thrombosis has been reported after aortic valve replacement using both surgical and transcatheter bioprostheses (1). It has been best characterized using 4-dimensional (4D) computed tomographic (CT) imaging of the aortic bioprosthesis and characterized as hypoattenuated leaflet thickening (HALT) and reduced leaflet motion (RLM). Although HALT and RLM have been reported in multiple series after transcatheter aortic valve replacement (TAVR) (1–7), the clinical implication of these findings and their relationship to clinical valve thrombosis and clinical events have been less clear.

To better assess the frequency and clinical importance of HALT and RLM after bioprosthetic valve replacement, we performed a prospective assessment of these parameters in randomized low-risk patients undergoing TAVR or surgery using 4D CT imaging early and later after aortic valve replacement. We then correlated these imaging findings with valve hemodynamic status and clinical outcomes.

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METHODS

The Evolut Low Risk trial was a multicenter, prospective, randomized trial in which the safety and efficacy of TAVR and surgery were compared in patients with an estimated risk for mortality after surgery <3% on the basis of heart team assessment. Primary results and details of patient selection and methodology have been published (8). The LTI substudy was a pre-specified component of the Evolut Low Risk trial. The trial, including the LTI substudy, was conducted in compliance with the International Conference on Harmonization and the Declaration of Helsinki. It was approved by local Institutional Review Boards or medical ethics committees. An informed consent addendum specific to this imaging substudy was signed by all patients.

STUDY DESIGN AND POPULATION. The LTI substudy was conducted at 49 sites in the United States, Canada, and Japan with the capability to perform high-quality electrocardiographically synchronized CT scans on validated equipment (see the Supplemental Appendix for a complete listing of investigators and study committees; Supplemental Table 1). Patients who underwent valve implantation in the Evolut Low Risk trial were eligible for inclusion in the LTI substudy, with the exclusion of those with histories of stage IV or V chronic kidney disease (estimated glomerular filtration rate <30 ml/min) or atrial fibrillation that could not be controlled to a ventricular response rate <60 beats/min. Use of oral anticoagulation (OAC) therapy post-procedure was an exclusion criterion to enrollment at the start of the study but was later allowed at the discretion of the operator so that patients could be on OAC at the time of the CT scan. The recommended post-procedural antithrombotic regimen for the TAVR group was 1 month of dual-antiplatelet therapy (aspirin plus a thienopyridine), followed by aspirin alone through 1 year. The recommended medication regimen for the surgery groups was aspirin alone or with OAC according to standard of care. However, empirical OAC

ABBREVIATIONS AND ACRONYMS

4D = 4-dimensional

CT = computed tomographic

HALT = hypoattenuated leaflet thickening

LTI = leaflet thickening or immobility

OAC = oral anticoagulation

RLM = reduced leaflet motion

TAVR = transcatheter aortic valve replacement

Abbott Vascular, Medtronic, Boston Scientific, and Edwards Lifesciences; and has served on Medical Advisory Boards for Boston Scientific and Edwards Lifesciences. Dr. Yakubov has received institutional research grants from Boston Scientific, Edwards Lifesciences, and Medtronic; and has served on the Medical Advisory Board for Medtronic and Boston Scientific. Dr. Deeb serves on an Advisory Board and as a proctor for Medtronic; is a consultant and research investigator for Edwards Lifesciences; is a consultant and proctor for Terumo; and is a research investigator for Gore Medical, with all fees paid to his institution. Dr. Gada has received personal fees from Medtronic, Abbott Vascular, Boston Scientific, and Bard. Dr. Mumtaz has received consulting fees from Medtronic, Abbott, the Japanese Organization for Medical Device Development, and Terumo; has received grants and consulting fees from Edwards Lifesciences; and serves on the cardiac events committee for Millipede. Dr. Ramlawi has received grants, personal fees, and nonfinancial support from Medtronic, Liva Nova, and AtriCure. Dr. Kleiman provides educational services to Medtronic. Dr. Meduri serves as the national principal investigator for the REPRISE IV trial, sponsored by Boston Scientific; serves on an Advisory Board and the APOLLO Trial Executive Committee for Medtronic; and is a consultant and an Advisory Board member for Admedus, 4Tech, and Cardiovalve; and has served as a consultant for Medtronic. Dr. Melnitchouk has been a consultant and has served as a member of the Advisory Board for Medtronic. Dr. Inglessis has been a consultant for Medtronic. Dr. Sorajja has received grants and consulting fees from Abbott Vascular, Boston Scientific, Edwards Lifesciences, and Medtronic; and has received consulting fees from Admedus, Gore, Integer, Abbott Structural, Medtronic, Boston Scientific, Edwards, Cardionomics, and Creganna Medical. Drs. Huang and Boulware are employees and shareholders of Medtronic. Dr. Reardon has received fees from Medtronic for providing educational services. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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was discouraged unless indicated by clinical findings (any neurological or potential embolic events, myocardial infarction, moderate or severe aortic regurgitation, or an increase of ≥50% in mean aortic valve gradient or Doppler velocity index).

The analysis cohort comprised patients who had evaluable CT scans, as determined by the independent computed tomography core laboratory (St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada), acquired 30 days post-procedure. The target sample size was at least 150 evaluable patients in each treatment group.

CT IMAGE ACQUISITION AND INTERPRETATION. Sites were instructed to perform 4D CT imaging prioritizing latest generation single-source scanners with wide detector coverage or dual-source systems. Electrocardiographically synchronized CT data of the aortic root were acquired using retrospective electrocardiographic gating when using systems with limited detector coverage, or electrocardiographically gated whole-beat coverage volume acquisition for systems with wide detector coverage to allow cine evaluation of the transcatheter valve leaflets. Coverage of the entire cardiac cycle was recommended while limiting dose modulation in order to achieve diagnostic image quality in systole and diastole. Further acquisition settings as well as contrast administration settings were left to the site's discretion. Thin-slice (≤0.625-mm) multiphasic CT images were reconstructed with either relative reconstruction in increments of 10% or less or absolute reconstruction with increments of 50 msec or less. To optimize image quality, sites were instructed to use heart rate control with either oral or intravenous beta-blockade with a target heart rate of ≤65 beats/min. The computed tomography core laboratory provided feedback to sites in the event of insufficient image quality.

CT images were transferred to an independent core laboratory for analysis. Image data were reviewed by 2 independent reviewers using post-processing workstations equipped with CVI42 (Circle Cardiovascular Imaging, Calgary, Alberta, Canada). Using multiplanar reformats aligned with the short- and long-axis dimensions of the bioprostheses, leaflets were evaluated for the presence of HALT.

TRANSTHORACIC ECHOCARDIOGRAPHY. Transthoracic echocardiograms were obtained at baseline, discharge, 30 days, and 1 year. All echocardiographic studies were analyzed by an independent core laboratory (Mayo Clinic, Rochester, Minnesota). The Doppler velocity index was calculated as the ratio of subvalvular velocity obtained on pulsed-wave Doppler and the maximum velocity obtained on continuous-wave Doppler across the prosthetic valve. Severe hemodynamic valve deterioration was defined as a change from baseline in the mean aortic valve gradient of ≥20 mm Hg (9).

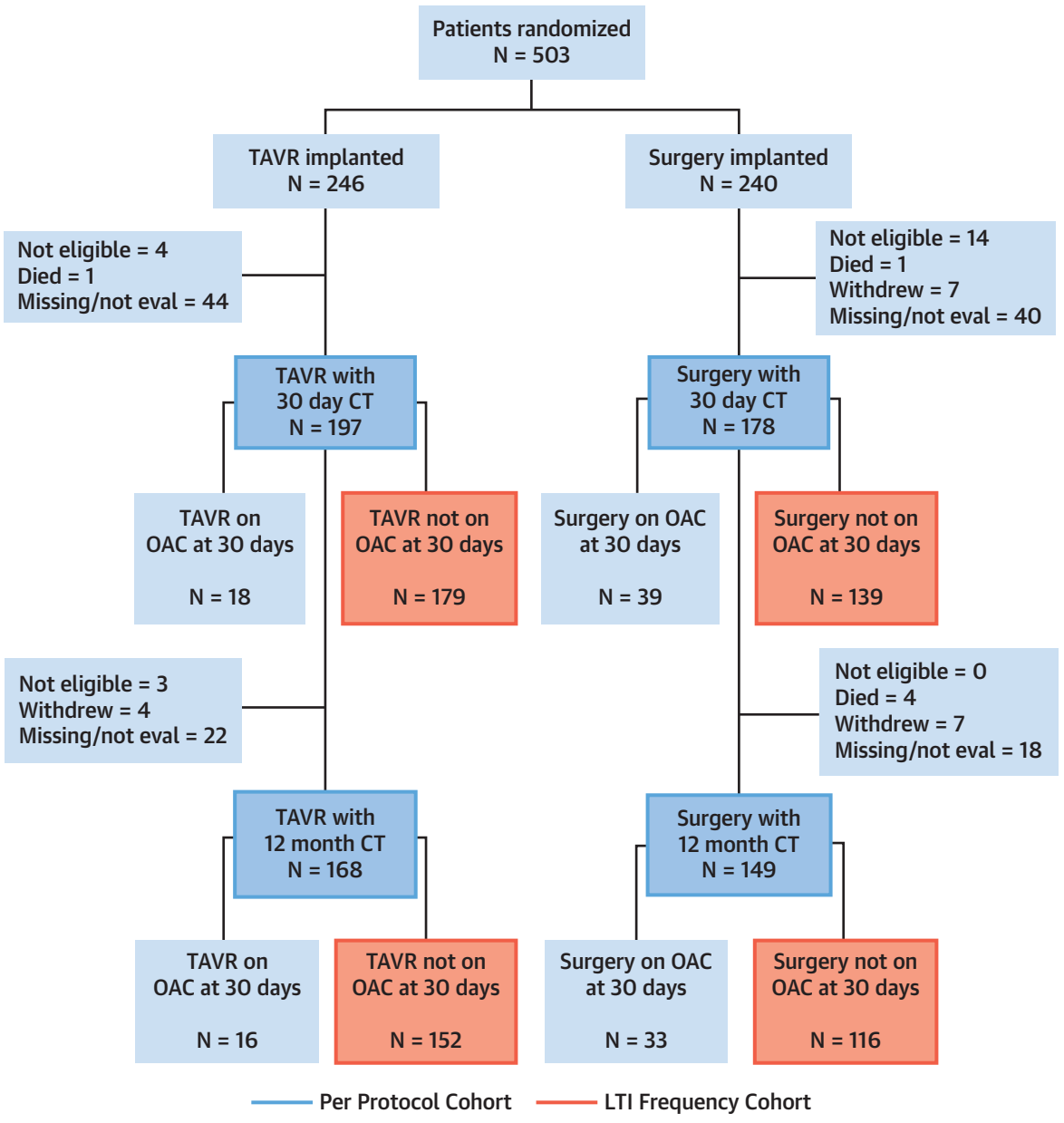
STUDY ENDPOINTS AND DEFINITIONS. The primary endpoint for the LTI substudy was the frequency and extent of any HALT at 30 days and 1 year. Secondary endpoints included the frequency and extent of RLM in the presence of HALT, mean aortic valve gradient and Doppler velocity index at 30 days and 1 year, and clinical events 7 to 30 days and 31 days to 1 year post-procedure in patients according to the presence or absence of HALT or RLM. Analysis of the frequency of HALT or RLM was evaluated in all patients who were not treated with OAC at the time of the 30-day CT study. Clinical and hemodynamic endpoints were analyzed in all patients regardless of OAC use (**Figure 1**).

HALT was defined as visually identified increased leaflet thickness with typical meniscal appearance on long-axis views as per recent guidelines (10). Extent of HALT was semiquantitatively graded by the primary reviewer on long-axis views carefully aligned with the leaflet center regarding involvement along the curvilinear leaflet beginning at the base, using a 5-tier grading scale: none, ≤25%, >25% to 50%, >50% to 75%, and >75%. Per-patient severity was defined by the leaflet with the highest grade of HALT. In the event of observed HALT, the presence of RLM (defined as incomplete leaflet opening in systole, see Video 1) was evaluated using a similar grading scale along the curvilinear leaflet beginning at the base (unrestricted, partial restriction limited to leaflet base [≤25%], partial restriction [>25% to 50%], partial restriction [>50% to 75%], and largely immobile [>75%]). Given the higher technical requirements for evaluation of RLM (diagnostic systolic imaging frames) compared with HALT (diagnostic image quality on at least 1 frame anywhere within the cardiac cycle), evaluation for HALT was prioritized and evaluated if datasets were nondiagnostic for RLM.

STATISTICAL ANALYSIS. Comparisons between categorical variables were performed using the Fisher exact test when the observed count was <5 and otherwise using a chi-square test.

Continuous variables are presented as mean ± SD and were compared using Student's *t*-test. Univariable logistic regression models were fit to identify clinical, procedural, echocardiographic, and CT variables associated with 30-day HALT in TAVR and surgery patients. Odds ratios with 95% confidence intervals and p values are reported. All tests were 2-sided, and p values were not adjusted for multiple comparisons. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

FIGURE 1 Patient Flow



Leaflet thickening and immobility (LTI) were evaluated at 30 days and 1 year in patients not on oral anticoagulation (OAC) at 30 days. All per protocol patients were included in the safety and hemodynamic analyses. The per protocol population includes all patients with evaluable computed tomographic (CT) studies at 30 days. eval = evaluated; TAVR = transcatheter aortic valve replacement.

RESULTS

PATIENTS. Between November 4, 2016, and November 30, 2018, a total of 503 patients who had been randomized to treatment in the Evolut Low Risk trial agreed to participate in the LTI substudy. Of these, 486 had bioprosthetic valve implants, and 375 patients had evaluable CT studies performed within 30 days of the procedure (197 TAVR, 178 surgery) (Figure 1).

At the time of the 30-day CT study, 18 TAVR and 39 surgery patients received OAC therapy and were excluded from the LTI frequency analyses but were included to assess the association of HALT and

TABLE 1 Baseline Demographics, Clinical Characteristics, and Oral Anticoagulation Use

	Per Protocol Population		Excluding Patients on OAC Therapy at the Time of 30-Day MDCT	
	TAVR (n = 197)	Surgery (n = 178)	TAVR (n = 179)	Surgery (n = 139)
Age, yrs*	74.0 ± 5.3	72.0 ± 6.1	74.0 ± 5.3	71.5 ± 6.4
Female	69 (35.0)	52 (29.2)	65 (36.3)	43 (30.9)
Body surface area, m^2	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.2
NYHA functional class				
I	17 (8.6)	16 (9.0)	15 (8.4)	13 (9.4)
II	135 (68.5)	109 (61.2)	124 (69.3)	84 (60.4)
III	45 (22.8)	52 (29.2)	40 (22.3)	41 (29.5)
IV	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.7)
STS PROM, %†	1.9 ± 0.6	1.8 ± 0.6	1.9 ± 0.6	1.7 ± 0.6
Diabetes mellitus	61 (31.0)	47 (26.4)	53 (29.6)	40 (28.8)
SCr >2 mg/dl	1 (0.5)	0 (0.0)	1 (0.6)	0 (0.0)
Hypertension	168 (85.3)	148 (83.1)	151 (84.4)	114 (82.0)
Peripheral arterial disease	12 (6.1)	15 (8.5)	12 (6.8)	14 (10.1)
Cerebrovascular disease	19 (9.6)	17 (9.6)	17 (9.5)	12 (8.6)
Prior CABG	3 (1.5)	4 (2.2)	2 (1.1)	4 (2.9)
Prior PCI	27 (13.7)	23 (12.9)	24 (13.4)	19 (13.7)
Previous MI	7 (3.6)	10 (5.6)	6 (3.4)	10 (7.2)
Pre-existing pacemaker or defibrillator‡	4 (2.0)	8 (4.5)	1 (0.6)	8 (5.8)
Atrial fibrillation/atrial flutter	18 (9.1)	24 (13.5)	6 (3.4)	8 (5.8)
AF and OAC use at baseline	12 (6.1)	15 (8.4)	1 (0.6)	3 (2.2)
AF and OAC use at 30 days	12 (6.1)	16 (9.0)	0 (0.0)	0 (0.0)
OAC use at 30 days	18 (9.1)	39 (21.9)	0 (0.0)	0 (0.0)
OAC use at 1 yr	25/192 (13.0)	29/169 (17.2)	11/174 (6.3)	9/133 (6.8)

Values are mean ± SD, n (%), or n/N (%). Except as indicated, there were no other significant differences between the treatment groups. *$p < 0.001$ for age difference in per protocol and OAC exclusion populations. †$p = 0.018$ for STS PROM difference in per protocol population and $p = 0.014$ for STS PROM difference. ‡$p = 0.012$ for difference in pre-existing pacemaker in the OAC exclusion population.

AF = atrial fibrillation; CABG = coronary artery bypass grafting; MDCT = multidetector computed tomography; MI = myocardial infarction; NYHA = New York Heart Association; OAC = oral anticoagulation; PCI = percutaneous coronary intervention; PROM = Predicted Risk of Mortality; SCr = serum creatinine; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement.

clinical events. The frequency of HALT at 30 days in patients not receiving OAC at the time of the 30-day CT study was 31 of 179 (17.3%) for TAVR and 23 of 139 (16.5%) for surgery ($p = 0.856$). At 1 year, the frequency of HALT in these patients was 47 of 152 (30.9%) for TAVR and 33 of 116 (28.4%) for surgery ($p = 0.661$). In patients with diagnostic CT studies for the presence or absence of RLM, the frequency of RLM at 30 days was 23 of 157 (14.6%) for TAVR and 19 of 133 (14.3%) for surgery ($p = 0.930$). At 1 year, the frequency of RLM was 45 of 145 (31.0%) for TAVR and 30 of 111 (27.0%) for surgery ($p = 0.485$).

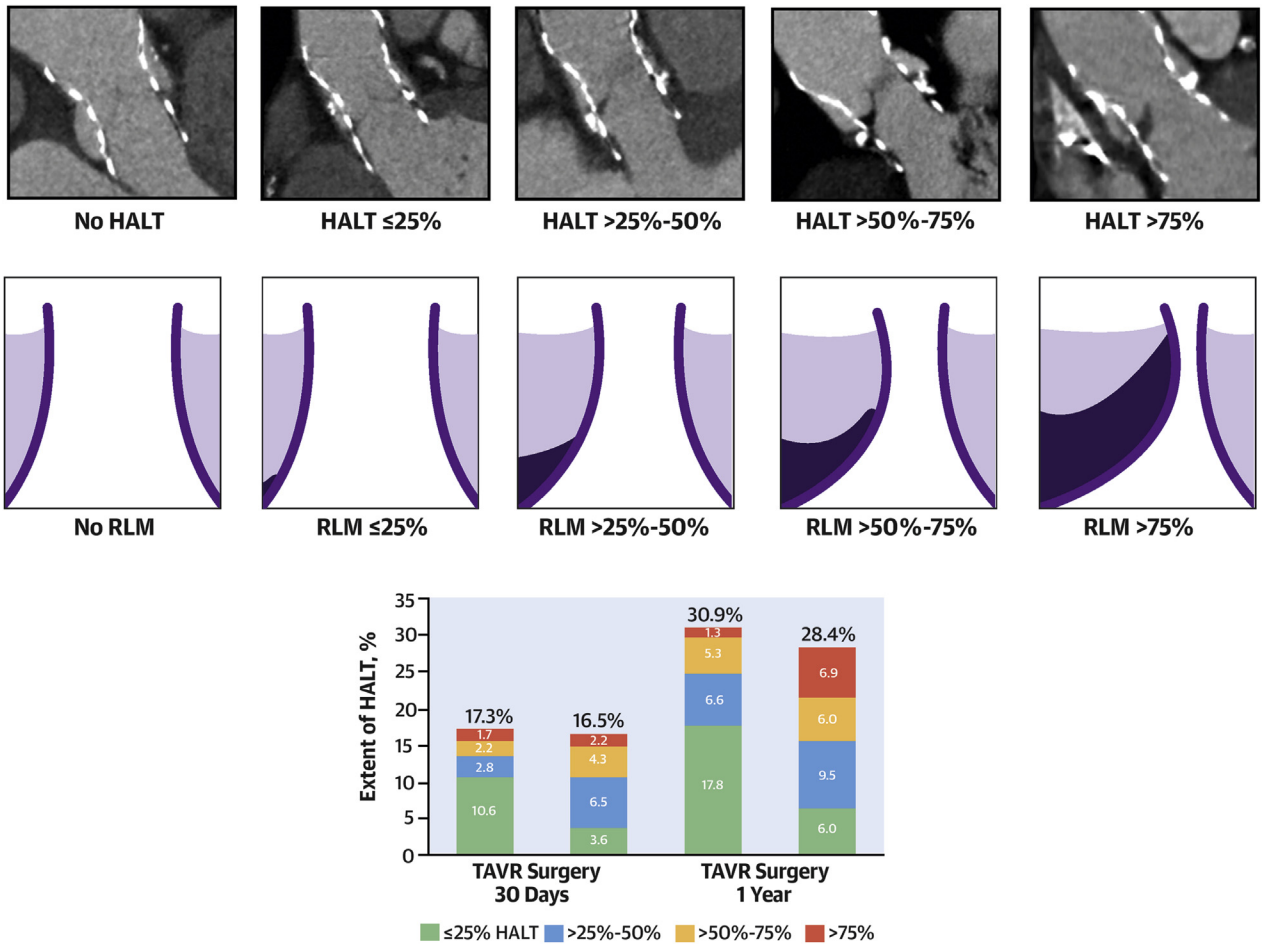
The baseline characteristics of all per protocol patients and all patients who were not on OAC at the time of the 30-day CT study are listed in **Table 1**. Baseline mean age was significantly lower for the surgery patients than for the TAVR patients, and the Society of Thoracic Surgeons score was significantly higher in TAVR compared with surgery patients in both populations. In the population excluding OAC use at 30 days, the proportion of patients with permanent pacemaker implantation or defibrillators was significantly lower in TAVR compared with surgery patients.

Baseline characteristics of TAVR and surgery patients with and without HALT at 30 days are presented in Supplemental Table 2.

PROCEDURAL CHARACTERISTICS. Procedural characteristics with and without HALT at 30 days for TAVR and surgery patients are listed in Supplemental Tables 2 and 3. Among the TAVR cohort, there was no significant difference in the use of pre- or post-dilatation or the use of the resheath or recapture mechanisms. However, there was a significantly smaller mean aortic annular perimeter in the TAVR patients with HALT (74.8 ± 5.9 mm) versus those without HALT (79.6 ± 6.9 mm) ($p < 0.001$), and smaller valves were implanted in the patients with HALT at 30 days (Supplemental Table 3).

In the surgery cohort, more sutureless valves and fewer small valves were used in patients with HALT

CENTRAL ILLUSTRATION **The Frequency and Extent of Hypoattenuated Leaflet Thickening**



Blanke, P. et al. J Am Coll Cardiol. 2020;75(19):2430–42.

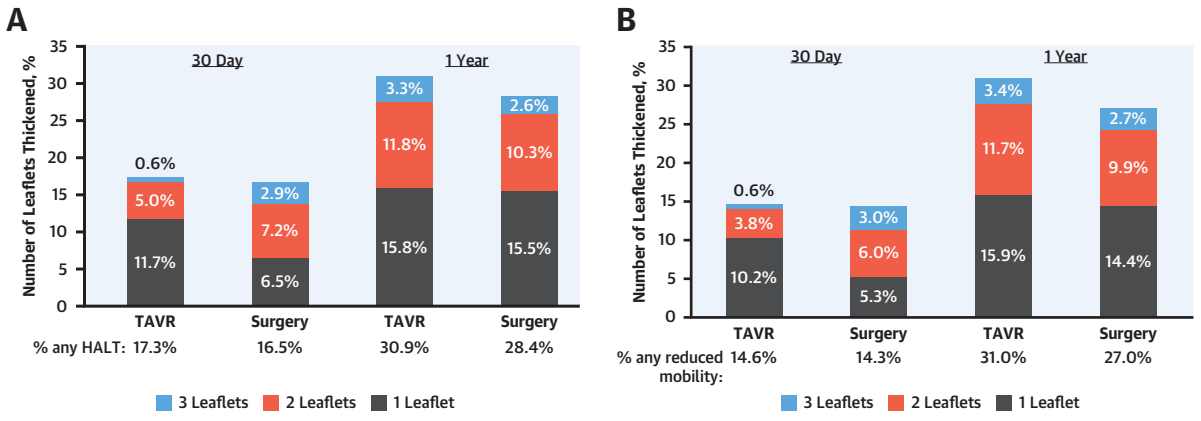
The extent of leaflet thickening and reduced leaflet motion is based on a 5-tier grading scale: none, ≤25%, >25% to 50%, >50% to 75%, >75% as illustrated by the 4-dimensionsl CT images and cartoons. In patients not receiving oral anticoagulation on day 30, the frequency of HALT in the TAVR and surgery groups is similar at 30 days and 1 year. Abbreviations as in Figures 1 and 2.

compared with those without HALT. There was no difference in aortic annular perimeter between surgery patients with and those without HALT (Supplemental Table 4).

FREQUENCY AND EXTENT OF LEAFLET THICKENING AND IMMOBILITY. In patients not receiving OAC therapy, the extent of HALT severity on the affected leaflet in the TAVR group at 30 days and 1 year was most commonly ≤25%, while in the surgery group it was more often in the >25% to 50% range. HALT of >75% severity was uncommon in both treatment groups at day 30 but at 1 year was significantly greater in surgery compared with TAVR patients (6.9% vs. 1.3% for TAVR; p = 0.008) (Central Illustration). At 30 days, the proportion of TAVR patients with HALT in 2 or 3 leaflets was significantly lower than that of the surgical patients (p = 0.036). At 1 year, the numbers of leaflets thickened were similar between the groups (Figure 2A). Similarly, at 30 days, the proportion of patients with RLM in 2 or 3 leaflets was significantly lower in the TAVR patients than in the surgical patients (p = 0.034) but was not different at 1 year (Figure 2B).

Analysis of individual leaflets in patients with HALT was performed to examine the relationship between extent of leaflet thickening and extent of leaflet immobility. This analysis showed that largely immobile leaflets occurred only when the extent of thickening at 30 days was >75% on the leaflet (Figure 3A).

FIGURE 2 Number of Leaflets Thickened in Patients With HALT or RLM



The proportion of observed hypoattenuated leaflet thickening (HALT) **(A)** or reduced leaflet motion (RLM) **(B)** that involved 1, 2, or 3 leaflets is shown at 30 days and 1 year post-procedure. Patients receiving anticoagulation therapy at the time of the 30-day computed tomographic imaging are excluded.

Similarly, if there was no leaflet thickening at 30 days, leaflet motion was unrestricted. The same pattern of increasing RLM with greater extent of HALT was also observed in valves with HALT at 1 year (Figure 3B).

In the surgery cohort, excluding patients on OAC, HALT at 30 days was detected in 9 of 80 stented valves (11.3%), 0 of 2 stentless valves, and 14 of 56 sutureless valves (25.0%). At 1 year, HALT was detected in 14 of 67 of stented valves (20.9%), 1 of 2 stentless valves (50%), and 17 of 46 of sutureless valves (37.0%) (Supplemental Table 5).

NATURAL COURSE OF HALT. The frequency of HALT and no HALT at 30 days and 1 year excluding patients on OAC at the time of the 30-day CT study and with evaluable CT studies at both time points is displayed in Figure 4. There were 32 TAVR patients and 20 surgery patients without HALT at 30 days who demonstrated HALT at 1 year. Of patients with HALT at 30 days, 11 TAVR and 5 surgery patients demonstrated resolution of HALT at 1 year, and 2 patients in each of the latter groups were noted to have received OAC therapy within 90 days subsequent to or at 1 year.

PREDICTORS OF 30-DAY HALT. Univariable predictors of any HALT at 30 days in TAVR patients included female sex, small aortic annulus, small height and diameter of sinus of Valsalva, total valvular calcium volume, and use of transcatheter valves smaller than 34 mm. Univariate predictors of any HALT at 30 days in surgery patients included a history of cerebral vascular disease, low baseline maximum aortic valve velocity, larger mean sinus of Valsalva diameter, and use of sutureless valves as opposed to stented valves (Table 2).

HEMODYNAMIC FINDINGS. The mean aortic valve gradients after TAVR remained consistently low regardless of extent of HALT at 30 days and 1 year (Table 3). Doppler velocity index after TAVR was also consistent, ranging from 0.6 to 0.7 at 30 days and 0.5 to 0.6 at 1 year. Mean gradients were higher after surgery than TAVR but did not consistently increase with increasing extent of HALT. Doppler velocity index after surgery was also consistent in the patients with and without HALT regardless of extent.

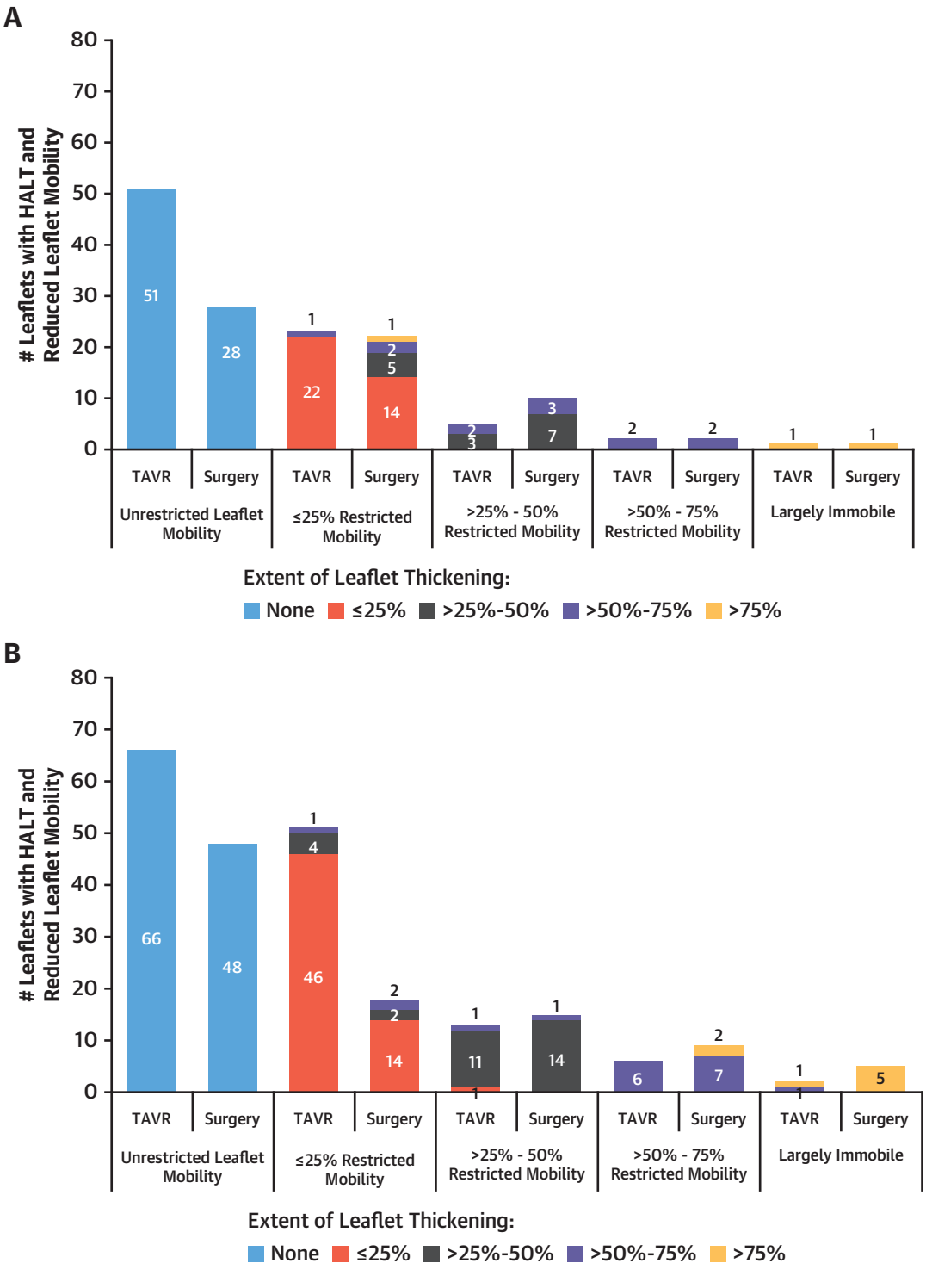
There was 1 patient in the surgical group with a change in mean gradient from post-procedure to 1 year who met the criteria for severe hemodynamic valve deterioration (Supplemental Figure 1). This surgery patient had a mean gradient of 40.3 mm Hg with >75% leaflet thickening identified by CT imaging and 2 leaflets affected. The patient received OAC, and the suspected thrombus resolved with no clinical sequalae.

CLINICAL OUTCOMES. In both the TAVR and surgery cohorts, there were no death, stroke, or transient ischemic attack events between 7 and 30 days in the patients who had HALT at 30 days (Table 4). Between 30 days and 1 year, there was no death, stroke, or transient ischemic attack in TAVR patients with HALT and 2 deaths and 1 stroke in surgery patients with HALT.

DISCUSSION

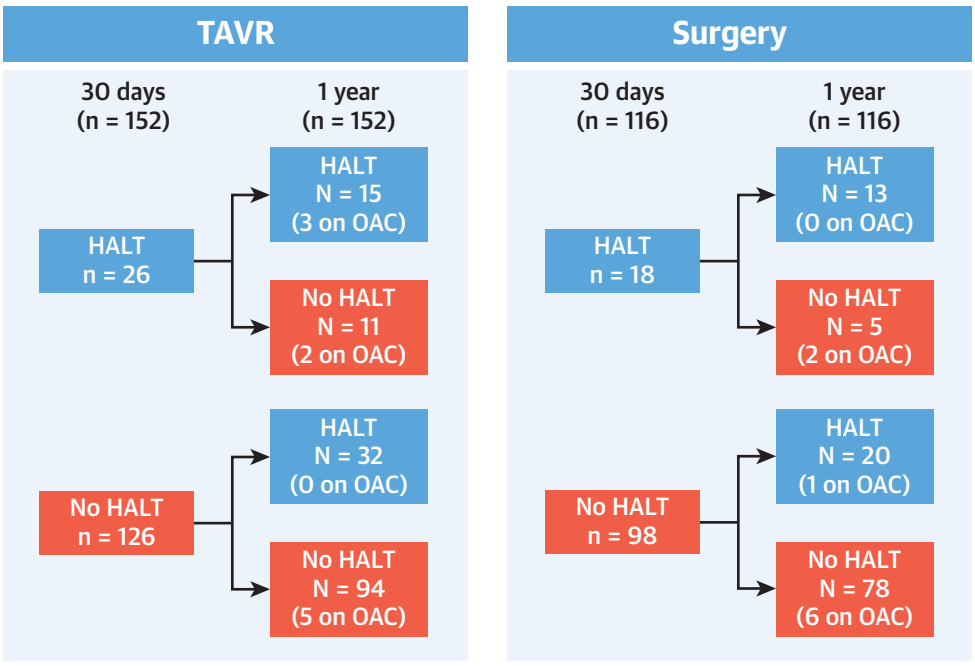
Our prospective, randomized study in patients with aortic stenosis at low surgical risk showed that 4D CT

FIGURE 3 Correlation of the Extent of HALT and RLM



In patients with >75% HALT, there was 1 leaflet in each group identified as largely immobile at 30 days **(A)**, and at 1 year, 1 TAVR and 5 surgical patient leaflets were largely immobile **(B)**. Abbreviations as in Figures 1 and 2.

FIGURE 4 HALT Progression From 30 Days to 1 Year



In patients not receiving oral anticoagulation at 30 days with an evaluable CT image at 30 days and 1 year, the dynamic nature of HALT can be observed. Some patients with HALT at 30 days did not have HALT at 1 year and some patients without HALT at 30 days had HALT at 1 year that did not always correlate with use of oral anticoagulation at 1 year.

detection of HALT occurs in 17% of patients at 30 days and in 30% of patients at 1 year after bioprosthetic aortic valve replacement. RLM occurred in 14% of patients at 30 days and in 29% of patients at 1 year. We found no differences in the occurrence of HALT or RLM after supra-annular, self-expanding TAVR or surgery at either time point. We found that HALT was dynamic in the first year after aortic valve replacement, with some patients showing spontaneous resolution of HALT from 30 days to 1 year and others developing HALT at 1 year after showing no signs of HALT at 30 days. We also found no clear relationship between HALT or RLM and aortic valve gradients, which were consistently lower in TAVR patients than surgery patients. We also did not find a relationship with HALT or RLM and adverse clinical events. These findings suggest a limited role for routine use of 4D CT after aortic valve replacement.

DETECTION OF SUBCLINICAL LEAFLET THROMBOSIS. Makkar et al. (1) described the potential occurrence of subclinical leaflet thrombosis in patients undergoing TAVR using another self-expanding annular bioprosthesis; subsequent registry reports suggested that similar findings were found with all transcatheter and a number of surgical valves (1,2,11). Initial reports used volume-rendered images to identify RLM and showed a trend toward an association with subsequent clinical events (1), spurring concern from the U.S. Food and Drug Administration (12) and professional societies (13,14) about the public health implications of subclinical leaflet thrombosis.

Given the excellent spatial resolution of CT imaging, HALT has emerged as a more reproducible measure of possible subclinical leaflet thrombosis (15,16), with demonstrated frequencies of HALT ranging from 4.0% to 38.1% after TAVR (4,15-18); less is known about HALT after surgery (18). Given the more modest temporal resolution of CT imaging compared with echocardiography, as well as the higher technical requirements for the diagnosis of RLM compared with HALT (diagnostic image quality throughout systole), RLM should be evaluated only in the setting of HALT to avoid overdiagnosis (10). Our study included a 5-tier, leaflet-based grading scale, allowing a blinded ordinal ranking of HALT and RLM over time. Most patients had no or ≤25% HALT at 30 days, and the overall frequencies of HALT and RLM were similar between TAVR and surgery at 1 year. Interestingly, 2- or 3-leaflet HALT involvement was more frequently

TABLE 2 Univariable Predictors of HALT at 30 Days

	TAVR		Surgery	
	Any HALT Odds Ratio (95% CI)	p Value*	Any HALT Odds Ratio (95% CI)	p Value*
Age, yrs	1.073 (0.997–1.154)	0.061	0.957 (0.892–1.027)	0.225
Female	2.660 (1.264–5.597)	0.001	0.836 (0.310–2.256)	0.724
STS PROM, %	1.695 (0.928–3.096)	0.086	0.654 (0.316–1.354)	0.253
NYHA functional class I/II vs. III/IV	0.689 (0.302–1.569)	0.375	1.233 (0.457–3.324)	0.679
Hypertension	0.503 (0.202–1.252)	0.140	0.692 (0.235–2.036)	0.504
Cerebrovascular disease	1.265 (0.393–4.070)	0.694	3.311 (1.046–10.483)	0.042
Use of anticoagulation	1.364 (0.421–4.425)	0.605	0.063 (0.004–1.095)	0.058
Post-procedural/discharge mean gradient	0.912 (0.812–1.024)	0.119	0.915 (0.822–1.019)	0.105
Post-procedural/discharge EOA, cm^2	0.517 (0.252–1.061)	0.072	2.008 (0.879–4.585)	0.098
Post-procedural/discharge DVI >0.5	3.590 (0.809–15.92)	0.093	0.900 (0.343–2.360)	0.830
Baseline maximal aortic valve velocity, m/s†	0.726 (0.343–1.538)	0.404	0.331 (0.130–0.840)	0.020
Resheath or recapture	1.886 (0.897–3.969)	0.095	NA	
Aortic annular perimeter, mm	0.898 (0.846–0.954)	<0.001	1.041 (0.946–1.146)	0.407
Aortic annular mean diameter, mm	0.708 (0.588–0.852)	<0.001	1.139 (0.846–1.534)	0.390
Mean sinus of Valsalva diameter, mm	0.885 (0.787–0.996)	0.043	1.136 (1.011–1.276)	0.032
Mean sinus of Valsalva height, mm	0.865 (0.770–0.973)	0.015	1.069 (0.957–1.193)	0.236
Total valvular calcium volume	0.998 (0.997–0.999)	0.002	NA	
Valve size implanted (reference 34 mm)				
23/26 mm	5.038 (1.627–15.597)	0.005		
29 mm	3.286 (1.153–9.374)	0.026		
Device/annular oversizing ratio	1.018 (0.959–1.079)	0.564	NA	
Sutureless bioprosthesis (reference stented)			2.478 (1.009–6.086)	0.048
Valve size implanted (reference ≥27 mm)				
≤21 mm			0.054 (0.006–0.463)	0.008
23–25 mm			0.218 (0.080–0.592)	0.003

*From logistic regression model. †Site reported.

CI = confidence interval; DVI = Doppler velocity index; EOA = effective orifice area; HALT = hypoattenuated leaflet thickening; NA = not applicable; other abbreviations as in Table 1.

seen after surgery at 30 days, and severe (>75%) HALT was observed more frequently at 1 year with surgery (6.9%) compared with TAVR (1.3%) (p = 0.008) (Central Illustration).

OAC therapy has been shown to reduce the occurrence and noted to resolve both RLM and HALT compared with dual-antiplatelet therapy. In a series of 231 patients undergoing successful TAVR, at least 1

TABLE 3 Impact of HALT on Valve Hemodynamic Status

	No HALT	≤25% HALT	>25%–50% HALT	>50%–75% HALT	>75% HALT	p Value*
30 days						
TAVR						
Mean gradient, mm Hg	8.6 ± 3.6 (160)	7.2 ± 3.0 (21)	8.1 ± 1.6 (6)	6.8 ± 3.0 (2)	5.9 ± 1.4 (4)	0.273
DVI	0.6 ± 0.1 (149)	0.6 ± 0.1 (21)	0.6 ± 0.1 (5)	0.7 ± 0.3 (2)	0.6 ± 0.2 (4)	0.154
Surgery						
Mean gradient, mm Hg	10.5 ± 3.6 (153)	9.4 ± 4.0 (5)	10.8 ± 3.7 (9)	12.2 ± 5.6 (6)	6.9 ± 3.5 (3)	0.331
DVI	0.5 ± 0.1 (146)	0.6 ± 0.0 (4)	0.4 ± 0.1 (9)	0.5 ± 0.1 (6)	0.6 ± 0.1 (3)	0.052
1 yr						
TAVR	8.5 ± 3.2 (114)	8.4 ± 2.8 (29)	7.1 ± 2.3 (9)	8.2 ± 4.0 (9)	11.6 ± NA (1)	0.600
Mean gradient, mm Hg	0.6 ± 0.1 (105)	0.6 ± 0.1 (27)	0.6 ± 0.1 (7)	0.6 ± 0.2 (9)	0.5 ± NA (1)	0.716
DVI						
Surgery	11.2 ± 4.6 (114)	9.7 ± 3.6 (7)	11.4 ± 3.7 (12)	11.5 ± 3.7 (7)	13.7 ± 11.2 (8)	0.628
Mean gradient, mm Hg	0.5 ± 0.1 (108)	0.6 ± 0.1 (6)	0.5 ± 0.1 (12)	0.5 ± 0.1 (7)	0.5 ± 0.1 (8)	0.148
DVI	8.5 ± 3.2 (114)	8.4 ± 2.8 (29)	7.1 ± 2.3 (9)	8.2 ± 4.0 (9)	11.6 ± NA (1)	0.600

Values are mean ± SD (n). *From analysis-of-variance F test.

NA = not analyzable; other abbreviations as in Table 3.

TABLE 4 Relationship Between HALT and Clinical Outcomes

	TAVR				Surgery			
	7-30 Days		31-365 Days		7-30 Days		31-365 Days	
	HALT at 30 Days (n = 35)	No HALT at 30 Days (n = 162)	HALT at 30 Days (n = 35)	No HALT at 30 Days (n = 162)	HALT at 30 Days (n = 23)	No HALT at 30 Days (n = 155)	HALT at 30 Days (n = 23)	No HALT at 30 Days (n = 155)
All-cause mortality or stroke or TIA	0 (0.0)	2 (1.3)	0 (0.0)	2 (1.3)	0 (0.0)	1 (0.7)	2 (8.7)	1 (0.7)
All-cause mortality or disabling stroke	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	2 (8.7)	1 (0.7)
All-cause mortality	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.7)	1 (0.7)
All stroke	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.7)	1 (4.5)	0 (0.0)
TIA	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)
Valve endocarditis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
Valve thrombosis*	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Aortic valve hospitalization*	0 (0.0)	0 (0.0)	0 (0.0)	5 (3.1)	1 (4.3)	4 (2.6)	1 (4.5)	5 (3.4)
Atrial fibrillation	2 (5.7)	1 (0.6)	0 (0.0)	3 (2.0)	0 (0.0)	2 (1.8)	0 (0.0)	6 (5.6)

Values are Kaplan-Meier rates expressed as number of events (%). *Clinical valve thrombosis was defined as any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Aortic valve hospitalization was defined as hospitalization for aortic valve-related disease. Rates are from time to first event analysis. One SAVR patient with HALT at 30 days experienced 2 strokes between 31 and 365 days. One TAVR patient with HALT at 30 days had 2 strokes on days 0 and 154 hence not shown in this landmarking approach.

TIA = transient ischemic attack; other abbreviations as in Tables 1 and 2.

prosthetic valve leaflet with >50% to 75% or higher motion reduction was found in 2.1% in the rivaroxaban group, compared with 10.9% in the antiplatelet group (19). HALT involving at least 1 leaflet was observed in 12.4% in the rivaroxaban group and in 32.4% in the antiplatelet group (19). However, the risk for death or thromboembolic events and the risk for life-threatening, disabling, or major bleeding was higher with rivaroxaban (19). Other studies have also demonstrated regression of RLM with the use of OAC, whereas there was no regression, and in some cases progression, with the use of dual-antiplatelet therapy (3,5,20).

In our study, although at least one-half of the patients with HALT after bioprosthetic valve replacement at 30 days had sustained HALT at 1 year, many patients experienced spontaneous resolution of HALT at 1 year without the use of OAC; 1 patient also developed HALT while on OAC. Moreover, some patients with no HALT at 30 days had HALT at 1 year after TAVR and surgery, suggesting that HALT can be a transient finding, uniquely identified by the nonbiased blinded analysis of the 30-day and 1-year CT studies. The dynamic nature of HALT may have implications for interpretation of observed frequencies of HALT among studies, as time points of CT examination vary among studies. Unlike other studies (19,21), our study also showed that the resolution and progression of HALT were not completely predictable by the use of OAC.

PREDICTORS OF HALT. Predictors of HALT after bioprosthetic valve replacement have included the use of balloon-expandable transcatheter bioprostheses (4,17); low-gradient, low-flow aortic stenosis (4,17); severe prosthesis-patient mismatch (17); and larger bioprosthesis sizes (4,17,22). Leaflet thrombosis has also been found to be more common in patients undergoing TAVR than surgery (5).

Our study showed that the rate of HALT was similar in patients undergoing TAVR and surgery. Univariable analysis showed that major predictors of HALT included female sex and small annular perimeter in the TAVR patients and having a sutureless valve in the surgical patients. Higher rates of HALT were observed with sutureless valves in another series (23). Uncharacterized anatomic and hemodynamic factors may have predisposed to the development of HALT, as post-implantation geometry has been shown to contribute to the occurrence of HALT (24).

RELATIONSHIP OF HALT AND VALVE HEMODYNAMIC STATUS. Although the presence of HALT and RLM has been correlated with higher gradients in some studies (5,17,21,25,26), our study showed no relationship between the presence or absence of HALT and valve hemodynamic performance at 30 days or 1 year, as measured by mean gradient or Doppler velocity index. Hemodynamic status for the transcatheter valve was superior to that for surgery in the Evolut Low Risk trial (8). The presence and severity of HALT or RLM did not change these findings. Although the relationship between HALT and structural valve deterioration cannot be determined from this study, all patients in this study will be followed for 10 years to determine correlates of long-term valve durability.

It is interesting to note that in a subgroup of surgical patients who were not on OAC, there were differences in the degree of HALT on the basis of the

type of valve implanted, with the rates of HALT highest in those with sutureless valves. The clinical importance of this difference in HALT between valve types is currently unknown.

RELATIONSHIP OF HALT AND CLINICAL EVENTS. The impact of HALT on clinical outcomes in patients after aortic valve replacement has been controversial (27). A number of studies have shown no association between HALT and clinical events (25,27), while others have shown a weak association of HALT and RLM on cerebrovascular events, including transient ischemic events (1,4). These correlations are more important if younger and lower risk patients are treated. However, our study showed no association of the presence or severity HALT or RLM on death, stroke, transient ischemic attack, or myocardial infarction up to 1 year post-procedure.

ROLE OF 4D CT IMAGING IN PATIENTS WITH CLINICAL LEAFLET THROMBOSIS. Despite the limited utility of the routine detection of HALT to predict aortic valve hemodynamic status or clinical events, 4D CT imaging is very useful in patients who develop structural valve deterioration or neurological event. One surgical patient in our series developed evidence of severe structural valve deterioration. The patient received OAC, and the suspected thrombus resolved with no clinical sequelae and a normalized aortic valve gradient. One other patient treated with TAVR in our series had <25% HALT at 30 days but later developed a retinal vein occlusion on day 151 that was adjudicated by the clinical events committee as an embolic event. Although the transthoracic echocardiogram was unchanged from the post-procedural imaging, the unscheduled CT study showed valve thrombus. The patient was treated with OAC, and the valve thrombus resolved at 1 year without further clinical issues. We recommend the use of 4D CT imaging to detect thrombus in the event of a change in the hemodynamic or clinical status of a patient.

STUDY LIMITATIONS. Although this trial was designed to study the frequency of HALT in TAVR and surgery patients, it was not powered to detect differences in clinical outcomes. The total number of patients in this substudy was relatively small, resulting in a small number of patients with HALT, thus precluding a reliable multivariable analysis. The transient and dynamic nature of HALT may make it difficult to capture its full spectrum over time using CT assessments at only 2 time points.

CONCLUSIONS

Our study found that 4D CT imaging abnormalities of aortic bioprostheses, such as HALT and RLM, were frequent but dynamic in the first year after surgery and supra-annular self-expanding TAVR. However, these imaging findings did not correlate with aortic valve hemodynamic status or clinical outcomes after aortic valve replacement in patients at low risk for surgery. Further research with longer follow-up is needed to understand the role of OAC and the possible impact of HALT on later events.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Bioprosthetic aortic valves, whether implanted surgically or by a catheter-based approach, may develop leaflet thrombosis leading to an increased systolic pressure gradient, aortic regurgitation, or ischemic stroke. Subclinical valve thrombosis may be detected by CT imaging as HALT or RLM, but these findings are frequent, dynamic, and not associated with worsening valve hemodynamics or clinical events.

TRANSLATIONAL OUTLOOK: Further studies are needed to identify indices of structural valve deterioration after surgical and transcatheter aortic valve replacement that are more predictive of long-term valve durability and adverse clinical events.

REFERENCES

1. Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. N Engl J Med 2015;373:2015–24.

2. Brown RA, Khanji MY, Mullen M, Patel RS, Bhattacharyya S. Hypoattenuated leaflet thickening associated with symptomatic thrombotic prosthetic valve obstruction: early complication following transcatheter aortic valve implantation. Eur Heart J Cardiovasc Imaging 2020;21:115.

3. Nuhrenberg TG, Hromek J, Kille A, et al. Impact of on-clopidogrel platelet reactivity on incidence

of hypoattenuated leaflet thickening after transcatheter aortic valve replacement. J Am Coll Cardiol Intv 2019;12:12–8.

4. Tang L, Lesser JR, Schneider LM, et al. Prospective evaluation for hypoattenuated leaflet thickening following transcatheter aortic valve implantation. Am J Cardiol 2019;123:658–66.

5. Chakravarty T, Sondergaard L, Friedman J, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. Lancet 2017;389:2383–92.

6. Rashid HN, Brown AJ, McCormick LM, et al. Subclinical leaflet thrombosis in transcatheter aortic valve replacement detected by multidetector computed tomography—a review of current evidence. Circ J 2018;82:1735–42.

7. Pache G, Schoechlin S, Blanke P, et al. Early hypo-attenuated leaflet thickening in balloon-expandable transcatheter aortic heart valves. Eur Heart J 2016;37:2263–71.

8. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med 2019;380:1706–15.

9. Capodanno D, Petronio AS, Prendergast B, et al. Standardized definitions of structural deterioration and valve failure in assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves: a consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) endorsed by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg 2017;52:408–17.

10. Blanke P, Weir-McCall JR, Achenbach S, et al. Computed tomography imaging in the context of transcatheter aortic valve implantation (TAVI)/transcatheter aortic valve replacement (TAVR): an expert consensus document of the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol Img 2019;12:1–24.

11. Ruile P, Minners J, Schoechlin S, et al. Impact of the type of transcatheter heart valve on the incidence of early subclinical leaflet thrombosis. Eur J Cardiothorac Surg 2018;53:778–83.

12. Laschinger JC, Wu C, Ibrahim NG, Shuren JE. Reduced leaflet motion in bioprosthetic aortic valves—the FDA perspective. N Engl J Med 2015; 373. 1996–8.

13. Holmes DR, Mack MJ. Uncertainty and possible subclinical valve leaflet thrombosis. N Engl J Med 2015;373:2080–2.

14. Holmes DR, Mack MJ. Aortic valve bioprostheses: leaflet immobility and valve thrombosis. Circulation 2017;135:1749–56.

15. Jilaihawi H, Asch FM, Manasse E, et al. Systematic CT methodology for the evaluation of subclinical leaflet thrombosis. J Am Coll Cardiol Img 2017;10:461–70.

16. Kanjanauthai S, Pirelli L, Nalluri N, Kliger CA. Subclinical leaflet thrombosis following transcatheter aortic valve replacement. J Interv Cardiol 2018;31:640–7.

17. Yanagisawa R, Tanaka M, Yashima F, et al. Early and late leaflet thrombosis after transcatheter aortic valve replacement. Circ Cardiovasc Interv 2019;12:e007349.

18. Sondergaard L, De Backer O, Kofoed KF, et al. Natural history of subclinical leaflet thrombosis affecting motion in bioprosthetic aortic valves. Eur Heart J 2017;38:2201–7.

19. De Backer O, Dangas GD, Jilaihawi H, et al. Reduced leaflet motion after transcatheter aortic-valve replacement. N Engl J Med 2020;382:130–9.

20. Rashid HN, Nasis A, Gooley RP, Cameron JD, Brown AJ. The prevalence of computed tomography-defined leaflet thrombosis in intra- versus supra-annular transcatheter aortic valve prostheses. Catheter Cardiovasc Interv 2018;92:1414–6.

21. Ruile P, Jander N, Blanke P, et al. Course of early subclinical leaflet thrombosis after transcatheter aortic valve implantation with or without oral anticoagulation. Clin Res Cardiol 2017;106:85–95.

22. Hansson NC, Grove EL, Andersen HR, et al. Transcatheter aortic valve thrombosis: incidence, predisposing factors, and clinical implications. J Am Coll Cardiol 2016;68:2059–69.

23. Dalen M, Sartipy U, Cederlund K, et al. Hypoattenuated leaflet thickening and reduced leaflet motion in sutureless bioprosthetic aortic valves. J Am Heart Assoc 2017;6:e005251.

24. Fuchs A, De Backer O, Brooks M, et al. Subclinical leaflet thickening and stent frame geometry in self-expanding transcatheter heart valves. EuroIntervention 2017;13:e1067–75.

25. Vollema EM, Kong WKF, Katsanos S, et al. Transcatheter aortic valve thrombosis: the relation between hypo-attenuated leaflet thickening, abnormal valve haemodynamics, and stroke. Eur Heart J 2017;38:1207–17.

26. Khan JM, Rogers T, Waksman R, et al. Hemodynamics and subclinical leaflet thrombosis in low-risk patients undergoing transcatheter aortic valve replacement. Circ Cardiovasc Imaging 2019; 12:e009608.

27. Rashid HN, Gooley RP, Nerlekar N, et al. Bioprosthetic aortic valve leaflet thrombosis detected by multidetector computed tomography is associated with adverse cerebrovascular events: a meta-analysis of observational studies. EuroIntervention 2018;13:e1748–55.

KEY WORDS aortic stenosis, aortic valve replacement, hypoattenuated leaflet thickening, leaflet thrombosis

APPENDIX For a complete list of investigators participating in the Evolut Low Risk LTI substudy, as well as supplemental tables and a figure, please see the online version of this paper.