Subclinical leaflet thrombosis in transcatheter and surgical bioprosthetic valves PARTNER 3 cardiac computed tomography substudy

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ORIGINAL INVESTIGATIONS

Subclinical Leaflet Thrombosis in Transcatheter and Surgical Bioprosthetic Valves

PARTNER 3 Cardiac Computed Tomography Substudy

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ABSTRACT

BACKGROUND Subclinical leaflet thrombosis, characterized by hypoattenuated leaflet thickening (HALT) and reduced leaflet motion observed on 4-dimensional computed tomography (CT), may represent a form of bioprosthetic valve dysfunction.

OBJECTIVES The U.S. Food and Drug Administration mandated CT studies to understand the natural history of this finding, differences between transcatheter and surgical valves, and its association with valve hemodynamics and clinical outcomes.

METHODS The PARTNER 3 (The Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low-Risk Patients With Aortic Stenosis) CT substudy randomized 435 patients with low-surgical-risk aortic stenosis to undergo transcatheter aortic valve replacement (n = 221) or surgery (n = 214). Serial 4-dimensional CTs were performed at 30 days and 1 year and were analyzed independently by a core laboratory.

RESULTS The incidence of HALT increased from 10% at 30 days to 24% at 1 year. Spontaneous resolution of 30-day HALT occurred in 54% of patients at 1 year, whereas new HALT appeared in 21% of patients at 1 year. HALT was more frequent in transcatheter versus surgical valves at 30 days (13% vs. 5%; p = 0.03), but not at 1 year (28% vs. 20%; p = 0.19). The presence of HALT did not significantly affect aortic valve mean gradients at 30 days or 1 year. Patients with HALT at both 30 days and 1 year, compared with those with no HALT at 30 days and 1 year, had significantly increased aortic valve gradients at 1 year (17.8 ± 2.2 mm Hg vs. 12.7. ± 0.3 mm Hg; p = 0.04).

CONCLUSIONS Subclinical leaflet thrombosis was more frequent in transcatheter compared with surgical valves at 30 days, but not at 1 year. The impact of HALT on thromboembolic complications and structural valve degeneration needs further assessment. (J Am Coll Cardiol 2020;75:3003-15) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

4D = 4-dimensional

AVR = aortic valve replacement

CI = confidence interval

CT = computed tomography

HALT = hypoattenuated leaflet thickening

MI = myocardial infarction

RLM = reduced leaflet motion

RR = risk ratio

TAVR = transcatheter aortic valve replacement

TIA = transient ischemic attacks

Subclinical leaflet thrombosis characterized by hypoattenuated leaflet thickening (HALT) and reduced leaflet motion (RLM) seen on high-resolution 4-dimensional (4D) cardiac computed tomography (CT) is found with significant frequency both in transcatheter and surgical bioprosthetic valves (1–9). The clinical significance of this finding is uncertain, but given its high prevalence in up to 15% of patients undergoing transcatheter aortic valve replacement (TAVR), the U.S. Food and Drug Administration mandated CT substudies in the pivotal trials designed to expand the role of TAVR in patients at low surgical risk. PARTNER 3 (The Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low-Risk Patients With Aortic Stenosis) was a randomized trial that compared the outcomes of TAVR to surgery in patients who were symptomatic for aortic stenosis and at low risk for open heart surgery (10). The purpose of the randomized PARTNER 3 CT substudy was to establish the frequency of subclinical leaflet thrombosis in patients without anticoagulation therapy in transcatheter versus surgical bioprosthetic valves, to understand its natural history, as well as to evaluate the impact of this finding on valve hemodynamics and clinical outcomes.

SEE PAGE 3016

METHODS

STUDY DESIGN AND PARTICIPANTS. The PARTNER 3 CT substudy was a randomized trial embedded in the PARTNER 3 randomized trial of TAVR with current-generation balloon-expandable valve compared with standard surgical AVR in patients at low surgical risk with symptomatic, severe aortic stenosis. Patients were enrolled at 48 centers in the United States and Canada. A list of participating sites and investigators

Pennsylvania, Philadelphia, Pennsylvania. This work was funded by Edwards Lifesciences. The trial sponsor funded the trial and developed the study protocol in collaboration with the steering committee, with guidance from the U.S. Food and Drug Administration. The sponsor was responsible for site selection, data monitoring, trial management, and statistical analysis. Dr. Makkar has received research grants from Edwards Lifesciences, Abbott, Medtronic, and Boston Scientific; has served as national Principal Investigator for Portico (Abbott) and Acurate (Boston Scientific) U.S. investigation device exemption trials; has received personal proctoring fees from Edwards Lifesciences; and has received travel support from Edwards Lifesciences, Abbott, and Boston Scientific. Dr. Blanke has Computed Tomography Core Laboratory contracts with Edwards Lifesciences, Medtronic, Abbott, and Neovasc (no direct compensation); and has received consulting fees from Edwards Lifesciences, Tendyne/Abbott Laboratories, Circle Cardiovascular Imaging, Neovasc, and Gore. Dr. Leipsic owns stock options in Circle CVI and HeartFlow; has received consulting fees from Circle CVI and HeartFlow; has Computed Tomography Core Laboratory contracts with Edwards Lifesciences, Medtronic, Abbott, and Neovasc (no direct compensation); and has received a research grant from Edwards Lifesciences. Dr. Thourani has received research support from Edwards Lifesciences, Boston Scientific, and JenaValve; and has received consulting fees from Edwards Lifesciences, Boston Scientific, Abbott, Gore Vascular, and JenaValve. Dr. Chakravarty has received consulting fees from Edwards Lifesciences, Abbott, Medtronic, and Boston Scientific. Dr. Brown has received research support to his institution (no direct compensation) from Edwards Lifesciences. Dr. Babaliaros has received research support to his institution (no direct compensation) from Edwards Lifesciences; has received consulting fees from Edwards Lifesciences and Abbott; and holds equity in Trans Mural Systems. Dr. Williams has received research support to his institution from Edwards Lifesciences. Dr. Jilaihawi has received consulting fees from Edwards Lifesciences, St. Jude Medical, Venus Medtech, Medtronic, and Boston Scientific; and has received research support from Medtronic, Abbott Vascular, and Edwards Lifesciences. Dr. Kodali has received research funding to his institution from Edwards Lifesciences, Medtronic, Boston Scientific, and Abbott; has received consulting fees from Abbott, Claret Medical, Admedus, and Meril Lifesciences; and has served on the Scientific Advisory Boards of Biotrace Medical, Dura Biotech, and Thubrikar Aortic Valve Inc. Dr. George has received consulting fees from Edwards Lifesciences; and has received institutional research support from Edwards Lifesciences. Dr. Lu is an employee of Edwards Lifesciences. Dr. McCabe has received research funding to his institution from Edwards Lifesciences; and has received consulting fees from Edwards Lifesciences. Dr. Smalling has received consulting fees and research support from St. Jude and Edwards Lifesciences. Dr. Yazdani has served as a proctor for Edwards Lifesciences. Dr. Bhatt has served on the Advisory Boards of Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, and Regado Biosciences; has served on the Boards of Directors of Boston Veterans Affairs Research Institute, Society of Cardiovascular Patient Care, and TobeSoft; has served as the Chair of American Heart Association Quality Oversight Committee; has served on the Data Monitoring Committees of Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards Lifesciences), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi-Sankyo), and Population Health Research Institute; has received honoraria from American College of Cardiology (Senior Associate Editor, *Clinical Trials and News,* ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; REDUAL PCI Clinical Trial Steering Committee funded by Boehringer Ingelheim; AEGIS-II Executive Committee funded by CSL Behring, Belvoir Publications (Editor-in-Chief, *Harvard Heart Letter*), Duke Clinical Research Institute (Clinical Trial Steering Committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor-in-Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), Medtelligence/ReachMD (Continuing Medical Education Steering Committees), Population Health Research Institute (for the COMPASS Operations Committee, Publications Committee, Steering Committee, and USA national coleader, funded by Bayer), Slack Publications (Chief Medical Editor,

is provided in the Supplemental Appendix. The protocol was approved by the institutional review board at each site.

Patients were eligible for inclusion in the study if they met the following criteria: severe aortic stenosis; low surgical risk as assessed by members of the local heart team and the trial case review committee, including no more than a predicted 4% risk of death by 30 days with surgery; no pre-existing indication for anticoagulation; and no contraindication to undergoing a CT scan with contrast. Among PARTNER 3 sites, only sites with the ability to perform high-quality multiphasic, electrocardiogram-gated 4D CT acquisitions were considered eligible for the study. A detailed list of inclusion and exclusion criteria is provided in the Supplemental Appendix. All patients provided written informed consent.

RANDOMIZATION AND MASKING. Eligible patients were randomized in a 1:1 ratio to undergo either TAVR with the SAPIEN 3 system by the transfemoral approach or surgery with a bioprosthetic valve. Patients underwent 4D CT at 30 days and 1 year after TAVR or surgery employing a dedicated multiphasic, electrocardiogram-gated, CT-acquisition protocol. All CTs were analyzed by an independent core laboratory (St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada) blinded to patient information, with 1-year CTs analyzed independently of the 30-day CT findings. The treating investigators were blinded to the results of the CT scans. Patients received aspirin (81 mg) and clopidogrel (≥300 mg) before TAVR and were advised to continue taking these medications (aspirin 81 mg and clopidogrel 75 mg) for at least 1 month after the procedure.

CT IMAGING AND EVALUATION. Details of the CT imaging protocol and image processing are provided in the Supplemental Appendix. Image data were reviewed by the core lab using dedicated post-processing workstations equipped with CVI42 (Circle Cardiovascular Imaging, Calgary, Alberta, Canada). Using multiplanar reformats, leaflets were evaluated for the presence of HALT and RLM (**Figure 1**). HALT was defined as visually identified increased leaflet thickness with typical meniscal appearance on long-axis views. Extent of leaflet thickening was semi-quantitatively graded on long-axis views carefully aligned with the leaflet center regarding involvement along the curvilinear leaflet beginning at the base, using a 4-tier grading scale: none; ≤25%; 26% to 50%; 51% to 75%; >75%. In the event of observed leaflet thickening, the presence of leaflet restriction (incomplete opening in systole) was evaluated as normal leaflet motion, partially restricted and immobile.

OUTCOMES. The primary objective of the study was to evaluate the prevalence of HALT and RLM in bioprosthetic aortic valves as well as to evaluate differences in transcatheter and surgical valves with regard to HALT and RLM. Based on serial CTs obtained at 30 days and 1 year, the study evaluated the natural history of HALT and RLM in the absence of anticoagulation. The study further evaluated the impact of HALT and RLM on valve hemodynamics and clinical outcomes. The clinical outcomes were

-*Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (Continuing Medical Education Steering Committees), *Clinical Cardiology* (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), and VA CART (U.S. Department of Veterans Affairs Clinical Assessment, Reporting, and Tracking) Research and Publications Committee (Chair); has received research funding from Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi, Synaptic, and The Medicines Company; has received royalties from Elsevier (Editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); has served as a site coinvestigator for Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), and Svelte; has served as a trustee of American College of Cardiology; and has performed unfunded research for FlowCo, Merck, Novo Nordisk, and Takeda. Dr. Bax has received grants to his institution from Medtronic, Biotronik, Edwards Lifesciences, Abbott Vascular, and Boston Scientific. Dr. Herrmann has received research support to his institution from Edwards Lifesciences, Abbott, Boston Scientific, Bayer, and Medtronic; and has received consulting fees from Edwards Lifesciences and Medtronic. Dr. Mack has received research funding to his institution from Edwards Lifesciences; has received consulting fees from Gore; has served as the Co-Principal Investigator of the PARTNER 3 trial (Edwards Lifesciences, no direct compensation) and as national Co-Principal Investigator of the COAPT trial (Abbott, no direct compensation); and has served as a study Chair for Medtronic. Dr. Leon has received research support to his institution from Edwards Lifesciences, Medtronic, Boston Scientific, and Abbott; has served on Advisory Boards for Medtronic, Boston Scientific, Gore, Meril Lifescience, and Abbott; and has served as the Co-Principal Investigator of the PARTNER 3 trial (Edwards Lifesciences, no direct compensation). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. John A. Bittl, MD, served as Guest Editor-in-Chief for this paper.

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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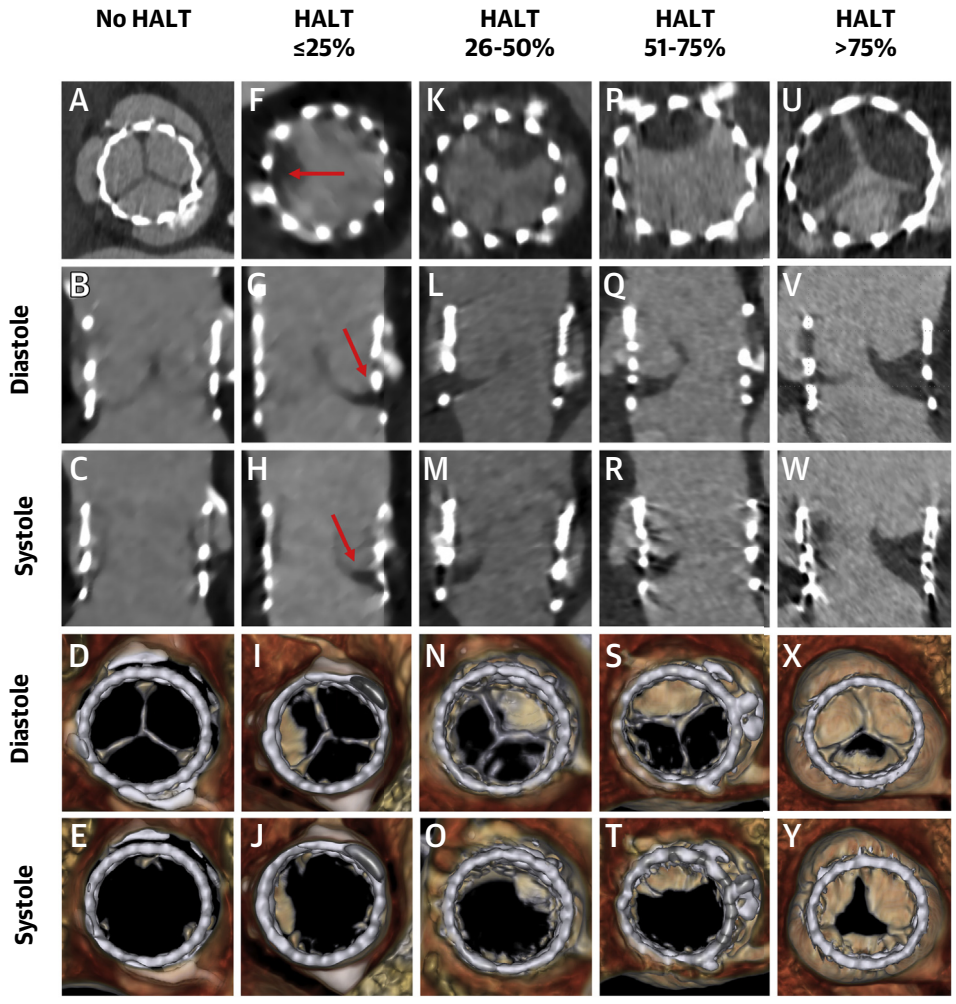
FIGURE 1 CT Assessment of HALT and RLM

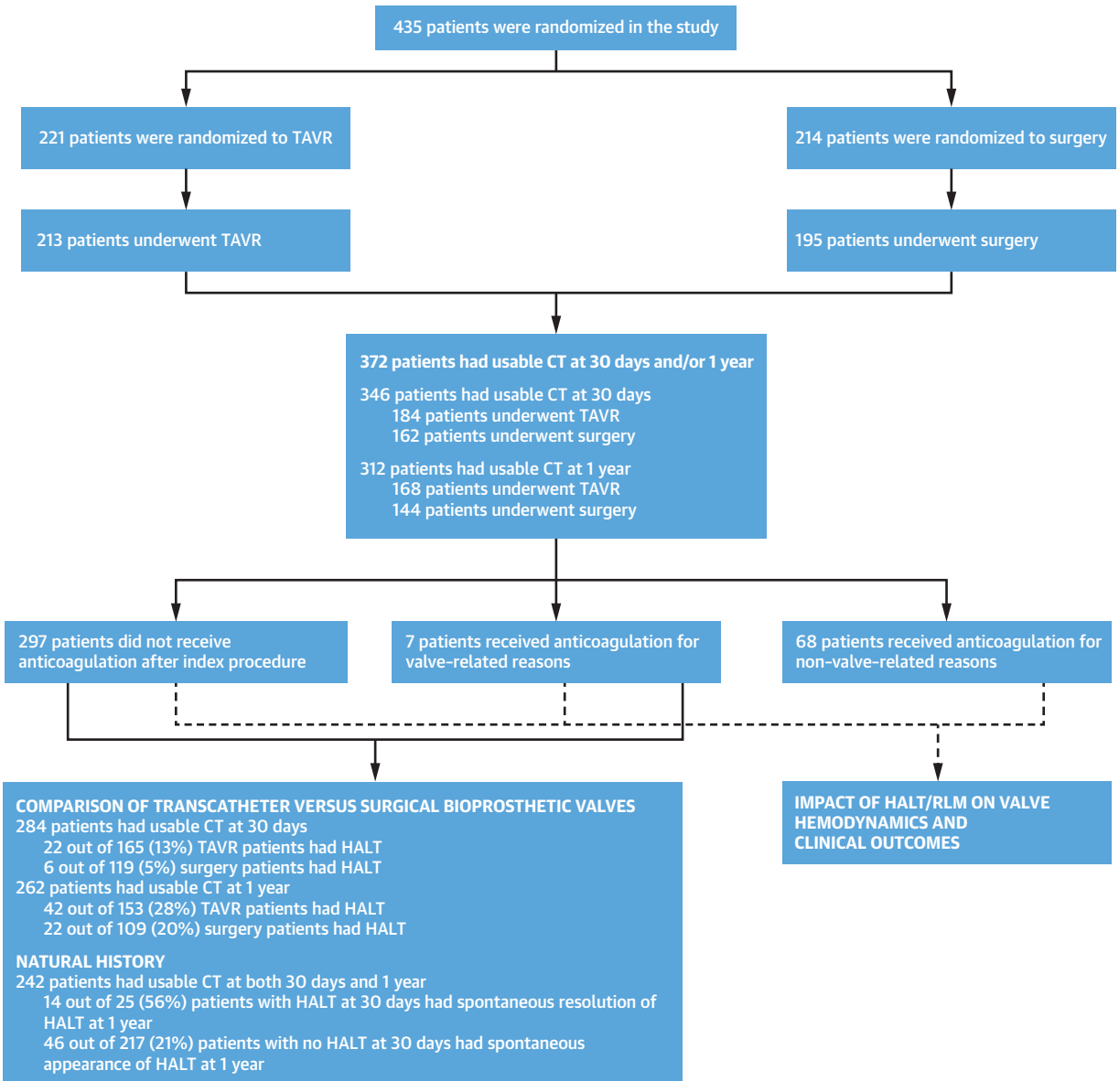


Computed tomography (CT) imaging was used to assess hypoattenuated leaflet thickening (HALT) and reduced leaflet motion (RLM). **(A to C, F to H, K to M, P to R, U to W)** HALT presenting as visually identified increased leaflet thickness with typical meniscal appearance on short- and long-axis views **(red arrows)**. Extent of leaflet thickening was semiquantitatively graded on long-axis views aligned with the leaflet center regarding involvement along the curvilinear leaflet beginning at the base, using a 4-tier grading scale: none **(A to C)**; ≤25% **(F to H)**; 26% to 50% **(K to M)**; 51% to 75% **(P to R)**; and >75% **(U to W)**. In the event of observed leaflet thickening, the presence of leaflet restriction (incomplete opening in systole) was evaluated as normal leaflet motion **(B, C)**, partially restricted **(G, H, L, M, Q, R)**, and immobile **(V, W)**. Volume-rendered images demonstrating normal leaflet motion **(D, E)**, partially reduced leaflet motion **(I, J, N, O, S, T)**, and immobile leaflets **(X, Y)**.

adjudicated by the clinical events committee according to Valve Academic Research Consortium-2 criteria (11). 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. The diagnosis of clinical valve thrombosis was made in the presence of symptoms attributable to valve thrombosis and the presence of either elevated gradients on echocardiogram or the presence of HALT on CT.

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD for baseline variables and mean ± SE for post-procedure variables. Categorical variables are presented as proportions. The comparisons between categorical variables are presented as risk ratios (RRs) with 95% confidence intervals (CIs). Continuous variables were compared using Student's

FIGURE 2 Study Design



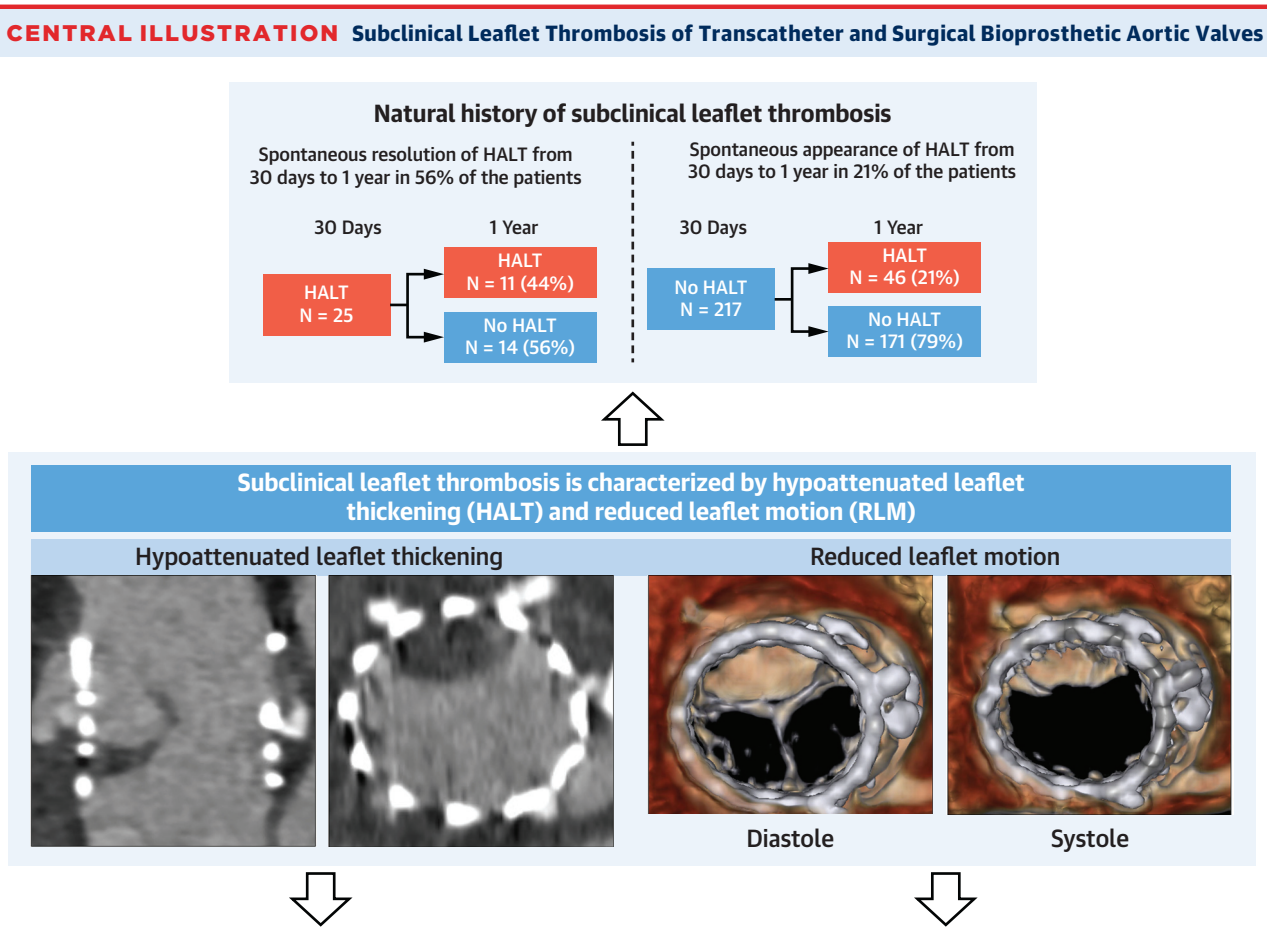
The incidence of HALT, natural history of this finding, and comparison between transcatheter and surgical valves was assessed based on the patients who either did not receive anticoagulation after the index procedure (n = 297) or received anticoagulation for valve-related clinical events (n = 7). The impact of HALT and RLM on valve hemodynamics and clinical outcomes was assessed based on all patients with usable CT. TAVR = transcatheter aortic valve replacement; other abbreviations as in Figure 1.

t-test. Predictors of HALT and RLM were assessed using multivariate logistic regression in the as-treated population for the overall cohort as well as for TAVR and surgical cohorts separately (see the detailed methodology in the Supplemental Appendix). All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

PATIENTS. The study design is summarized in Figure 2 and Supplemental Figure 1. From April 20, 2016, through March 16, 2018, a total of 435 patients at 48 sites were randomly assigned to undergo either TAVR (n = 221) or surgery (n = 214). The median duration of follow-up is 381.5 days (interquartile

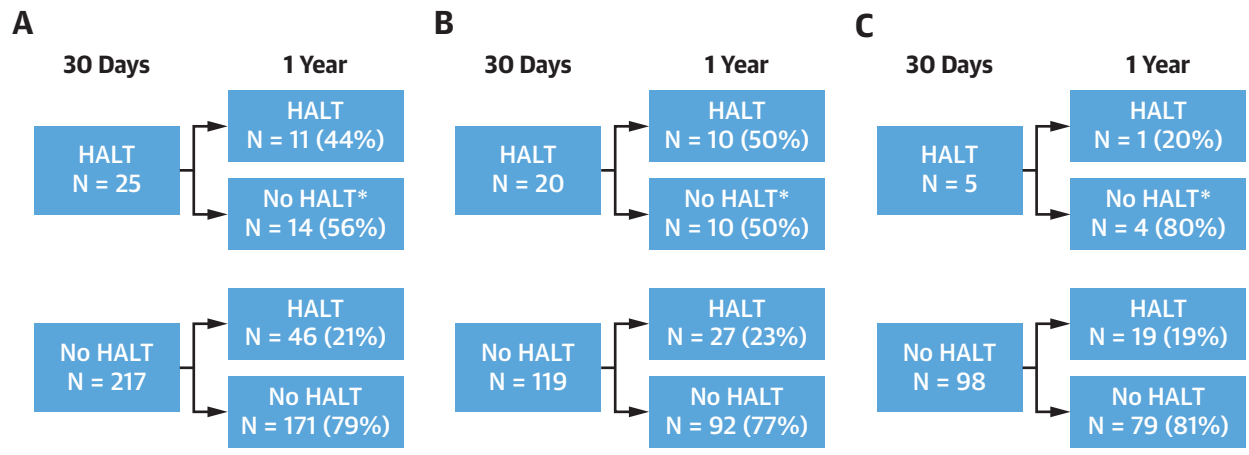
CENTRAL ILLUSTRATION **Subclinical Leaflet Thrombosis of Transcatheter and Surgical Bioprosthetic Aortic Valves**



Makkar, R.R. et al. J Am Coll Cardiol. 2020;75(24):3003–15.

Subclinical leaflet thrombosis, characterized by hypoattenuated leaflet thickening (HALT) and reduced leaflet motion (RLM) was a dynamic finding, with spontaneous resolution and new appearance in a significant proportion of patients, in the absence of anticoagulation. Subclinical leaflet thrombosis was more frequent in transcatheter versus surgical valves at 30 days, but not at 1 year. Increasing severity and persistence of subclinical leaflet thrombosis was associated with increased transaortic gradients. TAVR = transcatheter aortic valve replacement.

FIGURE 3 Natural History of HALT



Natural history of HALT based on patients with usable CTs at both 30 days and 1 year in the overall **(A),** TAVR **(B),** and surgery **(C)** cohorts. *None of the 14 patients experiencing spontaneous resolution of HALT received anticoagulation between 30-day and 1-year CT. Abbreviations as in **Figures 1 and 2**.

range: 370.0 to 446.0 days). The assigned procedure was performed in 408 patients, of whom 358 patients and 321 patients underwent a CT scan at 30 days and 1 year after the index procedure, respectively. Patients with CT scans that were usable for the assessment of HALT at either 30 days (n = 346) or 1 year (n = 312) were used for the analyses presented in this study. The baseline characteristics of patients who did not have a serial CT at 1 year and those who had a CT scan at 1 year but were not usable are summarized in Supplemental Table 1. The distribution of anticoagulation use is summarized in **Figure 2** and Supplemental Tables 2 to 6. The incidence of HALT, natural history of this finding, and comparison between transcatheter and surgical valves was assessed based on the patients that either did not receive anticoagulation after the index procedure (n = 297) or received anticoagulation for valve-related clinical events (n = 7). The impact of this finding on valve hemodynamics and clinical outcomes and the relationship between HALT and RLM was assessed based on all patients with usable CT.

INCIDENCE AND NATURAL HISTORY OF HALT. The incidence of HALT was 10% (28 of 284 patients) at 30 days and increased to 24% (64 of 262 patients) at 1 year. Baseline characteristics of patients with or without HALT at 30 days are summarized in Supplemental Table 7. A total of 242 patients with usable 30-day CT as well as 1-year CT were used to study the natural history of HALT (**Central Illustration, Figures 2 and 3**). Of the 25 patients with HALT at 30 days, spontaneous resolution was observed at 1 year in 14 patients (56%), in the absence of anticoagulation. Of the 217 patients without HALT at 30 days, new HALT was observed at 1 year in 46 patients (21%). Similar trends in natural history were observed in transcatheter and surgical valves analyzed separately, as well as in patients with different severity of HALT.

TRANSCATHETER VERSUS SURGICAL BIOPROSTHETIC VALVES. The comparison between transcatheter and surgical bioprosthetic valves is summarized in **Tables 1 and 2** and Supplemental Tables 8 and 9. A total of 4.7% of patients (10 of 213) after TAVR and 21.0% (41 of 195) after surgery were discharged on anticoagulation. The incidence of HALT at 30 days was significantly higher with transcatheter compared with surgical valves (22 of 165 patients, 13% vs. 6 of 119 patients, 5%; RR: 2.64; 95% CI: 1.11 to 6.32). At 1 year, the incidence of HALT was not significantly different between transcatheter and surgical valves (42 of 153 patients, 28% vs. 22 of 109 patients, 20%; RR: 1.38; 95% CI: 0.87 to 2.18). HALT >50% was more frequent in transcatheter valves than in surgical valves at 30 days (10 of 165 patients, 8.5% vs. 1 of 119 patients, 0.8%; RR: 7.21; 95% CI: 0.94 to 55.58), but not at 1 year (14 of 153 patients, 9.2% vs. 6 of 109 patients, 5.6%; RR: 1.68; 95% CI: 0.67 to 4.25).

HALT AND RLM. RLM was observed in 34 of 34 patients (100%) with HALT, and normal leaflet motion

TABLE 1 Baseline Characteristics of Patients Undergoing TAVR and Surgery

	TAVR (n = 179)	Surgery (n = 125)
Age, yrs	72.6 ± 5.8	71.1 ± 6.0
Male	127 (70.9)	82 (65.6)
Nonwhite race or ethnic group*	16 (8.9)	22 (17.6)
Body mass index, kg/m^2	29.8 ± 4.53	30.4 ± 4.97
STS-PROM score†	1.8 ± 0.7	1.7 ± 0.6
NYHA functional class III or IV	12 (6.8)	8 (6.4)
Coronary artery disease	56/179 (31.3)	37/125 (29.6)
Previous CABG	8/178 (4.5)	2/123 (1.6)
Previous stroke or TIA	10/179 (5.6)	7/125 (5.6)
Peripheral vascular disease	7/179 (3.9)	5/125 (4.0)
Diabetes	62/179 (34.6)	34/124 (27.4)
COPD	10/179 (5.6)	5/125 (4.0)
Pulmonary hypertension	8/178 (4.5)	5/125 (4.0)
Creatinine >2 mg/dl‡	0 (0.0)	0 (0.0)
Frailty (overall; >2/4+)§	0 (0.0)	0 (0.0)
Atrial fibrillation	10/179 (5.6)	4/125 (3.2)
Permanent pacemaker	5/179 (2.8)	1/125 (0.8)
Left bundle branch block	5/179 (2.8)	3/125 (2.4)
Right bundle branch block	16/179 (8.9)	9/125 (7.2)

Values are mean ± SD, n (%), or n/N (%).The study population includes the patients that either did not receive anticoagulation after the index procedure (297 patients) or received anticoagulation for valve-related clinical events (7 patients). *Race or ethnic group was reported by the patient. †The STS-PROM scores range from 0% to 100%, with higher scores indicating a greater risk of death within 30 days after the procedure. STS-PROM uses an algorithm that is based on the presence of coexisting illnesses to predict 30-day operative mortality. The STS-PROM score equals the predicted mortality expressed as a percentage. Less than 5% of patients in the population on which the STS-PROM algorithm is based had a predicted operative mortality (score) of more than 10%. ‡To convert the values for creatinine to micromoles per liter, multiply by 88.4. §Overall frailty was defined as the presence of 3 or more of the following criteria: grip strength of <18 kg, 5-m walk-test time of more than 6 s, serum albumin level of <3.5 g/dl, and Katz Activities of Daily Living total score of 4 or less (with scores ranging from 0 to 6 and higher scores indicating greater independence in performing activities of daily living).

CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association; STS-PROM = Society of Thoracic Surgery Predicted Risk of Mortality; TAVR = transcatheter aortic valve replacement; TIA = transient ischemic attack.

was observed in the 289 of 289 (100%) patients without HALT at 30 days. There was a similar relationship between HALT and RLM at 1 year (**Table 3**). The natural history of RLM with spontaneous resolution and appearance from 30 days to 1 year was similar to HALT (Supplemental Figure 2).

HALT AND VALVE HEMODYNAMICS. The valve hemodynamics are summarized in **Table 4** and Supplemental Figure 3. The mean aortic valve gradient was not significantly different in patients with HALT than in those without HALT at 30 days (13.2 ± 0.81 mm Hg vs. 11.7 ± 0.24 mm Hg; p = 0.08) or 1 year (13.7 ± 0.82 mm Hg vs. 12.6 ± 0.28 mm Hg; p = 0.24). At 1 year, there was a trend toward higher mean aortic valve gradients with greater degrees of HALT: HALT >25% versus ≤25% (15.1 ± 1.31 mm Hg vs. 12.6 ± 0.26 mm Hg; p = 0.07) and HALT >50% versus ≤50% (16.4 ± 2.05 mm Hg vs. 12.6 ± 0.26 mm Hg; p = 0.08). Because HALT is a dynamic finding and spontaneously resolved and appeared in a significant proportion of patients, we compared valve hemodynamics in patients with HALT present at both 30 days and 1 year versus those with no HALT at either 30 days or 1 year. The mean aortic valve gradients were significantly higher in patients with HALT at both 30 days and 1 year, compared with those who had no HALT at either 30 days or 1 year (17.8 ± 2.2 vs. 12.7 ± 0.3; p = 0.04). The baseline ejection fraction, velocity time integral ratio (left ventricular outflow tract velocity time integral-aortic valve velocity time integral) and frequency of central aortic regurgitation was similar in patients with or without HALT (Supplemental Table 10) or RLM (Supplemental Table 11).

HALT AND CLINICAL OUTCOMES. The clinical outcomes are summarized in **Table 5** and Supplemental Tables 12 to 16. The event rates at 1 year were low in the study cohort, with a total of 4 deaths, 2 strokes, 4 transient ischemic attacks (TIAs), 2 thromboembolic events (retinal artery occlusion), and 4 cases of clinical valve thrombosis in the entire cohort from day 7 to 1 year after index procedure. The individual endpoints of death, stroke, myocardial infarction (MI), TIA, or thromboembolic complications were not different between HALT and no HALT groups. At 30 days, the pooled rates of stroke, TIA, and thromboembolic complications (8.6% vs. 1.6%; RR: 5.3; 95% CI: 1.3 to 21.4); death, stroke, TIA, and thromboembolic complications (8.6% vs. 2.9%; RR: 3.0; 95% CI: 0.8 to 10.4), and incidence of clinical valve thrombosis (3 of 35, 8.6% vs. 1 of 311, 0.3%; RR: 26.7; 95% CI: 2.8 to 249.4) were higher in patients with HALT, than in patients with no HALT. Because HALT is a dynamic finding appearing and resolving in a significant proportion of patients, we further compared outcomes between patients with HALT at any time point (either at 30 days or at 1 year) versus those with no HALT at any time point (neither at 30 days nor at 1 year). Similar associations with clinical outcomes were noted when comparing outcomes between patients with HALT at any time point versus those with no HALT at any time point. There was no significant difference in quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire (Supplemental Figure 4) or New York Heart Association functional class (Supplemental Figure 5) in patients with or without HALT.

PREDICTORS OF HALT AND RLM. The predictors of HALT and RLM are mentioned in Supplemental Table 17. TAVR (vs. surgery) was a significant predictor of HALT (estimate: 1.40 ± 0.55; p = 0.0114) and RLM (estimate: 1.32 ± 0.57; p = 0.0204) at 30 days, but

TABLE 2 Incidence and Severity of HALT in Transcatheter and Surgical Bioprosthetic Valves

	30 Days				1 Year			
	TAVR (n = 165)	Surgery (n = 119)	RR (95% CI)	p Value*	TAVR (n = 153)	Surgery (n = 109)	RR (95% CI)	p Value*
HALT	22/165 (13)	6/119 (5)	2.64 (1.11–6.32)	0.03	42/153 (28)	22/109 (20)	1.38 (0.87–2.18)	0.19
1 leaflet	18	4			27	15		
2 leaflets	2	2			10	7		
3 leaflets	2	0			5	0		
HALT, 26% to 50%	14/165 (8.5)	4/119 (3.4)	2.52 (0.85–7.48)	0.09	23/153 (15.0)	10/109 (9.2)	1.66 (0.82–3.35)	0.19
1 leaflet	11	5			16	6		
2 leaflets	3	0			6	4		
3 leaflets	0	0			1	0		
HALT, >50%	10/165 (6.1)	1/119 (0.8)	7.21 (0.94–55.58)	0.03	14/153 (9.2)	6/109 (5.6)	1.68 (0.67–4.25)	0.35
1 leaflet	9	1			10	6		
2 leaflets	1	0			3	0		
3 leaflets	0	0			1	0		

Values are n/N (%) or n, unless otherwise indicated. *The p values were calculated using Fisher exact test.
CI = confidence interval; RR = risk ratio; other abbreviations as in Table 1.

not at 1 year. No significant baseline predictors were noted for HALT at 1 year. The percentage of oversizing, calculated as (area based on valve size - annular area from CT)/(annular area from CT), was a significant predictor of RLM at 1 year. For the TAVR subgroup, diabetes was negatively associated with HALT at 30 days (estimate: −1.16; p = 0.04). No other relationships were found between the predictors and HALT or RLM at 30 days or 1 year for TAVR or surgical subgroups.

DISCUSSION

The main findings of our study can be summarized as follows. First, the prevalence of subclinical leaflet thrombosis characterized by hypoattenuated leaflet thickening with reduced leaflet motion (HALT/RLM) on 4D CT was 10% at 30 days after transcatheter or surgical bioprosthetic valve replacement and further increased to 24% on serial CTs at 1 year. Second, this finding was dynamic and despite spontaneous resolution in one-half of the cases by 1 year, the new development in 20% of patients who had no HALT/RLM at 30 days increased the overall frequency to 1 of 4 patients at 1 year. Third, this finding was more frequent in transcatheter than in surgical valves at 30 days, but the differences were not significant at 1 year. Fourth, in most patients, this finding led to minimal increase in aortic valve gradients. Fifth, we did not see any significant association of this finding with the individual endpoints of death, MI, or stroke, but we did see an association with increased pooled thromboembolic event rates of stroke, TIA, and retinal artery occlusion.

The main significance of HALT/RLM is that it represents a mild form of valve dysfunction seen on imaging and is related to thrombus, a potentially reversible etiology. Since the initial reports, several questions have been raised regarding the true incidence, natural history, clinical impact, and differences between transcatheter and surgical valves (12). A recent study has suggested a link between thrombus and early calcification and degeneration of the valve leaflets (13). HALT/RLM also represents a potential mechanism of bioprosthetic valve degeneration and provides a possible target for intervention to favorably affect bioprosthetic valve durability (14,15).

TABLE 3 Association Between HALT and RLM

	Normal Leaflet Motion	Partially Restricted	Immobile
Leaflet Motion at 30 Days			
HALT at 30 days			
None	288	0	0
≤25%	0	11	0
26% to 50%	0	8	0
51% to 75%	0	12	1
>75%	0	1	1
Leaflet Motion at 1 Year			
HALT at 1 yr			
None	228	0	0
≤25%	0	31	0
26% to 50%	0	17	0
51% to 75%	0	13	0
>75%	0	3	6

Values are n.
HALT = hypoattenuated leaflet thickening; RLM= reduced leaflet motion.

TABLE 4 Impact of HALT on Valve Hemodynamics

	n	Gradient	p Value*
		30-Day Echo	
30-day CT			
HALT	35	13.2 ± 0.81	0.08
No HALT	310	11.7 ± 0.24	
HALT >25%	24	13.8 ± 1.11	0.08
HALT ≤25%	321	11.7 ± 0.23	
HALT >50%	15	14.6 ± 1.57	0.08
HALT ≤50%	330	11.7 ± 0.23	
HALT at 30 days and 1 yr	11	15.7 ± 1.9	0.09
No HALT at 30 days and 1 yr	171	12.0 ± 0.3	
		1-Year Echo	
1-yr CT			
HALT	72	13.7 ± 0.82	0.24
No HALT	232	12.6 ± 0.28	
HALT >25%	40	15.1 ± 1.31	0.07
HALT ≤25%	264	12.6 ± 0.26	
HALT >50%	22	16.4 ± 2.05	0.08
HALT ≤50%	282	12.6 ± 0.26	
HALT at 30 days and 1 yr	11	17.8 ± 2.2	0.04
No HALT at 30 days and 1 yr	166	12.7 ± 0.3	

Values are n or mean ± SD. *The p values are derived using Student's *t*-test.
CT = computed tomography; HALT = hypoattenuated leaflet thickening.

Previously reported studies on subclinical leaflet thrombosis were observational, with heterogeneous high-risk patient populations, multiple transcatheter and surgical valve types, and with variable timing of CTs (1,2). There are several unique methodologic strengths of the current study. This is the first randomized comparison between transcatheter and surgical bioprosthetic valves of the prevalence of subclinical leaflet thrombosis. Second, serial 30-day, and 1-year CTs were read by a blinded core laboratory, with analysis of the 1-year CTs blinded to findings at 30 days. Third, the treating physicians were blinded to CT findings to minimize anticoagulation treatment without sufficient clinical reasons, which would have altered the natural history. Fourth, the randomization of low-risk patients with fewer and comparable comorbidities between TAVR or surgery provides true differences between transcatheter versus surgical bioprosthetic valves.

The possible sequelae of subclinical leaflet thrombosis include central and systemic thromboembolism, progression to valve stenosis, and negative impact on long-term valve durability. The number of clinical events in this low-risk cohort with limited comorbidities was low and the study was not sufficiently powered to discern differences in clinical outcomes. We did not see an association among death, stroke, MI, and subclinical leaflet thrombosis. The pooled event rates of stroke, TIAs, and thromboembolic events were higher in patients with subclinical leaflet thrombosis. These findings are consistent with the previous observations from nonrandomized registries (1). However, given that total number of events was low, these findings need to be verified with longer follow-up and in larger cohorts of patients.

The differences in the frequency of valve-leaflet thickening and RLM between transcatheter and surgical valves are of great interest given the unknown long-term durability of transcatheter valves. Possible explanations for differences between transcatheter and surgical valves may include traumatic injury to the pericardial leaflets during valve crimping and barotrauma during deployment, differences in flow dynamics following aortic valve resection during surgery compared with leaving native aortic valve cusps in situ during TAVR, and asymmetric expansion and/or overexpansion or underexpansion of the transcatheter heart valves compared with a more circular geometry of the surgical valves (16–18). The differences in HALT between the surgical and transcatheter heart valves were not attributed to the higher rates of anticoagulation in the surgical cohort because we excluded the patients on anticoagulation for this analysis. Whereas this finding continued to be more prevalent in transcatheter valves at 1 year, the late differences were not statistically significant. Whether the early differences in HALT/RLM will affect valve durability remains unknown and will be addressed with long-term 10-year follow-up in this study.

The natural history of subclinical leaflet thrombosis derived from serial CTs in absence of anticoagulation was characterized by spontaneous resolution (50%), new appearance (20%), and increased frequency with time (24% at 1 year). These findings are novel and provide a perspective on the dynamic nature of this phenomenon and the challenges it may pose in the diagnosis, treatment, and design of clinical trials to study this phenomenon. From a practical viewpoint, these findings question the utility of routine CT scanning at a single early time point. Instead, clinical event-driven CT imaging for the detection of HALT/RLM would be more prudent.

Greater degrees of HALT (>50%) or HALT on both 30-day and 1-year CTs (**Table 4**) were associated with a 4- to 5-mm Hg increase in aortic gradients, which may be clinically relevant. It remains to be seen whether these small increases observed at 1 year will amplify over time to cause structural valve

TABLE 5 Impact of HALT at 30 Days on Clinical Outcomes

	Days 7-365			Days 7-30			Days 31-365		
	HALT+ (n = 35)	HALT− (n = 311)	RR (95% CI)	HALT+ (n = 35)	HALT− (n = 311)	RR (95% CI)	HALT+ (n = 35)	HALT− (n = 311)	RR (95% CI)
Death	0	4	NA	0	0	NA	0	4	NA
Heart failure	0	7	NA	0	1	NA	0	6	NA
Angina	0	9	NA	0	0	NA	0	9	NA
Myocardial infarction	0	3	NA	0	0	NA	0	3	NA
Clinical valve thrombosis*	3	1	26.7 (2.8-249.4)	0	0	NA	3	1	26.7 (2.8-249.4)
Stroke	1	1	8.9 (0.6-139.0)	1	0	NA	0	1	NA
TIA	1	3	3.0 (0.3-27.7)	0	1	NA	1	2	4.4 (0.4-47.8)
Retinal artery embolism	1	1	8.9 (0.6-139.0)	0	0	NA	1	1	8.9 (0.6-139.0)
Death, stroke, and myocardial infarction	1	8	1.1 (0.1-8.6)	1	0	NA	0	8	NA
Stroke and TIA	2	4	4.4 (0.8-23.4)	1	1	8.9 (0.6-139.0)	1	3	3.0 (0.3-27.7)
Stroke, TIA, and retinal artery embolism	3	5	5.3 (1.3-21.4)	1	1	8.9 (0.6-139.0)	2	4	4.4 (0.8-23.4)
Death, stroke, TIA, and retinal artery embolism	3	9	3.0 (0.8-10.4)	1	1	8.9 (0.6-139.0)	2	8	2.2 (0.5-10.1)

Values are n unless otherwise indicated. *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.

HALT+ = hypoattenuated leaflet thickening-positive; HALT− = hypoattenuated leaflet thickening-negative; NA = not available; other abbreviations as in Tables 1 and 2.

degeneration. Clinically significant valve thrombosis occurred in 2% of the transcatheter valves. Whereas there was a significant association of HALT with clinical valve thrombosis, 90% of patients with HALT at 30 days did not progress to clinical valve thrombosis during 1-year follow-up. The question of optimal antithrombotic therapy is best answered by dedicated clinical trials that evaluate both risk and benefits of anticoagulation after bioprosthetic valve replacement (19,20). In the recently published GALILEO (Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes) trial (21), in patients without an established indication for oral anticoagulation after successful TAVR, an anticoagulation treatment strategy with rivaroxaban at a dose of 10 mg daily combined with antiplatelet therapy was associated with a higher risk of death or thromboembolic complications and a higher risk of bleeding than an antiplatelet-based strategy. The lack of a clinical benefit of rivaroxaban was observed despite evidence from the 4D CT substudy of the GALILEO trial that rivaroxaban, compared with antiplatelet therapy, was associated with a lower incidence of subclinical valve leaflet thickening and RLM (21,22). The fundamental difference between the GALILEO 4D CT substudy compared with our study was that the GALILEO 4D CT substudy evaluated the impact of routine anticoagulation after TAVR on subclinical leaflet thrombosis in patients at high surgical risk. On the contrary, our study evaluated the natural history of subclinical leaflet thrombosis in patients undergoing either TAVR or surgery who were at low surgical risk, by performing serial CTs at 30 days and 1 year after AVR. Patients with planned use of anticoagulation were excluded in this trial to study the natural history of subclinical leaflet thrombosis. The average age of the patients in the GALILEO trial was 81 years with a significant prevalence of frailty and higher risks of bleeding, which may have resulted in the suboptimal risk-benefit ratio. Recently, TAVR use has been extended to younger and low-risk patients based on 2 low-risk clinical trials (10,23). Given the high frequency (1 in 4 patients) of subclinical valve leaflet thickening and RLM in our study in relatively younger patients and a possible connection of this finding with increased thromboembolic events, a strong argument can be made for additional clinical trials in the younger, healthier patients where the risk-benefit ratio for anticoagulation may be more favorable and valve durability is even more relevant. This argument holds true not only for TAVR, but for all bioprosthetic valves—transcatheter or surgical.

STUDY LIMITATIONS. First, the patients were followed up only to 1 year; longer follow-up data for up to 10 years are planned and needed to assess the full impact of this finding particularly on valve function and structural valve degeneration. Second, the study

was not powered to assess the impact on clinical outcomes or predictors of HALT or RLM. Third, our study does not address the issue of routine anticoagulation after bioprosthetic AVR or optimal antithrombotic therapy for the treatment of subclinical leaflet thrombosis in bioprosthetic valves.

CONCLUSIONS

Subclinical valve-leaflet thrombosis, characterized by leaflet thickening and RLM occurred in 1 of 4 patients with bioprosthetic valves on 1-year CT. The natural history was characterized by spontaneous resolution in one-half of the patients, new appearance in 4× as many patients and hence increased frequency on follow-up CT. This finding occurred more frequently in transcatheter compared with surgical bioprosthetic valves at 30 days but the differences were diminished at 1 year. Whereas there was no association with death, stroke, and MI, the pooled thromboembolic events were higher in patients with subclinical leaflet thrombosis. The impact on structural valve degeneration and thromboembolic events needs to be assessed in larger studies with long-term follow-up. This phenomenon may represent a potential therapeutic target to affect durability of transcatheter and surgical bioprosthetic valves.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Subclinical aortic valve leaflet thrombosis, characterized by thickening and reduced motion, is apparent in 1 of 4 patients with bioprosthetic valves 1 year after implantation. The finding is more frequent after transcatheter than surgical bioprosthetic valve replacement at 30 days, but this difference diminishes at 1 year. Spontaneous resolution occurs in one-half of cases.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine whether interventions that prevent or accelerate the resolution of subclinical leaflet thrombosis could reduce valve degeneration and lower the risk of thromboembolic events.

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KEY WORDS hypoattenuated leaflet thickening, leaflet thrombosis, reduced leaflet motion, subclinical leaflet thrombosis

APPENDIX For supplemental Methods, figures, and tables, please see the online version of this paper.