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ORIGINAL RESEARCH

Natural History of Leaflet Thrombosis After Transcatheter Aortic Valve Replacement: A 5-Year Follow-Up Study

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BACKGROUND: Subclinical leaflet thrombosis, characterized by hypoattenuated leaflet thickening (HALT) on multidetector computed tomography, is common after transcatheter aortic valve replacement (TAVR). Because little is known about the long-term natural history of subclinical HALT, we aimed to investigate this in patients who underwent TAVR without using additional anticoagulation.

METHODS AND RESULTS: We retrospectively evaluated patients who underwent TAVR with the Edwards SAPIEN-XT at our institute between October 2013 and December 2015. Patients were grouped according to the presence or absence of HALT within 1 year after TAVR (HALT and No-HALT groups). The primary outcome, defined as the composite of all-cause mortality, heart failure readmission, and ischemic stroke, was compared. Valve performance was assessed over time by transthoracic echocardiography. Among 124 patients (men: 29.1%; median age, 85 years), 27 (21.8%) showed HALT on multidetector computed tomography within 1 year after TAVR. No patient required additional anticoagulation for treating HALT because of the absence of valve-related symptomatic deterioration. During the median follow-up period of 4.7 years (interquartile range, 4.0–5.6), the rate of primary outcome and valve performance was not statistically different between the 2 groups (37.0% versus 38.1%; log-rank test P=0.92; mean pressure gradient, 9 mm Hg [8–14 mm Hg] versus 10 mm Hg [7–15 mm Hg]; P=0.51, respectively).

CONCLUSIONS: Approximately 20% of patients after TAVR had HALT within 1 year; however, that did not change the risk of subsequent adverse cardiovascular events or the valve performance with statistical significance for up to 5 years despite no additional anticoagulation therapy.

Key Words: aortic valve stenosis ■ hypoattenuated leaflet thickening ■ transcatheter aortic valve replacement

See Editorial by DeAnda and Jnei

Transcatheter aortic valve replacement (TAVR) is an established treatment for severe aortic stenosis.[1–3] Subclinical leaflet thrombosis, which is characterized by hypoattenuated leaflet thickening (HALT) and recurrent leaflet motion detected by multidetector computed tomography (MDCT), is common after TAVR (Figure 1).[4,5] Subclinical thrombosis on MDCT after transcatheter bioprosthetic aortic valve implantation has a higher incidence when compared with that in surgical bioprosthetic aortic valve replacement.[6] In the computed tomography (CT) substudy of the recent PARTNER (Placement of Aortic Transcatheter Valves) 3 trial, the incidence of HALT was 24% within 1 year.[5,7–9]

The impact of subclinical leaflet thrombosis on subsequent thromboembolic complications and valve function necessitates further investigation. Previously,

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CLINICAL PERSPECTIVE

What Is New?

- Hypoattenuated leaflet thickening (HALT) was not associated with future adverse cardiovascular events, especially ischemic stroke. It did not change valve performance, with statistical significance for up to 5 years despite using conservative management without administering additional antithrombotic agents.
- The treatment of subclinical HALT with additional anticoagulation may help resolve HALT. On the other hand, it may not reduce the incidence of subsequent adverse cardiovascular events and may increase the risk of bleeding for up to 5 years.

What Are the Clinical Implications?

- In an elderly cohort of patients who undergo transcatheter aortic valve replacement, conservative management with minimal to no additional antithrombotic agents could be a default strategy for managing HALT.
- HALT does not significantly change the risk of adverse events; therefore, it remains uncertain whether monitoring HALT using routine multidetector computed tomography would improve clinical outcomes.
- Conservative management for HALT may be an option, and the decision to treat subclinical HALT with additional anticoagulation therapy needs to be cautiously determined, considering each patient's risk.

Nonstandard Abbreviations and Acronyms

HALT	hypoattenuated leaflet thickening
MDCT	multidetector computed tomography
TAVR	transcatheter aortic valve replacement
TTE	transthoracic echocardiography

we reported that HALT did not affect the midterm outcomes and valve performance. Similarly, clinical outcomes, including all-cause mortality and stroke, were not significantly different between patients with and without HALT.[10] Several other reports have shown that HALT was not associated with either stroke or transient ischemic attack (TIA) at the 3-year follow-up.[7,8,10,11] Meanwhile, Chakravarty et al reported conflicting results in terms of the association of HALT, with increased rates of adverse cerebral ischemic events, mainly TIA.[6] Despite this evidence, controversy about the long-term clinical impact of leaflet thrombosis after TAVR exists. Therefore, long-term follow-up data are needed to define the long-term implications of leaflet thrombosis and valve durability. This study aimed to investigate the natural history of HALT and focused on the relationship between HALT and the long-term clinical outcomes among patients who underwent TAVR.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Design and Sample

All data were retrospectively collected from a dedicated database. The research was conducted at and all patients were treated at the Keio University Hospital. Written informed consent for data collection was obtained from all patients.

All patients received an Edwards SAPIEN-XT valve (Edwards Lifesciences, Irvine, CA), and underwent MDCT scanning and echocardiography before and after the procedure, at the time of discharge (within 3 days after implantation), and at the 6-month and 1-year follow-ups. We evaluated the prospectively collected MDCT, echocardiographic, and clinical data of consecutive patients who underwent TAVR.

In this study, 183 consecutive patients who underwent TAVR with the Edwards SAPIEN-XT between October 2013 and December 2015 at the Keio University Hospital were registered. Nineteen patients who died within 1 year were excluded. Furthermore, 12 and 28 patients with reduced renal function and poor imaging quality data, respectively, were consequently excluded; 124 patients were analyzed in the present study (Figure 2). We divided the patients into 2 groups (ie, HALT and No-HALT groups) according to the presence of HALT within 1 year after TAVR. HALT was defined as an increased leaflet thickness with a meniscal appearance on the long-axis views at the time of leaflet coaptation (diastole). We analyzed the baseline characteristics and clinical outcomes in both groups. The study protocol was approved by the institutional review board and conducted in accordance with the Declaration of Helsinki. According to the Ethical Guidelines for Medical and Health Research Involving Human Subjects and Personal Information Protection Law in Japan, prior informed consent was obtained from each patient.

Transcatheter Heart Valve Assessment Using MDCT Scanning

MDCT scanning is an emerging noninvasive and effective strategy for evaluating HALT in bioprosthetic aortic valves.[7,12,13] Therefore, all transcatheter heart valves were evaluated blindly twice using contrast-enhanced,

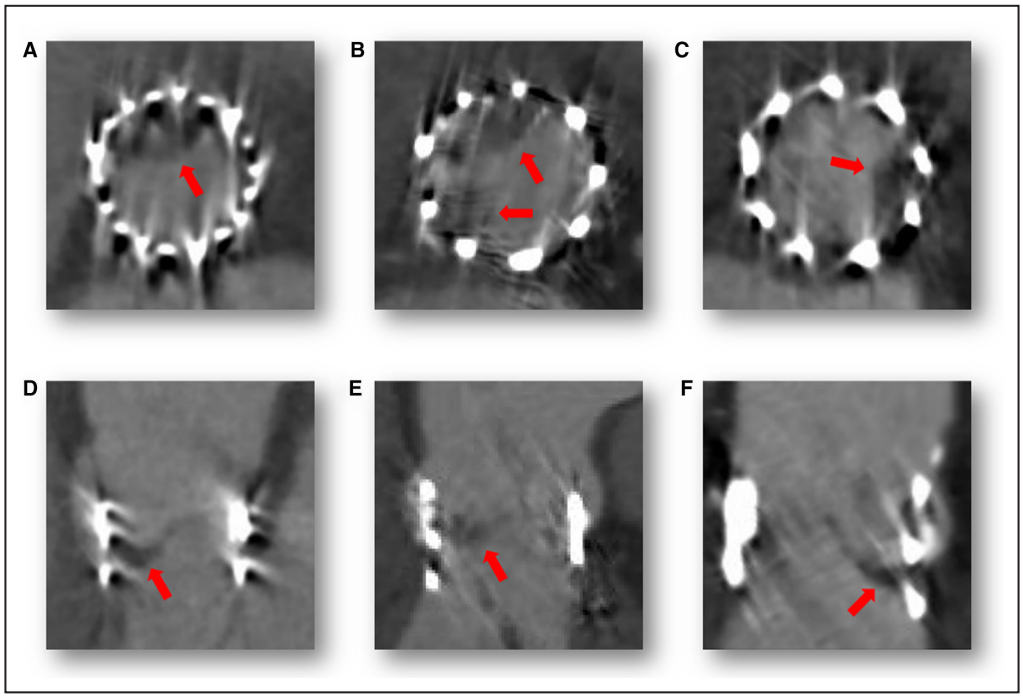

Figure 1. Multidetector computed tomography (MDCT) assessment of hypoattenuated leaflet thickening (HALT).
MDCT imaging was used to assess HALT. HALT is visually identified as increased leaflet thickness with a typical meniscal appearance on short- (**A** through **C**) and long-axis (**D** through **F**) views (red arrows).

electrocardiography-gated MDCT data by 2 experienced cardiologists. All patients with 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 measurements were performed during the diastolic phases at 75% of the R-R interval, which allowed optimal leaflet imaging.

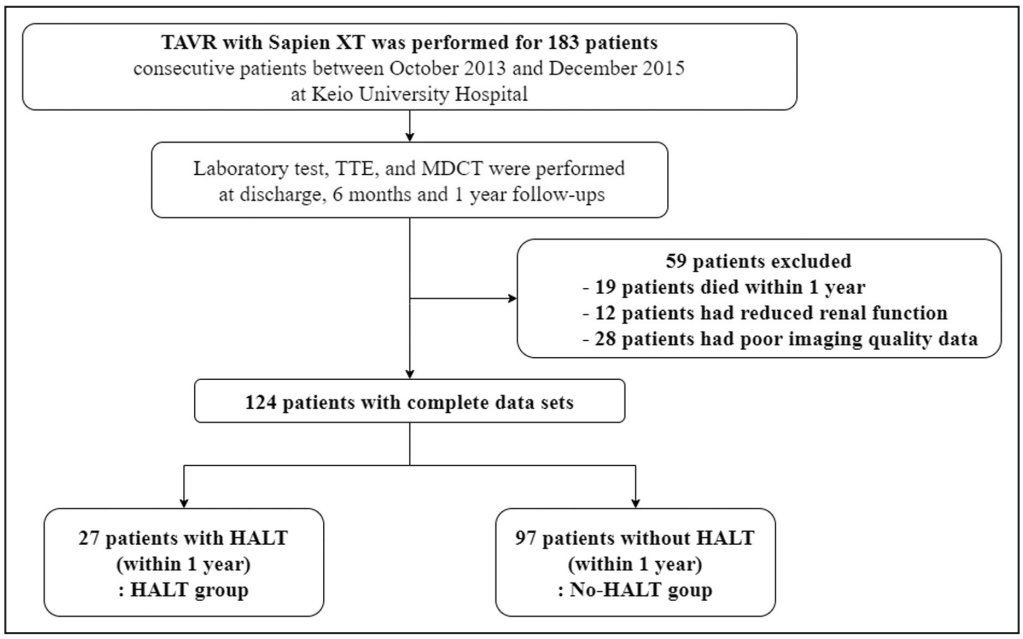

Figure 2. Patient flowchart.
HALT indicates hypoattenuated leaflet thickening; MDCT, multidetector computed tomography; TAVR, transcatheter aortic valve replacement; and TTE, transthoracic echocardiography.

Echocardiography

Transthoracic echocardiography (TTE) was performed along with CT scans at each follow-up visit. Left ventricular ejection fraction, aortic valve stenosis severity, and prosthetic valve function were evaluated using TTE and assessed by board-certified cardiologists. The results were analyzed by experienced echocardiographers.

MDCT Acquisition

All follow-up CT scans were performed before discharge (within 3 days after implantation) and at 6-month and 1-year follow-ups with 4-dimensional CT acquisition. The detailed imaging method is described in Data S1.

Definitions of Variables and Outcomes

TTE and laboratory tests were performed at each follow-up visit at the same time as the CT scan. The echocardiography parameters listed above were assessed. Laboratory tests included D-dimer level, platelet count, and brain natriuretic peptide level. The estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease Equation for Japanese Patients, as proposed by the Japanese Society of Nephrology.[14]

The primary end point was the composite of all-cause mortality, heart failure (HF) readmission, and ischemic stroke. The secondary end points were the incidences of all-cause death, cardiovascular death, HF readmission, and ischemic stroke. Ischemic stroke was defined according to the Valve Academic Research Consortium-3 criteria: acute onset of focal neurological signs or symptoms conforming to a focal or multifocal vascular territory within the brain, spinal cord, or retina and fulfilling 1 of the following criteria: signs or symptoms lasting ≥24 hours or until death, with pathology or neuroimaging evidence of central nervous system infarction, or absence of other apparent causes, or symptoms lasting <24 hours, with pathology or neuroimaging confirmation of central nervous system infarction in the corresponding vascular territory.[15] All events were adjudicated by our institute and were tracked from the time of discharge until the last follow-up listed in the medical records, where survival status was also confirmed. In terms of valve performance, we evaluated the indexed effective orifice area, mean pressure gradient, and indexed stroke volume over time.

Patient Follow-Up

All patients were observed in the intensive care unit for at least 24 hours after TAVR. Dual antiplatelet therapy was administered for 6 months, switching over to either aspirin or clopidogrel to continue indefinitely. If the patients received anticoagulation therapy before the procedure, only aspirin was added before valve implantation and continued during the follow-up period. Clinical follow-up was done at 1, 3, 6, and 12 months for the first year and annually thereafter. If HALT was detected, no additional medication was added because none of the patients developed significant symptoms with an increased pressure gradient across the valve.

Structural valve deterioration was defined according to the Valve Academic Research Consortium-3.[15] Severe hemodynamic structural valve deterioration was defined as the following: (1) increased mean transvalvular pressure gradient of ≥20 mm Hg resulting in a mean gradient of ≥30 mm Hg with a concomitant decrease in effective orifice area of ≥0.6 cm^2 or ≥50%; (2) and/or a decrease in Doppler velocity index of ≥0.2 or ≥40% compared with the echocardiographic assessment performed 1 to 3 months after the procedure, or new occurrence, or an increase of ≥2 grades of intraprosthetic aortic regurgitation resulting in severe aortic regurgitation.

Statistical Analysis

Baseline characteristics were compared between the HALT and No-HALT groups. Categorical and continuous variables were expressed as numbers (percentages) and medians (interquartile range, IQ1–IQ3), respectively. Two-sided χ^2 test or Fisher exact test (for cell count <10) was used to compare the categorical variables. All continuous variables were analyzed using the Mann-Whitney *U* test. The comparison between the 2 groups was made using the log-rank test and represented through Kaplan-Meier survival curves. All probability values were 2-tailed, and $P<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 26.0 (IBM SPSS Statistics; IBM, Armonk, NY).

RESULTS

Baseline Characteristics

The baseline characteristics of the HALT and No-HALT groups are shown in the Table. The incidence of HALT was 21.8% (27 out of 124) within 1 year. The timing of finding HALT on CT after TAVR was as follows: 2 patients within 1 week and 13 patients at the 6-month and 12 patients at the 1-year follow-ups. There were no statistically significant differences in their clinical characteristics except for the New York Heart Association class, the aortic valve complex measured on MDCT scan, echocardiographic findings, and procedural details between the 2 groups.

Outcomes

In this study, 19 patients, who died within 1 year after TAVR, were excluded. However, HALT was not observed in all of them (death from cardiovascular

Table. Baseline Characteristics of the Study Population in the HALT and No-HALT Groups

Characteristic	HALT, n=27	No-HALT, n=97	*P* value
Age, y	86 (82–88)	85 (81–87)	0.30
Men	10 (37.0%)	27 (27.8%)	0.36
Body mass index, kg/m^2	23.7 (20.2–26.1)	21.7 (19.6–24.1)	0.22
Diabetes	6 (22.2%)	23 (23.7%)	0.87
Dyslipidemia	10 (37.0%)	50 (51.5%)	0.18
Hypertension	23 (85.2%)	78 (80.4%)	0.57
eGFR <60 mL/min per 1.73 m^2	16 (59.3%)	57 (58.8%)	0.96
Pulmonary disease	7 (25.9%)	36 (37.1%)	0.28
Clinical frailty scale	3 (3–4)	3 (3–4)	0.89
MMSE	27 (24–28)	27 (24–29)	0.24
NYHA ≥3	9 (33.3%)	54 (55.7%)	0.04
Coronary artery disease	15 (55.6%)	43 (44.3%)	0.30
Peripheral artery disease	6 (22.2%)	18 (18.6%)	0.67
History of atrial fibrillation	4 (14.8%)	23 (23.7%)	0.32
Previous stroke	3 (11.1%)	5 (5.2%)	0.27
BNP, pg/mL	148.4 (69.1–296.1)	213.5 (100.6–398.2)	0.13
D-dimer, μg/mL	0.9 (0.6–1.4)	0.8 (0.5–1.7)	0.53
STS-PROM score (%)	6.2 (4.8–7.8)	5.8 (4.3–8.0)	0.61
Antithrombotic regimen at implantation			0.63
None	0 (0%)	1 (1.0%)	
Single antiplatelet therapy	2 (7.4%)	6 (6.2%)	
DAPT	20 (74.1%)	58 (59.8%)	
Triple	0 (0%)	1 (2.1%)	
OAC	0 (0%)	0 (0%)	
OAC+single antiplatelet therapy	5 (18.5%)	31 (32.0%)	
Aortic valve complex characteristics, measured on MDCT scan			
Annulus area	374.0 (331.1–416.9)	372.5 (338.7–417.4)	0.96
Sinus of Valsalva			
Mean diameter, mm	28.8 (27.9–30.9)	29.1 (27.1–31.8)	0.99
Sinus of Valsalva/THV diameter ratio	1.21 (1.17–1.25)	1.23 (1.17–1.28)	0.55
LVEF (%)	64.3 (57.1–70.8)	65.7 (58.3–71.2)	0.72
LFLG AS	1 (3.7%)	5 (5.2%)	0.76
SV indexed, mL/m^2	46.5 (40.7–53.7)	46.5 (38.9–53.8)	0.92
AVA indexed, cm^2/m^2	0.46 (0.41–0.53)	0.44 (0.37–0.52)	0.23
Mean pressure gradient, mm Hg	48.0 (33.0–61.0)	45.0 (38.0–56.5)	0.96
E/e′	20.8 (14.1–25.6)	20.9 (16.1–28.8)	0.95
Transfemoral approach	25 (92.6%)	82 (84.5%)	0.28
Valve size			0.25
20 mm	1 (3.7%)	2 (2.1%)	
23 mm	16 (59.3%)	66 (68.0%)	
26 mm	9 (33.3%)	29 (29.9%)	
29 mm	1 (3.7%)	0 (0%)	
Predilatation	14 (51.9%)	60 (61.9%)	0.35
Postdilatation	4 (14.8%)	19 (19.6%)	0.57
Major+life-threatening bleeding	0 (0%)	6 (6.2%)	0.19
Major vascular complication	1 (3.7%)	8 (8.2%)	0.42
Acute kidney injury	0 (0%)	5 (5.2%)	0.23
New atrial fibrillation	0 (0%)	3 (3.1%)	0.36
Periprocedural MI	0 (0%)	0 (0%)	1.00
Ischemic stroke	0 (0%)	0 (0%)	1.00
PVL more than mild	0 (0%)	0 (0%)	1.00
PVL less than mild	12 (44.4%)	42 (43.3%)	0.92
Device success	26 (96.3%)	93 (95.9%)	0.92
Antithrombotic regimen postoperative 1 year			0.23
None	0 (0%)	2 (2.1%)	
Single antiplatelet therapy	22 (81.5%)	59 (60.8%)	
DAPT	0 (0%)	8 (8.2%)	
Triple	0 (0%)	0 (0%)	
OAC	1 (3.7%)	2 (2.1%)	
OAC+single antiplatelet therapy	4 (14.8%)	26 (26.8%)	

Values are median (interquartile range) or n (%). AVA indicates aortic valve area; BNP, B-type natriuretic peptide; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; HALT, hypoattenuated leaflet thickening; LFLG AS, low-flow low-gradient aortic stenosis; LVEF, left ventricular ejection fraction; MDCT, multidetector computed tomography; MI, myocardial infarction; MMSE, Mini Mental State Examination; NYHA, New York Heart Association; OAC, oral anticoagulant; PVL, paravalvular leak; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; SV, stroke volume; and THV, transcatheter heart valve.

diseases in 2, cancer in 4, infections in 6, hepatic encephalopathy in 1, asthma in 1, and unknown causes in 5). During the median follow-up period of 4.7 years (interquartile range, 4.0–5.6) after TAVR, the rate of primary outcome, which was defined as the composite of all-cause death, HF readmission, and stroke was not significantly different between the groups (HALT: 37.0% versus No-HALT: 38.1%, log-rank test *P*=0.92) (Figure 3). The Kaplan-Meier curves demonstrated no significant differences in the 2 groups with respect to all secondary outcomes (all-cause mortality, log-rank test, *P*=0.97; cardiovascular death, *P*=0.86; HF readmission, *P*=0.54; ischemic stroke, *P*=0.88) (Figures 4A through 4D).

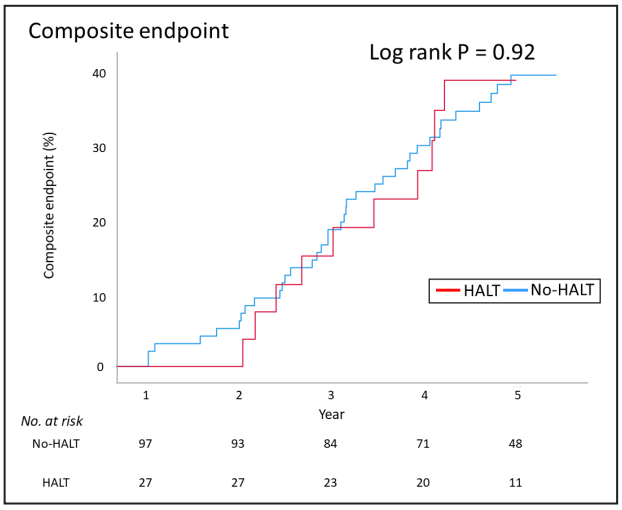

Figure 3. Kaplan-Meier curves of the composite outcome.
HALT indicates hypoattenuated leaflet thickening.

The presence of HALT was not associated with either decreased indexed effective orifice area (1.01 cm^2/m^2 [0.92–1.18 cm^2/m^2] versus 1.07 cm^2/m^2 [0.91–1.21 cm^2/m^2], *P*=0.59), increased mean pressure gradient (9 mm Hg [8–13 mm Hg] versus 10 mm Hg [8–13 mm Hg], *P*=0.76), or with decreased indexed stroke volume (46.9 mL/m^2 [39.2–53 mL/m^2] versus 48.3 mL/m^2 [41.7–56 mL/m^2], *P*=0.29) at the 1-year follow-up (n=114). The findings were consistent for the mean pressure gradient and indexed stroke volume at the 5-year follow-up (n=33) (mean pressure gradient, 9 mm Hg [8–14 mm Hg] versus 10 mm Hg [7–15 mm Hg], *P*=0.51; indexed stroke volume, 38.5 mL/m^2 [36.6–47.3 mL/m^2] versus 49.1 mL/m^2 [39.1–53.9 mL/m^2], *P*=0.07) (Figures 5A through 5C). However, the indexed effective orifice area decreased significantly in the HALT group at the 5-year follow-up (0.88 cm^2/m^2 [0.81–0.97 cm^2/m^2] versus 1.09 cm^2/m^2 [0.86–1.24 cm^2/m^2], *P*=0.04), after staying consistent until the 4-year follow-up.

In the HALT group, additional anticoagulants were not administered, and there were no significant differences in the use of antithrombotic agents at 1 year between the 2 groups (Table). During the follow-up period, 1 patient each in the HALT and No-HALT groups developed severe structural valve deterioration,

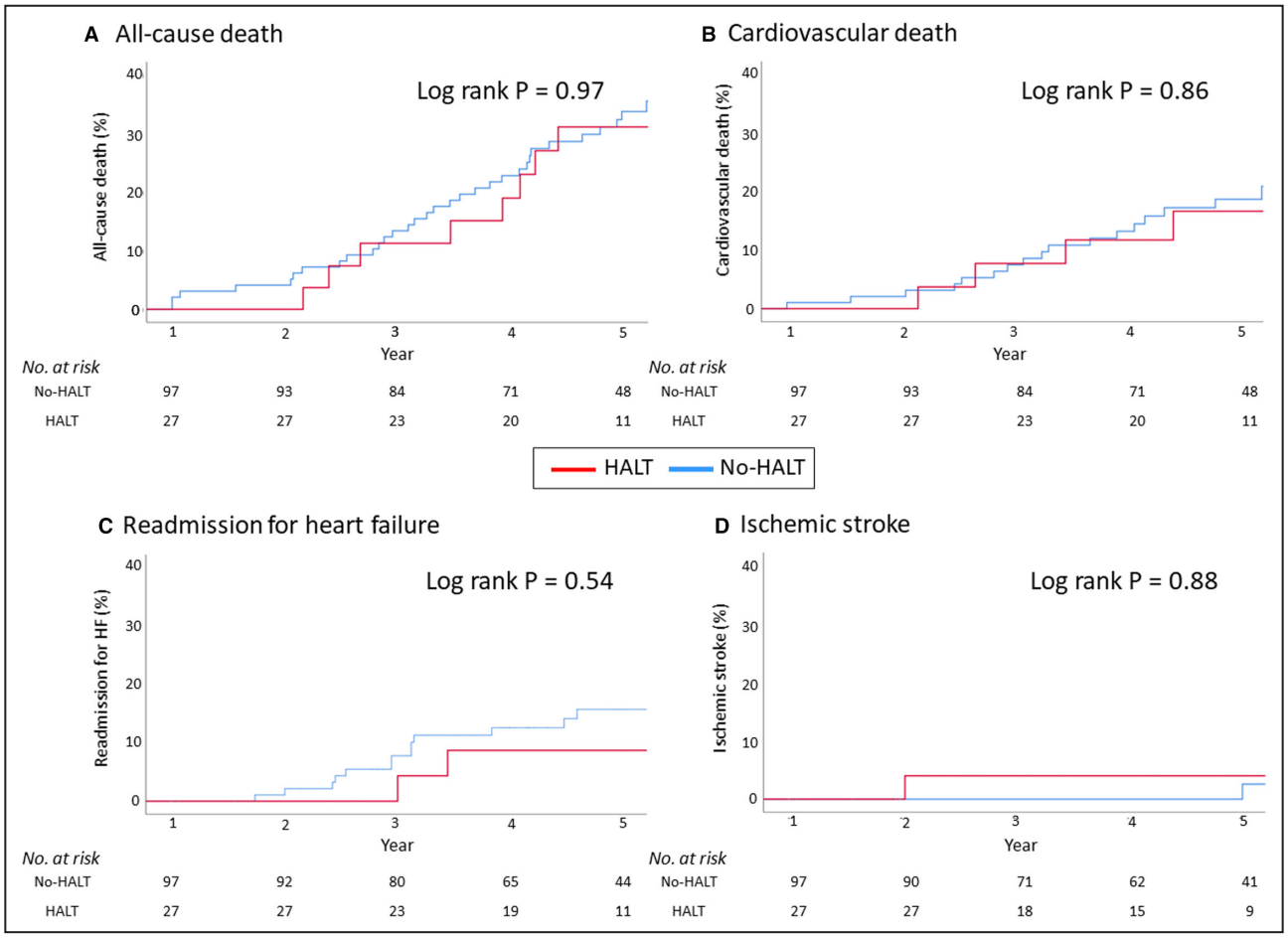

Figure 4. Kaplan-Meier curves of the all-cause death (A), cardiovascular death (B), heart failure (HF) readmission (C), and ischemic stroke (D).
HALT indicates hypoattenuated leaflet thickening.

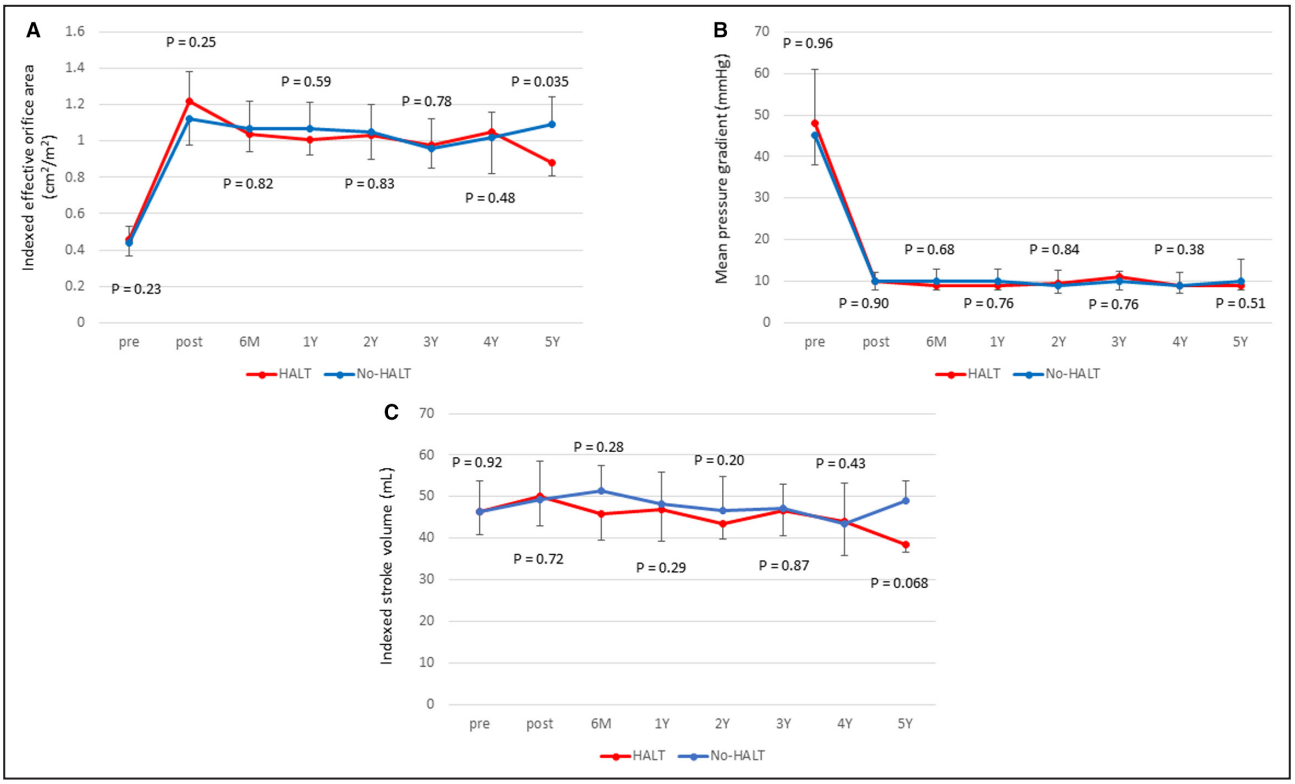

Figure 5. Follow-up data over 5 years after transcatheter aortic valve replacement.
HALT indicates hypoattenuated leaflet thickening; M, month; and Y, year.

with an increased mean pressure gradient of 32 and 31 mm Hg, respectively; however, none had shortness of breath or required surgical aortic valve replacement or valve-in-valve.

DISCUSSION

In the current study, we found the following: (1) The incidence of HALT was 21.8% (27 out of 124) within 1 year after TAVR. (2) The patient backgrounds between the 2 groups were similar, including TTE and CT findings. (3) HALT was not a statistically significant factor in the cumulative event rate for the end point of all-cause death, cardiac death, stroke, or HF readmission during the 5-year follow-up. (4) HALT did not significantly impact the long-term valve performance and structural valve deterioration as assessed by TTE. To the best of our knowledge, this is the first study that demonstrates the natural history of HALT with a 5-year follow-up after TAVR without resorting to additional antithrombotic therapy for HALT.

Although several studies have reported midterm follow-up findings, the association of HALT with outcomes was inconsistent. The PARTNER 3-substudy reported that the presence of HALT was 24% within 1-year after TAVR.[9] Additionally, the presence of HALT was not associated with individual end points such as death, myocardial infarction, and stroke at 1 year; however, it was associated with an increased thromboembolic event rate of pooled stroke, TIA, and retinal artery occlusion. Vollema et al reported a subgroup analysis of an observational study of 128 patients who underwent MDCT after TAVR and compared 16 and 112 patients in the HALT and No-HALT groups, respectively.[16] There were no significant differences in the effective orifice area and mean pressure gradients on TTE between the 2 groups during the 3-year follow-up period. Only 1 patient with HALT on MDCT revealed abnormal valve hemodynamics on echocardiography, and HALT was not associated with an increased risk of ischemic stroke and TIA. Meanwhile, a meta-analysis of 25 studies, including the 2 aforementioned trials, suggested that HALT increased the risk of stroke or TIA in the included population.[17] However, this was contradictory to our findings, but the difference in the definition of the neurological end point could explain this gap. In the meta-analysis, the increased risk of neurological events was mainly derived from TIAs. TIA was not included as a clinical outcome, and stroke was the only ascertained neurological end point in our study. Notably, on limiting the end point to only stroke, HALT was not associated with the risk of the neurological end point, which was consistent with our results.[10,11,18] Our study expanded these findings and demonstrated

that the presence of HALT did not significantly impact either clinical outcomes or valve performance for up to 5 years after TAVR.

The strength of the present study lies in its long-term follow-up. We previously reported no increase in stroke events and mean pressure gradients on TTE despite not using additional anticoagulant therapy in the midterm follow-up.[10] The findings were consistent, and no association was found between HALT and adverse clinical events for up to 5 years after TAVR. At 5 years after TAVR, there was a statistically significant difference in indexed effective orifice area, but not in indexed stroke volume and mean pressure gradient between the HALT and No-HALT groups. In our study cohort, additional anticoagulant therapy was not added despite detection of HALT by MDCT. Furthermore, the presence of HALT did not statistically impact the outcome with respect to all-cause mortality and HF readmission in the long-term follow-up, which demonstrates the natural history of HALT and suggests that anticoagulation therapy may not be warranted in such cases. Given that the presence of HALT does not warrant altering the antithrombotic regimen, a routine assessment by MDCT for detecting HALT is not necessary until clinical signs of valve dysfunction appear.

Recent randomized trials have raised questions on the benefit of anticoagulation therapy for treating valve leaflet thickening or HALT after TAVR despite the greater risk reduction of valve leaflet thickening with oral anticoagulation than that with antiplatelet therapy.[5,6,8,11,19,20] In the GALLILEO (Global Study Comparing a Rivaroxaban-Based Antithrombotic Strategy to an Antiplatelet-Based Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes) trial that compared the efficacy and safety of rivaroxaban against antiplatelet-based strategy after TAVR, a reduction in leaflet motion and in the incidence of leaflet thickening was observed in the rivaroxaban group. However, the use of rivaroxaban was associated with a higher risk of death, thromboembolic events, and bleeding events.[21,22] The ATLANTIS (Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Hemorrhagic Events After Trans-Aortic Valve Implantation for Aortic Stenosis) trial achieved consistent results in comparing the apixaban-based strategy with antiplatelet-based strategy.[23] These findings imply that HALT treatment with anticoagulation therapy may not lead to improvement in clinical outcomes but rather confers an increased risk of thrombotic and bleeding events. Furthermore, the POPULAR TAVI (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation) trial suggested that fewer antithrombotic agents were preferable for patients after TAVR. Compared with single antiplatelet therapy, dual antiplatelet therapy was associated with an increased risk of major adverse events after TAVR, primarily major bleeding; however, it did not reduce the incidence of ischemic events. It also showed that the rate of bleeding was lower in the anticoagulant monotherapy group than in the anticoagulant plus clopidogrel group and without an increased risk of ischemic events in the anticoagulant monotherapy group.[24,25] Our study clearly demonstrated the natural history of HALT and showed that the presence of HALT was not associated with future adverse cardiovascular events, despite conservative management without additional antithrombotic agents. Given the cohort of elderly patients who undergo TAVR, conservative management with either less or without additional antithrombotic agents could be a default strategy for treating HALT. Hence, further prospective studies are necessary to clarify the indication of additional antithrombotic therapy for treating HALT.

Limitations

This study had several limitations. First, this retrospective study was conducted at a single center and was not a randomized trial. Because of the relatively small sample size, this study's findings should be interpreted cautiously. Consequently, further studies are required to corroborate our findings. Second, the lack of systematic assessment of cases by neurologists may have influenced the absence of complications in this study. Although previous studies have suggested the association between HALT and TIA, the incidence of TIA was not evaluated in this study and therefore is not available. In this regard, this study has limited evaluation on the association between HALT and neurologic findings. Third, the patients, who died during follow-up may have died because of transcatheter valve thrombosis, which may have underestimated the true incidence of this complication. Finally, only the Edwards SAPIEN-XT valve was used, and these results might not be applicable to newer aortic valve prostheses (Edwards SAPIEN 3 and Medtronic Evolut Pro Plus). Therefore, studies comparing the incidence of HALT with other transcatheter and surgical aortic bioprostheses are required.

CONCLUSIONS

Our study demonstrated that approximately 20% of patients after TAVR showed HALT on MDCT; however, its presence was not statistically significant in changing the risk of subsequent adverse cardiovascular events, especially ischemic stroke, valve performance, or durability, for up to 5 years after TAVR despite no additional anticoagulation therapy. Hence, further studies with longer follow-up periods are necessary to corroborate our findings and assess the need for anticoagulation therapy in subclinical HALT.

ARTICLE INFORMATION

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Supplemental Material

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SUPPLEMENTAL MATERIAL

Data S1. 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. These were performed using a 320-detector-row CT scanner (Aquilion ONE/ViSION Edition, Toshiba Medical Systems, Ottawa, Japan) using the following parameters: peak tube voltage, 100 kV; tube current, 10 to 350 mA (determined on the basis of a pre-specified body mass index protocol); rotation speed, 0.275 s; and slice collimation, 0.5 × 100 mm. We used variable helical pitch scanning, which allowed a seamless change in the scan pitch during one continuous acquisition and enabled a combination of gated and nongated acquisitions within one 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 thoracic scan. Furthermore, a double-channel injection system (Dual Shot, Nemoto, Tokyo, Japan) via the right antecubital venous access was used [26].

The volume of the 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. This 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 initiated 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 using the adaptive iterative dose reduction 3-dimensional algorithm [27].

Image analysis was performed using axial images and 3-dimensional multiplanar reformatting on an independent workstation (Advantage Workstation 4.5, GE Healthcare, Waukesha, Wisconsin), and artifacts due to the prosthesis itself and aortic valve calcification were avoided.