JACC: CARDIOVASCULAR IMAGING
VOL. 10, NO. 1, 2017

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2016.11.005

ORIGINAL RESEARCH

# Incidence, Predictors, and Mid-Term Outcomes of Possible Leaflet Thrombosis After TAVR

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## ABSTRACT

**OBJECTIVES** This study sought to clarify the incidence and predictors of hypoattenuated leaflet thickening (HALT) and mid-term outcomes after transcatheter aortic valve replacement.

**BACKGROUND** HALT detected on multidetector computed tomography (MDCT) scanning raised concerns about possible subclinical leaflet thrombosis.

**METHODS** We studied 70 of 100 consecutive patients from a single-center registry who underwent implantation with the Edwards SAPIEN-XT device. MDCT results, echocardiographic data, and laboratory findings obtained at the 6-month and 1-year follow-ups were analyzed.

**RESULTS** Of 70 patients, MDCT scans revealed HALT in 1 patient (1.4%) at discharge, 7 (10.0%) at 6 months, and 10 (14.3%) at 1 year post-transcatheter aortic valve replacement cumulatively. The degree of leaflet immobility correlated with the HALT area on 4-dimensional MDCT ($r = 0.68$) on the basis of data from 10 patients. HALT was associated with male sex (70% vs. 25%; $p = 0.008$) and larger sinus of Valsalva (31.0 ± 2.0 mm vs. 28.6 ± 2.6 mm; $p = 0.005$). HALT was found in 3 of 49 patients with a 23-mm bioprosthesis and in 7 of 21 patients with a 26-mm bioprosthesis (6.1% vs. 33.3%; $p = 0.006$). D-dimer levels were significantly increased in the HALT group at the 6-month (2.3 μg/ml [interquartile range (IQR): 2.1 to 6.1 μg/ml] vs. 1.1 μg/ml [IQR: 0.8 to 2.2 μg/ml]; $p = 0.002$) and 1-year (2.7 μg/ml [IQR: 1.7 to 4.8 μg/ml] vs. 1.2 μg/ml [IQR: 0.9 to 2.1 μg/ml]; $p = 0.006$) follow-ups, despite no differences at discharge. The pressure gradient was decreased in the HALT group at the 1-year follow-up (8.3 ± 0.8 mm Hg vs. 11.1 ± 4.9 mm Hg; $p = 0.005$). After detecting HALT, additional anticoagulation therapy was not administered. Clinical outcomes, including all-cause mortality (0% vs. 1.7%; $p = 1.00$) and stroke (0% vs. 0%; $p = 1.00$), were similar between the groups.

**CONCLUSIONS** HALT with reduced leaflet motion was not rare but usually subclinical. Valve hemodynamics and mid-term outcomes were uneventful even without additional anticoagulant therapy in our limited number of cases. Male sex, larger sinus and bioprosthesis size, and elevated D-dimer levels during follow-up were associated with this phenomenon. (J Am Coll Cardiol Img 2017;10:1–11) © 2017 by the American College of Cardiology Foundation.

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Manuscript received April 28, 2016; revised manuscript received October 22, 2016, accepted November 10, 2016.

**ABBREVIATIONS AND ACRONYMS**

**ECG** = electrocardiography

**HALT** = hypoattenuated leaflet thickening

**iEOA** = indexed effective orifice area

**IQR** = interquartile range

**MDCT** = multidetector computed tomography

**TAVR** = transcatheter aortic valve replacement

**THV** = transcatheter heart valve

**TTE** = transthoracic echocardiography

Transcatheter aortic valve replacement (TAVR), or transcatheter aortic valve implantation, was developed to improve survival and quality of life in patients with severe symptomatic aortic stenosis who are inoperable or at high risk for conventional surgical aortic valve replacement (1–5). The mid-term outcome of TAVR is well established (6,7), and long-term safety and efficacy must be proven before expanding the use of TAVR to younger and lower risk patients. Thrombus formation may complicate transcatheter heart valve (THV) placement, infrequently (<1%) causing heart failure symptoms due to increased pressure gradients (8–12) as well as thrombus after surgery (13).

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Hypoattenuated leaflet thickening (HALT) and reduced leaflet motion detected on multidetector computed tomography (MDCT) scanning raised concerns about possible leaflet thrombosis, based on its imaging characteristics and its resolution with additional anticoagulation therapy in patients who were undergoing either TAVR or surgical aortic valve bioprosthesis implantation (14). Leaflet thrombosis could possibly threaten THV durability (15). However, little is known about this condition owing to the lack of systematic all-comer screening and follow-up (16). The goal of the present study was to identify the incidence and predictors, and eventually mid-term clinical outcomes, of HALT by using systematic post-procedural multiple imaging modalities, including MDCT scanning, transthoracic echocardiography (TTE), and laboratory findings.

## METHODS

**STUDY POPULATION AND DESIGN.** This study was conducted at Keio University Hospital, and all data were prospectively collected in a dedicated database. Written informed consent for data collection was obtained from all patients.

All patients received an Edwards SAPIEN-XT valve (Edwards Lifesciences, Irvine, California); the available THV sizes during the study period were 23 and 26 mm in diameter. All patients underwent MDCT scanning and echocardiography before and after the procedure, at the time of discharge (within 3 days after implantation), and at 6-month and 1-year follow-ups. Patients were excluded if they died, had physical deconditioning, reduced renal function, or poor-quality imaging data. We evaluated the prospectively collected MDCT, echocardiographic, and clinical data of the consecutive patients who underwent TAVR.

**ECHOCARDIOGRAPHY AND LABORATORY TESTS.** TTE and laboratory tests were performed at each follow-up visit when CT scanning was performed. Left ventricular ejection fraction, aortic valve stenosis severity, and prosthetic valve function were evaluated by using TTE. Results were analyzed by experienced echocardiographers. The laboratory tests included D-dimer level, platelet count, and brain natriuretic peptide level.

**MDCT ACQUISITION.** All follow-up CT scans were routinely performed before discharge (within 3 days after implantation) and at 6-month and 1-year follow-ups with 4-dimensional CT acquisition. All CT examinations were performed by using a 320-detector-row CT scanner (Aquilion ONE/ViSION Edition, Toshiba Medical Systems, Ottawa, Japan). CT examinations were performed by using the following parameters: peak tube voltage, 100 kV; tube current, 10 to 350 mA (determined on the basis of a prespecified body mass index protocol); rotation speed, 0.275 s; and slice collimation, 0.5 × 100 mm. We used variable helical pitch scanning, which allows a seamless change in the scan pitch during 1 continuous acquisition and enables a combination of gated and nongated acquisitions within 1 scan. A pitch of 0.15 to 0.17 was chosen for electrocardiography (ECG)-gated thoracic imaging depending on the patient's heart rate, and 0.87 was used for non-ECG-gated abdominal scans to detect subclinical findings. Retrospective ECG-gated scanning was used to examine the thorax from approximately 2 cm above the lung apex to the bottom of the heart. Non-ECG-gated scanning of the abdomen and pelvis (to the level of the proximal thigh) was performed immediately after the thorax scan. A double-channel injection system (Dual Shot, Nemoto, Tokyo, Japan) via right antecubital venous access was used.

The volume of contrast medium (Iopamiron 370 or 350 mg/ml iodine concentration, Bayer, Osaka, Japan) was calculated as follows: scanning time (approximately 13 s, depending on the patient's habitus and heart rate) × weight × 0.06 ml. Contrast medium was injected at a rate of 0.06 ml/s × weight, followed by 20 ml of saline at a rate of 0.06 ml/s × weight. Scanning was automatically started with a 3-s delay after the attenuation of the region of interest placed in the ascending thoracic aorta reached the threshold of 150 Hounsfield units. Contiguous 1-mm-thick CT images (from above the apex to the proximal femoral region) were reconstructed by using the adaptive iterative dose reduction 3-dimensional algorithm (17). Image analysis was performed by using axial images and 3-dimensional

multiplanar reformatting on an independent workstation (Advantage Workstation 4.5, GE Healthcare, Waukesha, Wisconsin). Particular attention was paid to avoid artifacts due to the prosthesis itself and aortic valve calcification.

**THV ASSESSMENT USING MDCT SCANNING.** MDCT scanning is an emerging noninvasive strategy with proven usefulness for evaluating HALT in bioprosthetic aortic valves (8,9,18,19). Therefore, all THVs were evaluated blindly twice by using contrast-enhanced ECG-gated MDCT data by 2 experienced cardiologists. All patients who had HALT extending >3 mm in the lateral and longitudinal directions on the aortic aspect of the leaflet on 2-dimensional CT scanning were classified into the HALT group. The HALT area was measured by tracing at the level at which the largest HALT was observed on axial imaging. The measurements were performed in the diastolic phases of the cardiac cycle at 75% of the R-R interval, allowing optimal leaflet imaging. Moreover, depth of valve implantation was measured in millimeters beneath the aortic annulus based on MDCT scans performed before discharge.

Reduced leaflet motion was estimated with 4-dimensional CT scanning. Four-dimensional CT images were processed by using the Ziostation2 PhyZiodynamics software (Ziosoft Inc., Tokyo, Japan). Each phase of the 10-phase datasets was processed by using this software, and 2 additional phases between the original phases were inserted between the originals for improving motion coherence (20). The degree of leaflet motion immobility was classified into 5 groups (normal, mild, moderate, severe, and immobile) as previously described (14).

**PATIENT FOLLOW-UP.** All patients were observed in the intensive care unit for at least 24 h after TAVR. Dual antiplatelet therapy was continued for 6 months; thereafter, aspirin or clopidogrel was continued indefinitely. If the patients received anticoagulation therapy before their procedure, only aspirin was added before valve implantation and continued during the follow-up period. Clinical follow-up was performed at 1, 3, and 6 months and 1 year for the first year and annually thereafter.

**ENDPOINT DEFINITION.** The main endpoints of this study were HALT and reduced leaflet motion detected by using MDCT, and all-cause mortality. Other clinical endpoints, including stroke and transient ischemic attack, were evaluated as defined by the Valve Academic Research Consortium-2 criteria (21).

**STATISTICAL ANALYSIS.** All data analyses were performed with SPSS version 23.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York). Histograms and QQ-plots were used to test the distribution of continuous variables for normality. Continuous variables were expressed as mean ± SD, or as medians and interquartile ranges (IQRs), as appropriate. For comparison of continuous variables between data at each follow-up time, unpaired Student *t* tests or Wilcoxon rank sum tests were used, depending on variable distribution. Categorical variables (presented as numbers and percentages) were compared by using the Fisher exact test. Spearman's rank correlation coefficient was used to identify the strength of a relationship between the degree of leaflet immobility and HALT area. Receiver-operating characteristic curve analysis and the Youden index were used to identify the optimal cutoff values of D-dimer for the prediction of HALT. All tests were 2-sided, and p values $<0.05$ were considered statistically significant.

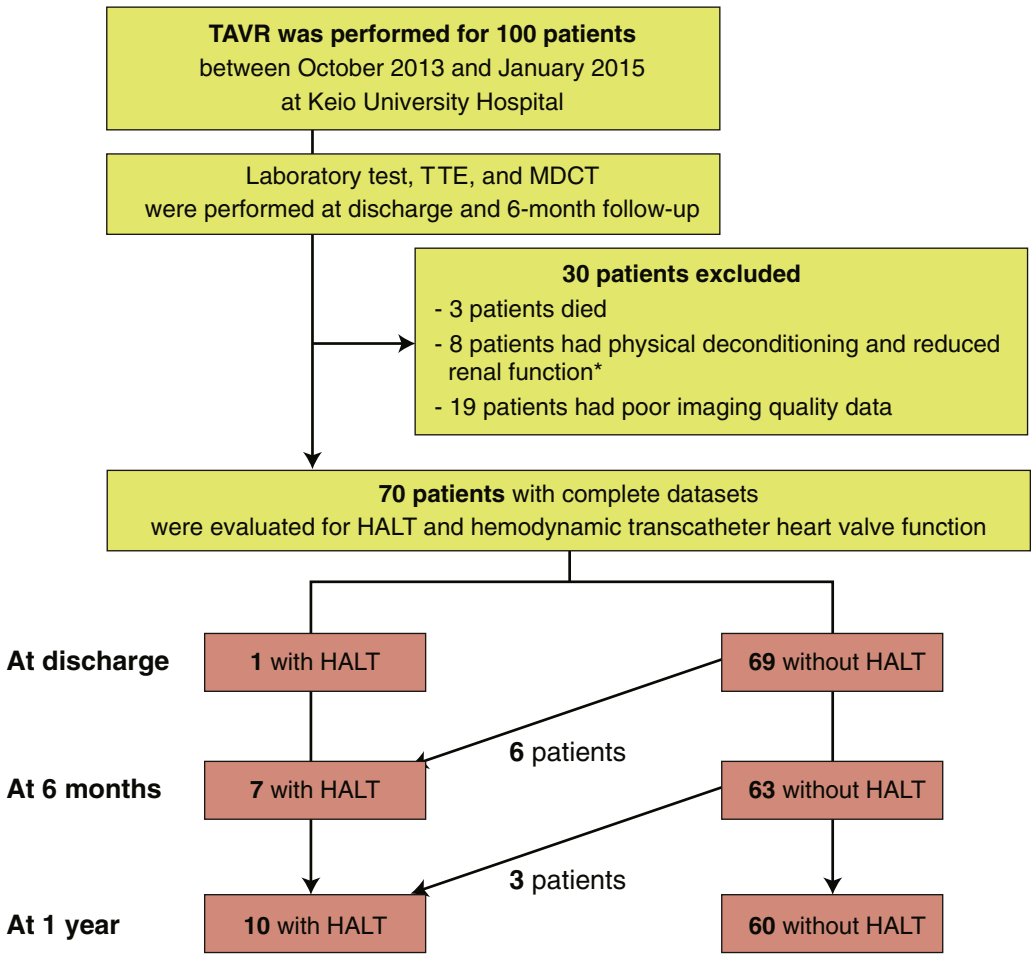
## RESULTS

**PATIENT CHARACTERISTICS.** Of 100 consecutive patients treated with TAVR between October 2013 and January 2015, a total of 70 who underwent a complete MDCT study before TAVR, at discharge, and at the 6-month and 1-year follow-ups with complete datasets (laboratory test, TTE, and MDCT) were included in this study. Patients who died (n = 3) or had physical deconditioning or reduced renal function (n = 8) were excluded. Moreover, 19 (21.3%) of 89 patients who underwent MDCT study were excluded because of poor-quality imaging data (**Figure 1**).

Of the 70 patients, 10 developed HALT (1 patient [1.4%] at discharge, 7 [10.0%] at the 6-month follow-up, and 10 [14.3%] at the 1-year follow-up; i.e., the HALT group). Three of these 10 patients received oral anticoagulation therapy at the time of discharge. HALT was not detected in the remaining 60 patients (i.e., the non-HALT group). The 10 patients in the HALT group did not develop any symptoms or show an increase in pressure gradient according to echocardiography during follow-up; therefore, they received no additional anticoagulation therapy.

Patients in the HALT group were more commonly men, compared with the non-HALT group (70% vs. 25%; p = 0.008) (**Table 1**). Other clinical characteristics were similar between the groups, including active cancer and antithrombotic regimens. The mean diameter of sinus of Valsalva was significantly larger in the HALT group in the MDCT study (mean diameter 31.0 ± 2.0 mm vs. 28.6 ± 2.6 mm; p = 0.005), despite no significant difference in annulus area (397 ± 49 $mm^2$ vs. 368 ± 58 $mm^2$; p = 0.13). A 26-mm SAPIEN-XT valve was more frequently used in the HALT group (70% vs.

**FIGURE 1 Study Design**




In the present study, 30 patients were excluded because of death, physical deconditioning, or unusable multidetector computed tomography (MDCT) imaging. *Reduced renal function was defined as an estimated glomerular filtration rate (eGFR) <30 ml/[min • 1.73 $m^2$]. HALT = hypoattenuated leaflet thickening; TAVR = transcatheter aortic valve replacement; TTE = transthoracic echocardiography.

23%; p = 0.006), presumably owing to the increased incidence of male sex and larger sinus of Valsalva in the HALT group. The ratio of the sinus of Valsalva to the THV diameter was similar between groups (1.24 ± 0.07 mm vs. 1.21 ± 0.08 mm; p = 0.23). Other procedural factors including the approach site and underfilling of the THV were similar between groups (30% vs. 43%; p = 0.51). In terms of the depth of valve implantation, THVs were implanted lower in the HALT group, with borderline statistical significance (4.7 ± 1.5 mm vs. 3.9 ± 1.3 mm; p = 0.07).

In the 30 excluded patients, the Society of Thoracic Surgeons' score was relatively high (7.5% [IQR: 5.0% to 10.9%] vs. 6.1% [IQR: 4.5% to 8.7%]; p = 0.02), and the estimated glomerular filtration rate was lower (46.0 ± 22.6 ml/min vs. 56.2 ± 18.4 ml/min; p = 0.02) compared with the remaining 70 patients analyzed in the study. We presumed that reduced renal function was related to higher Society of Thoracic Surgeons score because there were no differences in other baseline characteristics. Even in 11 of the 30 patients who died or had physical deconditioning, the characteristics did not differ from the overall study population. Three patients died of interstitial pneumonia, stroke with pre-existing atrial fibrillation, and congestive heart failure, respectively. Ischemic stroke occurred during the procedure in 1 patient. Therefore, no death or adverse event was related to leaflet thrombosis among the excluded cases.

**TABLE 1 Baseline Characteristics**

| | Total (N = 70) | HALT (n = 10) | Non-HALT (n = 60) | p Value |
|---|---|---|---|---|
| Pre-operative characteristics | | | | |
| Age, yrs | 85 (82–87) | 86 (83–87) | 85 (81–87) | 0.30 |
| Male | 22 (31) | 7 (70) | 15 (25) | 0.008 |
| STS score, % | 6.0 (4.5–8.7) | 7.6 (4.9–9.1) | 5.9 (4.4–8.5) | 0.24 |
| Body mass index, kg/m$^2$ | 21.9 (19.5–24.7) | 23.3 (20.5–24.9) | 21.6 (19.4–24.7) | 0.40 |
| Hypertension | 52 (74) | 6 (60) | 46 (77) | 0.27 |
| Dyslipidemia | 41 (59) | 7 (70) | 34 (57) | 0.51 |
| IDDM | 0 (0) | 0 (0) | 0 (0) | 1.00 |
| NYHA functional class III/IV | 37 (53) | 2 (20) | 35 (58) | 0.04 |
| Previous CABG | 2 (3) | 0 (0) | 2 (3) | 1.00 |
| eGFR <60 ml/min | 47 (67) | 6 (60) | 41 (68) | 0.72 |
| History of atrial fibrillation | 17 (24) | 3 (30) | 14 (23) | 0.70 |
| Previous pacemaker | 3 (4) | 0 (0) | 3 (5) | 1.00 |
| Peripheral artery disease | 17 (24) | 3 (30) | 14 (23) | 0.70 |
| Chronic lung disease | 13 (19) | 1 (10) | 12 (20) | 0.68 |
| Active cancer | 7 (10) | 0 (0) | 7 (12) | 0.58 |
| Warfarin | 11 (16) | 1 (10) | 10 (17) | 1.00 |
| Antithrombotic regimen at implantation | | | | 0.81 |
| Single antiplatelet therapy | 26 (37) | 5 (50) | 21 (36) | |
| DAPT | 26 (37) | 3 (30) | 23 (38) | |
| OAC + single antiplatelet therapy | 12 (17) | 2 (20) | 10 (17) | |
| Echocardiographic characteristics | | | | |
| LVEF, % | 65.0 ± 13.0 | 63.7 ± 17.3 | 65.2 ± 12.3 | 0.74 |
| Indexed AVA, cm$^2$ | 0.46 ± 0.10 | 0.47 ± 0.10 | 0.45 ± 0.10 | 0.68 |
| Mean pressure gradient, mm Hg | 47.6 ± 16.3 | 52.4 ± 16.2 | 46.8 ± 16.3 | 0.31 |
| Indexed stroke volume, ml | 45.8 ± 9.7 | 47.4 ± 10.2 | 45.5 ± 9.7 | 0.58 |
| Aortic valve complex characteristics (measured on MDCT scan) | | | | |
| Annulus area, mm$^2$ | 372 ± 58 | 397 ± 49 | 368 ± 58 | 0.13 |
| Sinus of Valsalva, mm | | | | |
| Mean diameter | 28.9 ± 2.6 | 31.0 ± 2.0 | 28.6 ± 2.6 | 0.005 |
| Sinus of Valsalva/THV diameter ratio | 1.21 ± 0.08 | 1.24 ± 0.07 | 1.21 ± 0.08 | 0.23 |
| Procedural characteristics | | | | |
| Approach | | | | 1.00 |
| Transfemoral access | 59 (84) | 9 (90) | 50 (83) | |
| Transapical access | 11 (16) | 1 (10) | 10 (17) | |
| Prosthesis size | | | | 0.006 |
| 23 mm | 49 (70) | 3 (30) | 46 (77) | |
| 26 mm | 21 (30) | 7 (70) | 14 (23) | |
| Underfilling of THV | 29 (41) | 3 (30) | 26 (43) | 0.51 |
| Post-dilation | 11 (16) | 2 (20) | 9 (15) | 0.66 |
| PVL more than moderate | 0 (0) | 0 (0) | 0 (0) | 1.00 |
| Depth of valve implantation, mm | 4.0 ± 1.3 | 4.7 ± 1.5 | 3.9 ± 1.3 | 0.07 |

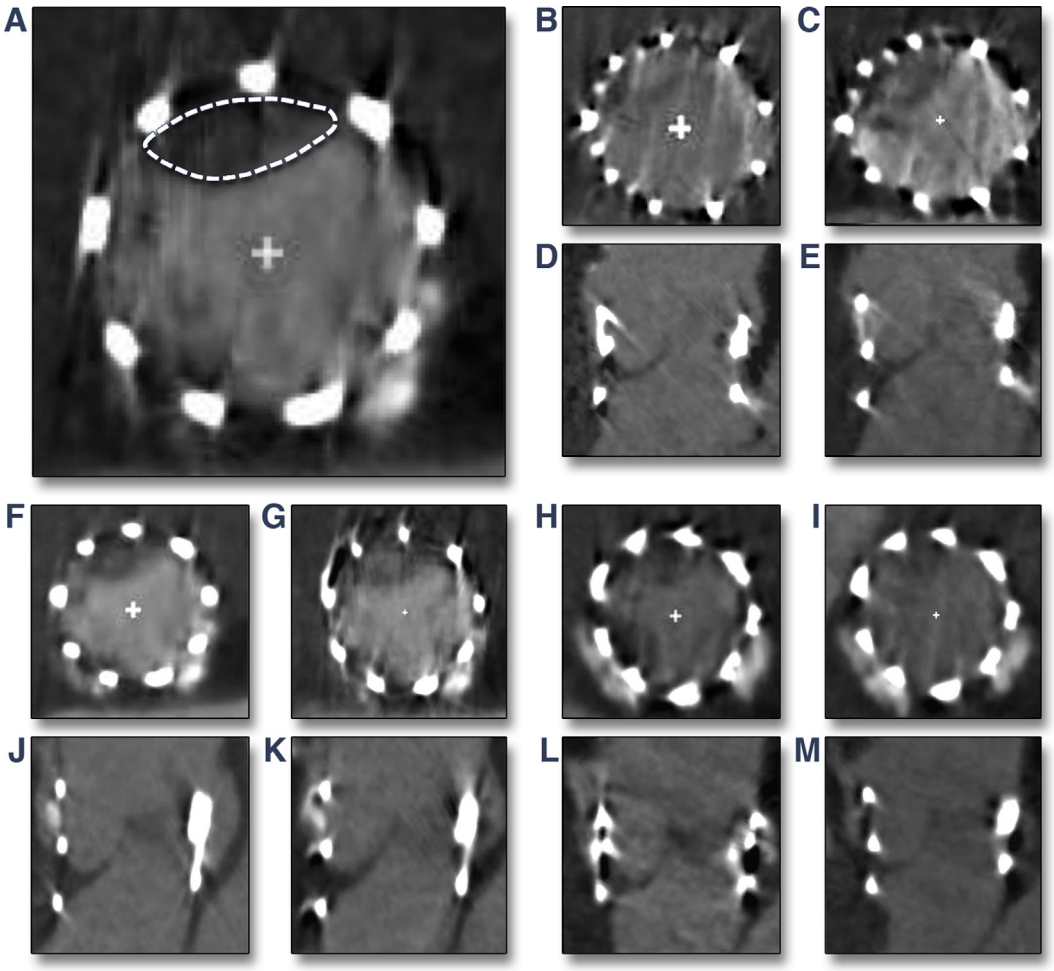
Values are median (interquartile range), n (%), or mean ± SD.

AVA = aortic valve area; CABG = coronary artery bypass graft surgery; DAPT = dual antiplatelet therapy; eGFR = estimated glomerular filtration rate; HALT = hypoattenuated leaflet thickening; IDDM = insulin-dependent diabetes mellitus; LVEF = left ventricular ejection fraction; MDCT = multidetector computed tomography; NYHA = New York Heart Association; OAC = oral anticoagulant; PVL = paravalvular leak; STS = Society of Thoracic Surgeons; THV = transcatheter heart valve.

In all of the 19 cases excluded for poor CT imaging, studies were unreadable due to either artifacts from the stent frame, or blurred images caused by motion artifacts or insufficiency of breath-hold, and were not related to the iodine dose.

**DISTRIBUTION AND 4-DIMENSIONAL ASSESSMENT OF THV USING MDCT SCANNING.** All HALT were attached on the outflow, low-pressure side of the leaflet (i.e., the aortic side) beginning from the bottom of the cusps. In 9 of 10 patients, HALT was located on the leaflets corresponding to the native right coronary or noncoronary cusp regions. In 4 of the 9 patients, HALT overlapped the right coronary and noncoronary regions. The frequency of the HALT corresponding to the native left coronary cusp region was considerably lower without statistical significance (only 1 patient). Four-dimensional CT scanning revealed that the

**FIGURE 2 HALT Area and Interval Changes During Follow-Up**




The **(A)** hypoattenuated leaflet thickening (HALT) area was measured by tracing at the level where the largest HALT was observed on axial imaging **(white dotted circle)**. The representative data in patients with increased HALT (from **B** and **D** to **C** and **E**), stable (from **F** and **J** to **G** and **K**), and regressed (from **H** and **L** to **I** and **M**) are shown. First and third rows show axial images in diastole; second and fourth rows, the corresponding sagittal images. See Online Videos 1 and 2.

locations of reduced leaflet motion completely matched the leaflets with HALT (Online Video 1). The degree of leaflet immobility and the HALT area (**Figure 2A**) are shown in **Table 2** with details of patients in the HALT group. Nine of 10 patients had some degree of leaflet immobility (mild in 2 patients, moderate in 1 patient, severe in 4 patients, and immobile in 2 patients). The HALT area ranged from 33.4 to 100.3 $mm^2$, and positive correlation was found between the degree of leaflet immobility and the HALT area ($r = 0.68$; $p = 0.03$) based on the 10 patients. Less amount of HALT was observed in 3 patients with a small reduction of the leaflet mobility (cases 1, 4, and 5). Furthermore, spontaneous regression was observed in 1 patient between 6 months and 1 year, without anticoagulation therapy (case 5 in **Table 2**). In the other patients in whom HALT was detected at ≥2 points of follow-up, HALT increased in 4 patients and was stable in 2 patients (**Figure 2**).

**HEMODYNAMIC ASSESSMENT OF THV USING TTE.** As shown in **Figures 3A** to **3C**, the incidence of HALT was not associated with increased mean pressure gradient ($9.8 \pm 3.1$ mm Hg vs. $11.0 \pm 4.4$ mm Hg; $p = 0.41$), decreased indexed effective orifice area (iEOA) ($1.11 \pm 0.21$ $cm^2$ vs. $1.07 \pm 0.21$ $cm^2$; $p = 0.54$), or decreased

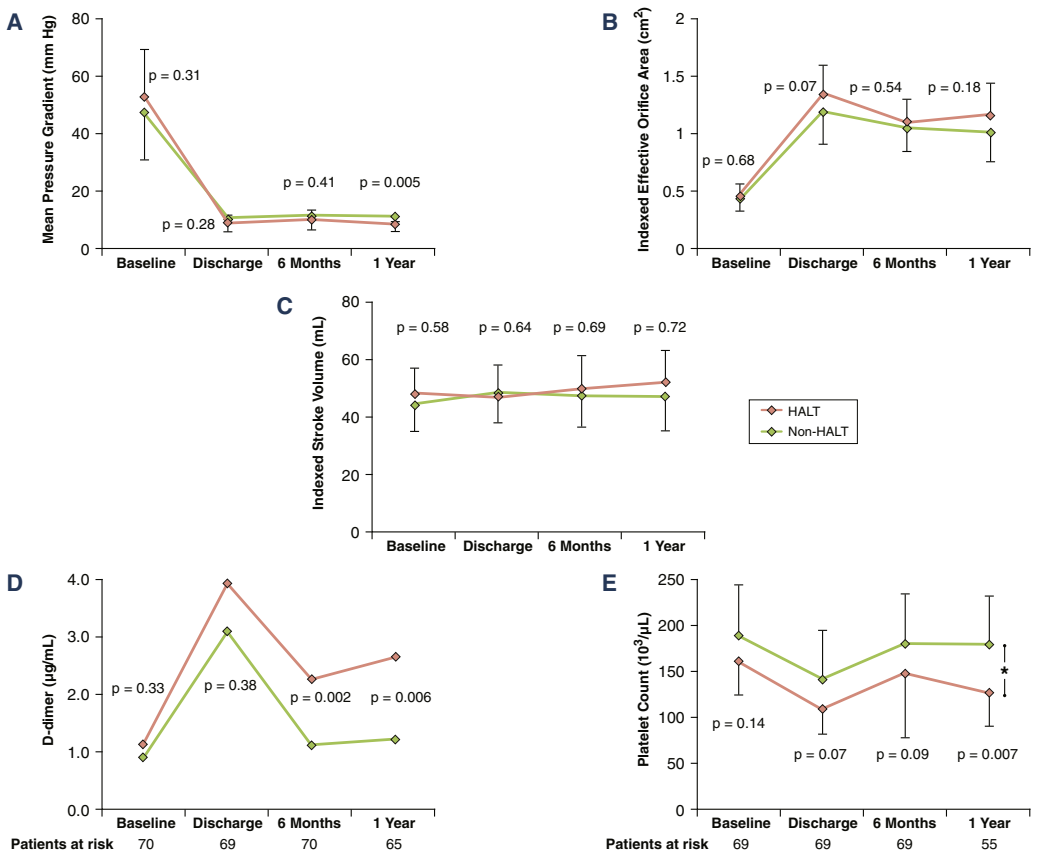
**TABLE 2** Patient Characteristics in the HALT Group

| | Diagnosed THV Thrombosis | | | Antithrombotic Therapy | | | |
|---|---|---|---|---|---|---|---|
| Case # | Discharge | 6 Months | 1 Year | At Discharge | At the Timing of Detection | Degree of Leaflet Immobility | HALT Area ($mm^2$) |
| 1 | No | Yes | Yes | Aspirin + clopidogrel | Aspirin | Mild | 54.7 |
| 2 | No | No | Yes | Aspirin + clopidogrel | Aspirin | Immobile | 60.2 |
| 3 | Yes | Yes | Yes | Aspirin + dabigatran | Aspirin + dabigatran | Severe | 67.2 |
| 4 | No | Yes | Yes | Aspirin + clopidogrel | Aspirin + clopidogrel | None | 33.4 |
| 5 | No | Yes | Yes* | Aspirin + clopidogrel | Aspirin | Mild | 54.5 |
| 6 | No | Yes | Yes | Warfarin + clopidogrel† | Warfarin + clopidogrel | Severe | 62.8 |
| 7 | No | Yes | Yes | Aspirin + clopidogrel | Aspirin + clopidogrel | Moderate | 78.9 |
| 8 | No | No | Yes | Aspirin + rivaroxaban | Aspirin + rivaroxaban | Immobile | 100.3 |
| 9 | No | No | Yes | Aspirin | Aspirin | Severe | 87.4 |
| 10 | No | Yes | Yes | Aspirin + clopidogrel | Aspirin + clopidogrel | Severe | 79.0 |

*Despite discontinuation of clopidogrel therapy 6 months after implantation, HALT tended to regress spontaneously without warfarin. †The patient was taking warfarin for chronic atrial fibrillation. However, the anticoagulation therapy was not effective because of inadequate prothrombin time–to-international normalized ratio (<1.6 throughout the follow-up period).

Abbreviations as in Table 1.

**FIGURE 3** Follow-Up Data During 1 Year After Transcatheter Aortic Valve Replacement




The between-group differences in the echocardiographic parameters, including the **(A)** mean pressure gradient, **(B)** indexed effective orifice area, and **(C)** indexed stroke volume and in the laboratory tests, including **(D)** D-dimer and **(E)** platelet count of patients at risk. *Statistically significant difference was observed at 1-year follow-up.

indexed stroke volume (47.3 ± 10.5 ml vs. 48.9 ± 11.4 ml; p = 0.69) at the 6-month follow-up (n = 70), as well as the 1-year follow-up in 61 patients (iEOA: 1.18 ± 0.27 $cm^2$ vs. 1.03 ± 0.25 $cm^2$ [p = 0.18]; indexed stroke volume: 50.3 ± 10.4 ml vs. 48.4 ± 12.1 ml; p = 0.72). The mean pressure gradient was decreased in the HALT group at the 1-year follow-up (8.3 ± 0.8 mm Hg vs. 11.1 ± 4.9 mm Hg; p = 0.005). Compared with the THV size, mean pressure gradients at 1 year were similar between the HALT group and the non-HALT group both in patients with the 26-mm THV (8.3 mm Hg vs. 9.6 mm Hg; p = 0.47) and those with the 23-mm THV (9.0 mm Hg vs. 11.5 mm Hg; p = 0.64).

In 1 patient with HALT, severely reduced motion of leaflets was detected on 4-dimensional CT scanning (Online Video 2). TTE also revealed an increased mean pressure gradient from 6 to 11 mm Hg and transvalvular velocity from 1.7 to 2.2 m/s, and decreased iEOA from 1.61 to 0.84 $cm^2$, as well as reduced indexed stroke volume from 53.8 to 32.6 ml.

**LABORATORY FINDINGS DURING FOLLOW-UP.** Serum D-dimer levels and blood platelet counts were compared between the groups. Although D-dimer levels did not differ significantly between the groups at baseline (n = 70; 1.1 μg/ml [IQR: 0.7 to 2.2 μg/ml] vs. 0.9 μg/ml [IQR: 0.4 to 1.7]; p = 0.33) and at discharge (n = 69; 4.0 μg/ml [IQR: 2.0 to 4.7 μg/ml] vs. 3.1 μg/ml [IQR: 1.8 to 4.3 μg/ml]; p = 0.38), sustained elevation in D-dimer levels was detected in the HALT group at both the 6-month (n = 70; 2.3 μg/ml [IQR: 2.1 to 6.1 μg/ml] vs. 1.1 μg/ml [IQR: 0.8 to 2.2 μg/ml]; p = 0.002) and 1-year (n = 65; 2.7 μg/ml [IQR: 1.7 to 4.8 μg/ml] vs. 1.2 μg/ml [IQR: 0.9 to 2.1 μg/ml]; p = 0.006) follow-ups (Figure 3D). The optimal cutoff values of D-dimer for the prediction of HALT were found to be 2.0 at the 6-month follow-up (C-index 0.82; sensitivity 0.90; specificity 0.75; accuracy 0.76) and 1.8 at the 1-year follow-up (C-index 0.78; sensitivity 0.80; specificity 0.71; accuracy 0.72).

Despite blood platelet counts being similar at baseline (159 ± 35 $10^3$/μl vs. 187 ± 57 $10^3$/μl; p = 0.14), there was a trend toward a lower platelet count at discharge (108 ± 26 $10^3$/μl vs. 140 ± 53 $10^3$/μl; p = 0.07) and the 6-month follow-up (146 ± 68 $10^3$/μl vs. 179 ± 55 $10^3$/μl; p = 0.09) in the HALT group. The difference reached significance at the 1-year follow-up (126 ± 36 $10^3$/μl vs. 178 ± 53 $10^3$/μl; p = 0.007) (Figure 3E).

Brain natriuretic peptide levels were similar between the groups (baseline, n = 70; 229 pg/ml [IQR: 124 to 538 pg/ml] vs. 223 pg/ml [IQR: 128 to 474 pg/ml], p = 0.91; at discharge, n = 69; 116 pg/ml [IQR: 84 to 231 pg/ml] vs. 174 pg/ml [IQR: 108 to 375 pg/ml], p = 0.20; at the 6-month follow-up, n = 70; 124 pg/ml [IQR: 52 to 189 pg/ml] vs. 110 pg/ml [IQR: 58 to 176 pg/ml], p = 0.71; and at the 1-year follow-up, n = 66; 129 pg/ml [IQR: 86 to 233 pg/ml] vs. 111 pg/ml [IQR: 48 to 184 pg/ml], p = 0.71).

**CLINICAL OUTCOMES.** Clinical outcomes are summarized in Table 3. Clinical outcomes, including all-cause mortality (0% vs. 1.7%; p = 1.00), New York Heart Association functional class (p = 0.90), stroke (0% vs. 0%; p = 1.00), myocardial infarction (0% vs. 0%; p = 1.00), and transient ischemic attack (0% vs. 1.7%; p = 1.00), did not significantly differ between the groups.

**TABLE 3 Clinical Outcomes at 1 Year After TAVR in the Study Group**

| | Total (N = 70) | HALT (n = 10) | Non-HALT (n = 60) | p Value |
|---|---|---|---|---|
| Death* | 1 (1) | 0 (0) | 1 (1.7) | 1.00 |
| NYHA functional class | | | | 0.90 |
| 1 | 57 (81) | 9 (90) | 48 (80.0) | |
| 2 | 11 (16) | 1 (10) | 10 (16.7) | |
| 3 | 1 (1) | 0 (0) | 1 (1.7) | |
| 4 | 0 (0) | 0 (0) | 0 (0) | |
| Myocardial infarction | 0 (0) | 0 (0) | 0 (0) | 1.00 |
| Stroke | 0 (0) | 0 (0) | 0 (0) | 1.00 |
| Transient ischemic attack† | 1 (1) | 0 (0) | 1 (1.7) | 1.00 |

Values are n (%). *1 patient in the non-HALT group died of aspiration pneumonia at 1 year after the procedure. †1 patient in the non-HALT group had a transient ischemic attack 6 months after transcatheter aortic valve replacement (TAVR).

Abbreviations as in Table 1.

## DISCUSSION

To the best of our knowledge, this study is one of the few to demonstrate systematic and prospective 1-year follow-up with MDCT studies to detect HALT. Our results showed that the accumulated incidence of HALT was 1.4%, 10.0%, and 14.3% at discharge, 6 months, and 1 year, respectively, and that HALT was not associated with clinical events or increased pressure gradient at the 1-year follow-up in our limited number of cases. Although Leetmaa et al. (18) reported the frequency of HALT in Edwards SAPIEN-XT THV of 4% (median follow-up time of 91 days), our data at discharge showed a markedly lower frequency. The interstudy difference in the follow-up time point can lead to this discrepancy. Moreover, HALT may predominantly develop between these points.

Male sex was associated with a higher prevalence of HALT. Larger THV size and sinus of Valsalva were also significantly associated with this finding,

although that variability may be partly explained by sex-related differences in physique. The retention of blood flow in a large sinus of Valsalva may increase the risk of HALT. Interestingly, the mean pressure gradient at 1 year was decreased in the HALT group. This contrasting result could be associated with the frequency of larger THV size. Although comorbid conditions (including atrial fibrillation, left ventricular dysfunction, previous thromboembolism, and hypercoagulable states) increase the risk of valve thrombosis in patients with surgical bioprostheses (22), there was no significant association in this study. Importantly, the THVs tended to be implanted lower in the HALT group with borderline statistical significance, and this could be a risk factor for HALT. Moreover, although decreased platelet count was seen in the HALT group, the mean count remained $>100 \times 10^3/\mu l$, and this phenomenon may not negatively affect clinical outcomes (23).

Anticoagulation with warfarin prevents and treats reduced leaflet motion (14). Notably, none of the patients in this series was symptomatic or developed stroke or other thrombotic events, despite not receiving additional anticoagulation or antiplatelet therapy after detection of HALT by MDCT scanning. Furthermore, in contrast to our results, an increased incidence of stroke and transient ischemic attack has been reported to be associated with reduced leaflet motion. The difference in the type of bioprosthesis used (100% of the study cohort used the SAPIEN-XT valve) or the lower coagulability in patients of Japanese ethnicity could be an explanation.

With respect to antithrombotic regimens, HALT was observed in 3 patients receiving oral anticoagulation therapy. Although 1 patient taking warfarin had subtherapeutic anticoagulation, the other 2 patients accurately took dabigatran and rivaroxaban, respectively, as new oral anticoagulant agents. In any case, the decision to use additional anticoagulant agents in patients with HALT remains controversial in view of the low frequency of clinical events and the risks of anticoagulation-related bleeding complications (24). In this very elderly cohort of TAVR patients, anticoagulation therapy in addition to antiplatelet agents increased the risk of bleeding complications. Identifying patients at high risk of thrombotic events and who would clearly benefit from additional anticoagulation therapy is one of our future targets of research.

In our cohort with reduced renal function, only 1 (1.4%) of 70 patients developed acute kidney injury. Our MDCT protocol (variable helical pitch scanning) was useful for reducing the amount of contrast (usually 30 to 40 ml) required compared with that used previously (25). However, contrast-enhanced MDCT scanning may still increase the risk of acute kidney injury in patients with impaired renal function. TTE was inadequate to detect HALT because of the limited resolution and artifacts of the stent frame itself.

We considered HALT to be THV thrombus, because sustained elevations in D-dimer levels during follow-up were significantly associated with HALT, decreased platelet count was associated with increased HALT incidence, the degree of leaflet immobility correlated with the HALT area, and there was a case of spontaneous regression of HALT. These findings suggest that HALT represents THV thrombus, influencing leaflet mobility once it accumulates to more than a certain threshold.

We found the D-dimer levels to be a simple and powerful marker that is useful for screening for possible THV thrombosis, and an optimal patient selection strategy for post-procedural MDCT study. Our results provide insight for optimal and appropriate application of post-procedural MDCT scanning to detect HALT.

**STUDY LIMITATIONS.** First, despite the longest follow-up period for a study that evaluated HALT with MDCT scanning, this was a single-center study and 30 of 100 patients were excluded mainly due to inadequate imaging. It is thus statistically underpowered for evaluating the clinical implication of HALT and predictors for this event because of its relatively small sample size. Therefore, a prospective study in a larger cohort is required. However, all HALT were measured by using the same MDCT protocol by the same investigators, and the antithrombotic regimen was consistent among these patients. A uniform study cohort and the same treatment approach were thus used in our study. Second, HALT detected on MDCT scanning was not confirmed as a thrombus on a histopathological examination because no adverse events occurred in the HALT group, although MDCT scanning has previously been shown to be helpful in identifying thrombus (26). Third, lack of systematic neurologist evaluation of cases could potentially influence the absent complication in this study. Fourth, there is the lack of data at 1 month, which previous studies have used (14,18). Although this factor can be a limitation for interstudy comparison, the present study presents unique data on discharge. Finally, only Edwards SAPIEN-XT valves were used in our cohort.

Comparison with other transcatheter and surgical aortic bioprosthetic valves would be relevant.

## CONCLUSIONS

The incidence of HALT was relatively high in the present study. Although insufficiently powered to demonstrate a relationship to hemodynamic and clinical endpoints, there were no reported strokes or increases in gradient even in the HALT cases despite the absence of additional anticoagulant therapy. Male sex and large sinus of Valsalva and bioprosthesis size were associated with an increased incidence of this finding. The association between the HALT area and the degree of leaflet immobility supports the idea that HALT could reflect THV thrombosis. D-dimer level may also be useful for screening for possible THV thrombosis. These findings will help post-procedural management and shed light on the future optimal care for patients who receive TAVR.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** HALT on mid-term follow-up is not rare but usually subclinical even without additional anticoagulation therapy.

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:** Patients with elevated D-dimer levels during follow-up, male sex, or large sinus of Valsalva and bioprosthesis size can be candidates for post-procedural MDCT scanning to detect HALT. If HALT is detected, the evaluation of hemodynamics and the need for anticoagulant therapy should be considered carefully.

**TRANSLATIONAL OUTLOOK 1:** Because this study included a relatively small number of patients, larger systematic studies are required for a better understanding of HALT.

**TRANSLATIONAL OUTLOOK 2:** This study evaluated only a single type of bioprosthetic valve (Edwards SAPIEN-XT). An appropriate antithrombotic therapy should be established for each type of bioprostheses, including surgical valves.

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**KEY WORDS** aortic stenosis, D-dimer, reduced leaflet motion, TAVR, thrombosis

**APPENDIX** For supplemental videos and their legends, please see the online version of this article.