Prospective Evaluation for Hypoattenuated Leaflet Thickening Following Transcatheter Aortic Valve Implantation

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Prospective investigations for the frequency of hypoattenuated leaflet thickening (HALT) and its clinical implications in transcatheter aortic valve implantation (TAVI) patients are limited. We initiated a prospective screening program of TAVI patients for HALT beginning in July 2015. Eligible patients were evaluated with gated, contrast-enhanced multidetector computed tomography within 30 days of TAVI, and examined for HALT and clinical outcomes. During the study period, 287 patients (81 ± 8 years; 53% men) who underwent TAVI with commercially approved devices were examined. Overall, 26 patients (9.1%) had occurrence of HALT, and only one of these patients had detectable hemodynamic changes on echocardiography at diagnosis. Notably, 9 of 26 HALT patients had been receiving warfarin, however, the HALT patients more often had subtherapeutic international normalized ratio whereas using warfarin than patients without HALT on index multidetector computed tomography imaging (p = 0.01). Patients who developed HALT had lower baseline aortic gradient, valvuloarterial impedance, and peak aortic velocity, and more commonly had been treated with balloon-expandable valves (73% of all HALT cases) with a higher incidence among those who received larger prostheses. All patients with HALT were placed on anticoagulation at diagnosis, and valvular function remained unchanged at follow-up. Two patients with HALT (7.7%) experienced ischemic stroke. A statistical trend for more major adverse clinical events was present in HALT patients. In conclusion, HALT was detected in 9% of TAVI cases in this prospective observational cohort, with a greater frequency in patients with large, balloon-expandable prostheses. Prospective screening may be considered as early HALT is reversible by timely therapeutic anticoagulation. **(Am J Cardiol 2019;123:658−666)**

Transcatheter aortic valve implantation (TAVI) is a revolutionary innovation that provides life-saving therapy for patients with symptomatic, severe aortic stenosis (AS). To date, hundreds of thousands of patients have undergone TAVI worldwide, with continued volume growth expected due to population aging.[1−3] Moreover, randomized trials for those at low risk are well underway.[4−6] However, recent studies have demonstrated the presence of hypoattenuated leaflet thickening (HALT) following TAVI, as detected by high-resolution computed tomography.[7−10] The presence of HALT, commonly regarded as leaflet thrombosis, can cause prosthetic dysfunction and hemodynamic compromise, as well as potentially accelerate valve degeneration.[11,12] In some studies, HALT in patients with TAVI has been associated with a significantly increased risk of thromboembolic events.[8,13] To date, prospective investigations for the frequency of HALT and its clinical implications in TAVI patients are limited, and few comparative data on the different prosthetic types and their association with HALT are available. This prospective study aimed to investigate the contemporary incidence and clinical outcomes of HALT in a relatively large patient cohort undergoing TAVI with commercially available valves.

Methods

In July 2015, we initiated a hospital-wide program of prospective screening for HALT with cardiac multidetector computed tomography (MDCT) for patients who received TAVI. All patients who underwent TAVI on a commercial or research basis at Minneapolis Heart Institute at Abbott Northwestern Hospital (Minneapolis, MN) between July 1, 2015 and December 14, 2017 were considered for evaluation. TAVI was performed via transfemoral or alternative access, according to standard practice.[14] In the majority of the patients, the procedure was performed under conscious sedation. Predilatation was performed in selected cases at the operator's discretion. The selection of transcatheter heart valve (THV) size was based on pre-TAVI MDCT

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measurements of the effective aortic annular diameter and area as previously described.[15,16] Initially, some patients underwent MDCT imaging for HALT following TAVI and before hospital discharge. In some patients, the MDCT study could not be performed due to risk of contrast nephropathy from either acute or chronic renal insufficiency, as well as logistical barriers to performing MDCT imaging when hospital discharge occurred on a weekend day. Following the first 6 months, the program was amended for performance of MDCT imaging at 30-day follow-up. The study population in the present investigation consists of patients who were treated with TAVI with commercially-approved devices (Sapien XT, Sapien 3, Edwards Lifesciences Inc., Irvine, CA; CoreValve, Evolut R, Evolut Pro, Medtronic Inc., Galway, IR), and completed screening for HALT with contrast-enhanced, gated MDCT. All patients provided written informed consent for the use of their medical record for this research. The study was conducted in accordance with the Declaration of Helsinki and approved by the Allina Institutional Review Board.

Before TAVI, patients routinely received loading dose of aspirin (325 mg), with some previously treated with both aspirin (325 mg) and clopidogrel (300 mg). During the procedure, weight-adjusted unfractionated heparin was given to achieve an activated clotting time (ACT) of ≥250 seconds. After the procedure, patients received oral aspirin and clopidogrel for 3 to 6 months, followed by lifelong aspirin therapy. For patients with indications for long-term anticoagulation, a combination of warfarin or direct oral anticoagulation (DOAC) and single antiplatelet therapy for 3 to 6 months was administrated, followed by lifelong anticoagulation therapy based on the risks of stroke/thromboembolism and bleeding. In patients with HALT on MDCT, the decision to initiate anticoagulation for 3 months, and continuation of anticoagulation after resolution of HALT was based on the bleeding risk and preference of the physician and patient.

Transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE) was performed by experienced cardiologists using a Philips IE33-system (Philips, Netherlands). TTE or TEE was performed at discharge, 1, 6, and 12 months, and yearly thereafter to assess the transcatheter valve hemodynamics over time. Abnormal valve hemodynamics indicating possible THV thrombosis was based on the criteria of THV dysfunction: a mean transvalvular gradient ≥20 mm Hg with an aortic valve area ≤1.1 cm^2 in a patient with previously successful TAVI therapy (VARC-2 definition).[9,17,18]

A second generation (Siemens Definition Flash 2 × 128 × 0.6 mm; TR 75 ms, from 2015 to 2016) or a third generation (Siemens Definition Force 2 × 192 × 0.6 mm; TR 66 ms, from 2016 to 18) dual source scanner (Siemens Healthcare, Germany) was used for MDCT imaging. Tube voltage ranged from 80 to 120 kV and tube current was adjusted according to Care kV and an in-house algorithm. A retrospective ECG-gating sequence was used. Contrast (Omnipaque 350, GE healthcare) doses ranged from 40 to 120 ml at injection rates from 4 to 8 ml/sec depending upon the patient's renal function, size, and kV used. Leaflet morphology was analyzed using multiplanar reconstructions (Vital Images software, Cannon). The TAVI leaflets were assessed in double oblique orthogonal orientations throughout the cardiac cycle. HALT was defined as the presence of hypoattenuated thickening with or without rigidity of one or more leaflets identifiable in at least 2 different multiplanar reformation projections and 2 different reconstruction time intervals.[9,10]

The medical record was manually reviewed for data on patient demographics, echocardiographic findings, MDCT imaging, and clinical outcomes. Valvulo-arterial impedance (Zva), which reflects the global hemodynamic afterload faced by the left ventricle (LV), was calculated as the estimated LV systolic pressure (systolic arterial pressure + mean transvalvular gradient) divided by the stroke volume indexed for the body surface area.[19] Left ventricular outflow tract calcification was semi-quantitatively graded as follows: grade 0 = no calcification; grade 1 = small, nonprotruding calcifications; grade 2 = protruding (<1 mm) or extensive (<50% of cusp sector) calcifications; grade 3 = protruding (>1 mm), and extensive (>50% of cusp sector) calcifications.[20] The annular area was planimetered directly in the short-axis plane. The area cover index was defined as the percentage of oversizing of the THV as compared with the annulus area measured by computed tomography angiography and was calculated using the formula ([nominal THV area − measured area]/nominal THV area) × 100%.[21] Standard definitions for major adverse clinical events (i.e., death, ischemic stroke, transient ischemic attack, myocardial infarction, and rehospitalization for heart failure) were utilized.[17] Occurrence of death was confirmed through examination of Minnesota Department of Health records. For each patient, the Society of Thoracic Surgeons' Predicted Risk of Mortality (STS-PROM) was calculated conventionally using the online tool (Online STS risk calculator. Available at: *http://riskcalc.sts.org/STSWebRiskCalc273*).

Categorical variables were expressed as frequencies and percentages, and continuous variables as mean ± SD or median with interquartile (IQR) ranges (25th, 75th percentiles). Continuous variables were assessed for normality using the Shapiro-Wilk normality tests. If variables are found to be normally distributed, independent t-tests or analysis of variance were used to test for group differences. For data not normally distributed, Wilcoxon rank-sum or Kruskal-Wallis tests were used. Categorical data were compared using chi-square or Fisher's exact tests, where appropriate. The Kaplan-Meier method was used to calculate survival estimates, with comparisons performed using the log-rank test. Patients who were lost to follow up were censored at the time of last clinical encounter. A value of $p < 0.05$ was considered statistically significant, and p-values were two-sided where possible. All statistical analyses were performed with Stata 14.1 (StataCorp, College Station, TX) or SAS 9.3 (SAS Institution Inc., Cary, NC).

Results

During the study period, a total of 287 patients who underwent TAVI with commercially-approved devices at our institution were prospectively evaluated for HALT with contrast-enhanced, gated MDCT imaging, including 38 patients underwent MDCT before discharge and 249 patients at 30 days after procedure. In accordance with commercial indications for TAVI, all patients (81±8 years; 53% men) were intermediate or high surgical risk (STS-PROM, 4.4 ± 2.6%) with frequent co-morbidity or frailty (Table 1). Overall, 26 patients (or 9.1%) were found to have HALT on MDCT imaging performed after TAVI. There were no differences in patient demographics, symptom status, nor co-morbidity between patients with and without HALT. Compared to patients who did not develop HALT, those who did had lower peak aortic velocity, mean aortic gradient, and Zva, and also a lower incidence of concomitant moderate or severe mitral regurgitation on baseline echocardiography (Table 2). On preprocedural MDCT imaging, patients who developed HALT also had larger annular area, larger annular perimeter, and a higher incidence of left ventricular outflow tract calcification. Among these 26 patients with HALT, 3 leaflets were involved in 5 patients, 2 leaflets in 4 patients, and 1 leaflet was involved in 17 patients. The low attenuation material was predominantly found on the leaflet base (22 cases or 84.6%), and found on the cusps of aortic side in 4 (15.4%) cases. Reduced leaflet motion on MDCT was identified in 30.8% (8 patients) of HALT cases.

Occurrence of HALT was more common among patients treated with balloon-expandable prosthesis (73.1% of HALT cases) than those who received a self-expanding prosthesis (26.9% of HALT cases; Table 3). The frequency of HALT was greatest among those who received a 29-mm balloon-expandable prosthesis (n = 11 or 42.3% of HALT

Table 1
Baseline clinical characteristics (n = 287)

Variable	All (n = 287)	HALT (n = 26)	Non-HALT (n = 261)	*p Value*
Age (years)	81.1 ± 8.1	83.2 ± 4.5	80.9 ± 8.4	0.16
Men	151 (52.6%)	17 (65.4%)	134 (51.3%)	0.17
New York Heart Association functional class				
II	59 (20.6%)	5 (19.2%)	54 (20.7%)	0.95
III	196 (68.3%)	19 (73.1%)	177 (67.8%)	
IV	32 (11.1%)	2 (7.7%)	30 (11.5%)	
Angina pectoris	23 (8.0%)	2 (7.7%)	21 (8.0%)	1.00
Syncope or presyncope	28 (9.8%)	1 (3.8%)	27 (10.3%)	0.49
Current smoker	5 (1.7%)	0	5 (1.9%)	1.00
Diabetes mellitus	90 (31.4%)	6 (23.1%)	84 (32.2%)	0.34
*Hypertension	239 (83.3%)	21 (80.8%)	218 (83.5%)	0.78
#Hyperlipidemia	206 (71.8%)	19 (73.1%)	187 (71.6%)	0.88
Coronary artery disease	154 (53.7%)	11 (42.3%)	143 (54.8%)	0.22
Prior percutaneous coronary intervention	78 (27.2%)	7 (26.9%)	71 (27.2%)	0.98
Prior coronary artery bypass grafting	50 (17.4%)	3 (11.5%)	47 (18.0%)	0.59
Previous myocardial infarction	23 (8.0%)	4 (15.4%)	19 (7.3%)	0.14
Atrial fibrillation	109 (38.0%)	10 (38.5%)	99 (37.9%)	0.96
Previous stroke or TIA	42 (14.6%)	3 (11.5%)	39 (14.9%)	0.78
History of thromboembolism	6 (2.1%)	1 (3.8%)	5 (1.9%)	0.44
History of malignancy	56 (19.5%)	7 (26.9%)	49 (18.8%)	0.32
Peripheral vascular disease	52 (18.1%)	3 (11.5%)	49 (18.8%)	0.59
Permanent pacemaker	32 (11.1%)	2 (7.8%)	30 (11.5%)	0.75
Implanted defibrillator	6 (2.1%)	1 (3.8%)	5 (1.9%)	0.44
Number of sternotomies ≥1	65 (22.6%)	3 (11.5%)	62 (23.8%)	0.22
Chronic obstructive pulmonary disease	34 (11.8%)	1 (3.8%)	33 (12.6%)	0.34
Body mass index (kg/m^2)	29.9 ± 7.8	29.7 ± 5.9	29.9 ± 8.0	0.89
Anemia	98 (34.1%)	5 (19.2%)	93 (35.6%)	0.09
Creatinine (mg/dl)	1.10 ± 0.86	1.10 ± 0.37	1.20 ± 0.89	0.66
Estimated glomerular filtration rate, (ml/min/1.73 m^2)	63.4 ± 18.8	64.5 ± 15.0	63.2 ± 19.2	0.74
Estimated glomerular filtration rate <60 ml/min/1.73 m^2	117 (40.8%)	9 (34.6%)	108 (41.4%)	0.50
Preprocedure medication				
Aspirin	198 (69.0%)	19 (73.1%)	179 (68.6%)	0.64
P2Y12 receptor inhibitor	37 (12.9%)	5 (19.2%)	32 (12.3%)	0.35
Warfarin	68 (23.7%)	4 (15.4%)	64 (24.5%)	0.35
Direct oral anticoagulant	16 (5.6%)	0	16 (6.1%)	0.38
Angiotensin-converting enzyme inhibitor/Angiotensin II receptor blocker	138 (48.1%)	13 (50.0%)	125 (47.9%)	0.84
Beta-blockers	164 (57.1%)	18 (69.2%)	146 (55.9%)	0.19
Diuretic	153 (53.3%)	14 (53.8%)	139 (53.3%)	0.95
Aldosterone antagonist	15 (5.2%)	0	15 (5.7%)	0.38
Society of Thoracic Surgery predicted risk of mortality (%)	4.4 ± 2.6	3.9 ± 1.9	4.5 ± 2.7	0.33

HALT= Hypoattenuated leaflet thickening.

* Hypertension was defined as systolic blood pressure >140 mm Hg or diastolic pressure >90 mm Hg, or on antihypertensive treatment.

Dyslipidemia was defined as a high level of low-density lipoprotein cholesterol ≥160 mg/dl or low level of high-density lipoprotein cholesterol defined as ≤40 mg/dl.

Table 2
Baseline echocardiographic and multi-detector computed tomography data (n = 287)

Variable	All (n = 287)	HALT (n = 26)	Non-HALT (n = 261)	*p Value*
Peak aortic velocity (m/s)	4.0 ± 0.6	3.7 ± 0.5	4.0 ± 0.6	0.03
Aortic valve area (cm^2)	0.78 ± 0.22	0.78 ± 0.21	0.78 ± 0.22	0.99
Aortic valve area index (cm^2/m^2)	0.40 ± 0.11	0.40 ± 0.10	0.40 ± 0.11	0.92
Mean aortic gradient (mmHg)	38.6 ± 12.8	33.6 ± 9.6	39.1 ± 13.0	0.04
Dimensionless index	0.23 ± 0.06	0.23 ± 0.05	0.23 ± 0.06	0.71
Bicuspid aortic valve	7 (2.4%)	0	7 (2.7%)	1.00
Left ventricular ejection fraction (%)	57 ± 13	56 ± 11	57 ± 14	0.82
Stroke volume index (ml/m^2)	36.5 ± 10.9	37.3 ± 9.6	36.4 ± 11.0	0.70
Left ventricular end-diastolic diameter (mm)	45.5 ± 8.0	46.1 ± 8.5	45.5 ± 7.9	0.72
Left ventricular end-systolic diameter (mm)	31.0 ± 9.3	30.8 ± 8.8	31.1 ± 9.3	0.88
Left ventricular outflow tract diameter(max) (cm)	2.07 ± 0.19	2.12 ± 0.19	2.07 ± 0.19	0.19
Left atrium volume index (ml/m^2)	44.1 ± 20.4	40.3 ± 17.5	44.4 ± 20.6	0.42
Left atrium diameter (mm)	43.3 ± 8.3	41.8 ± 9.3	43.5 ± 8.2	0.35
Valvulo-arterial impedance (mm $Hg/ml/m^2$)	4.93 ± 1.38	4.25 ± 1.07	4.99 ± 1.39	0.01
Moderate or severe aortic regurgitation	45 (15.7%)	3 (11.5%)	42 (16.1%)	0.78
Moderate or severe mitral regurgitation	71 (24.7%)	2 (7.7%)	69 (26.4%)	0.04
Moderate or severe tricuspid regurgitation	53 (18.5%)	5 (19.2%)	48 (18.4%)	1.00
Estimated right ventricular systolic pressure (mmHg)	34.0 ± 10.6	30.2 ± 7.2	34.4 ± 10.8	0.10
Annulus area (mm^2)	4.80 ± 1.00	5.24 ± 1.32	4.76 ± 0.95	0.02
Annular perimeter (mm)	78.5 ± 8.2	82.0 ± 9.9	78.1 ± 8.0	0.02
Annular mean diameter (mm)	24.8 ± 2.5	25.7 ± 3.2	24.7 ± 2.5	0.05
Maximum ascending aortic size (mm)	34.1 ± 4.1	34.8 ± 5.1	34.0 ± 4.0	0.37
Maximum LVOT diameter (cm)	2.81 ± 0.36	2.92 ± 0.40	2.80 ± 0.36	0.10
Left ventricular outflow tract calcification grade				
0	174 (60.8%)	12 (46.2%)	162 (62.3%)	0.03
1	49 (17.1%)	10 (38.5%)	39 (15.0%)	
2	32 (11.2%)	1 (3.8%)	31 (11.9%)	
3	31 (10.8%)	3 (11.5%)	28 (10.8%)	
Sinotubular junction diameter (mm)	29.2 ± 3.8	30.3 ± 3.6	29.0 ± 3.8	0.12
Sinuses of Valsalva height (mm)				
Left coronary sinus	21.6 ± 3.2	22.6 ± 2.4	21.5 ± 3.3	0.10
Right coronary sinus	22.0 ± 3.7	23.2 ± 3.4	21.9 ± 3.7	0.09
Noncoronary sinus	22.3 ± 3.8	22.5 ± 2.6	22.3 ± 3.9	0.85
Sinuses of Valsalva diameter (mm)				
Left coronary sinus	32.5 ± 4.1	34.1 ± 4.4	32.4 ± 4.0	0.04
Right coronary sinus	31.3 ± 3.7	32.0 ± 3.6	31.2 ± 3.8	0.29
Noncoronary sinus	32.3 ± 3.9	33.1 ± 4.2	32.2 ± 3.9	0.29
Sinus of Valsalva/Transcatheter heart valve diameter ratio	1.18 ± 0.14	1.21 ± 0.10	1.18 ± 0.14	0.31

HALT = Hypoattenuated leaflet thickening.

cases). For patients who received a self-expanding prosthesis, there was no association of HALT occurrence with prosthesis size. Occurrence of HALT also was not related to area cover index in balloon-expandable patients, nor to the annular perimeter or Sinus of Valsalva diameter in self-expandable patients. Notably, 9 of the 26 cases of HALT were being treated with warfarin at the time of diagnosis, however, the international normalized ratio (INR) was subtherapeutic (INR <2.0) in 6 of these 9 patients (Table 4). The HALT patients more often had subtherapeutic INR whereas using warfarin than those who did not develop HALT on index MDCT imaging ($p = 0.01$).

The vast majority of patients with HALT had normal valve hemodynamics at the time of MDCT imaging, similar to those without HALT (Figure 1). For the patients with HALT, abnormal valve hemodynamics on echocardiogram indicating possible THV thrombosis were observed in 0 (0%) patients before discharge, 1 (3.8%) patient at 1 month, 1 (3.8%) patient at 3 months, 1 (3.8%) patient at 6 months, 0 (0%) at 1-year follow-up. Follow-up MDCT was conducted in 21 of the 26 patients (80.8%) after a median of 84 days (IQR: 64 to 97 days). There was no significant difference in echocardiographic effective orifice area, mean transvalvular gradient, and peak aortic velocity between patients with and without HALT at 6-month and 1-year follow-up.

Median duration of follow-up for the study population was 7.6 months (IQR: 3.4 to 12.5 month) (100% complete). Following diagnosis of HALT, all patients were placed on oral anticoagulation. Two patients treated with warfarin had bleeding episodes, including one who suffered hemorrhagic stroke and the other suffered lower gastrointestinal bleeding. In 2 patients, weaning of anticoagulation was attempted, but was associated with relapses of HALT (Figure 2), and symptomatic, obstructive thrombosis. Lifelong warfarin anticoagulation therapy was then recommended. Overall, 20 (76.9%) of the HALT cases were maintained on oral anticoagulation at last follow-up, and there were no changes in aortic prosthesis function. In all but 2 cases, therapeutic anticoagulation resulted in

Table 3
Procedural characteristics (n = 287)

Variable	All (n = 287)	HALT (n = 26)	Non-HALT (n = 261)	*p Value*
TAVI access route				
Transfemoral	274 (95.5%)	26 (100%)	248 (95.0%)	0.62
Transapical	1 (0.3%)	0	1 (0.4%)	1.00
Transaortic	9 (3.1%)	0	9 (3.4%)	1.00
Subclavian	3 (1.0%)	0	3 (1.1%)	1.00
Balloon-expandable valve	152 (53.0%)	19 (73.1%)	133 (51.0%)	0.03
Valve size (mm)				
20	6 (4.0%)	1 (5.3%)	5 (3.8%)	0.01
23	44 (29.0%)	3 (15.8%)	41 (30.8%)	
26	61 (40.1%)	4 (21.1%)	57 (42.9%)	
29	41 (27.0%)	11 (57.9%)	30 (22.6%)	
Area cover index (%)	4.7 ± 8.2	2.7 ± 12.1	4.9 ± 7.5	—
20	0.6 ± 9.4	−0.6	0.9 ± 10.5	
23	2.6 ± 5.6	4.5 ± 10.9	2.4 ± 5.2	
26	5.4 ± 7.6	8.3 ± 2.0	5.2 ± 7.8	
29	6.4 ± 10.6	0.5 ± 14.7	8.5 ± 7.9	
Self-expanding valve	135 (47.0%)	7 (26.9%)	128 (49.0%)	0.03
Valve size (mm)				
23	13 (9.6%)	0	13 (10.2%)	0.97
26	31 (23.0%)	2 (28.6%)	29 (22.7%)	
29	56 (41.5%)	4 (57.1%)	52 (40.6%)	
31	7 (5.2%)	0	7 (5.5%)	
34	28 (20.7%)	1 (14.3%)	27 (21.1%)	
Annular perimeter (mm)	77.8 ± 8.6	76.3 ± 6.3	77.8 ± 8.7	—
23	68 ± 6.2	—	68 ± 6.2	
26	68 ± 3.4	68.5 ± 0.7	68.0 ± 3.5	
29	77.2 ± 4.6	78 ± 2.9	77.1 ± 4.8	
31	88.4 ± 2.9	—	88.4 ± 2.9	
34	87.8 ± 4.8	85	87.9 ± 4.9	
Mean Sinus of Valsalva diameter (mm)	32.0 ± 3.7	33.1 ± 3.9	31.9 ± 3.7	0.12
Valve-in-valve implant	21 (7.3%)	0 (0)	21 (8.0%)	0.23
Postdilatation performed	10 (3.5%)	1 (3.8%)	9 (3.4%)	1.00
Aspirin loading	259 (90.2%)	26 (100%)	233 (89.3%)	0.09
Clopidogrel loading	113 (39.4%)	13 (50.0%)	100 (38.3%)	0.24
Activated coagulation time during procedure (seconds)	254 ± 43	251 ± 37	255 ± 44	0.69
Protamine use (%)	243 (84.7%)	23 (88.5%)	220 (84.3%)	0.78
Protamine dose (mg)	83.9 ± 25.5	93.1 ± 29.5	83.0 ± 25.0	0.18
Periprocedure hemorrhage complications	2 (0.7%)	0	2 (0.8%)	1.00
Time from TAVI to index CT (days)	31 (28, 34)	30.5 (29, 31)	31 (28, 34)	0.95

HALT = hypoattenuated leaflet thickening; TAVI = transcatheter aortic valve implantation.

Table 4
Antithrombotic regimens at discharge until post-transcatheter aortic valve implantation computed tomography angiography follow-up

Variable	All (n = 287)	HALT (n = 26)	Non-HALT (n = 261)	*p Value*
None	1 (0.3%)	1 (3.8%)	0	0.09
Aspirin only	24 (8.4%)	1 (3.8%)	23 (8.8%)	0.71
Clopidogrel or Ticagrelor only	1 (0.3%)	0	1 (0.4%)	1.00
Aspirin + Clopidogrel or Ticagrelor	157 (54.7%)	15 (57.7%)	142 (54.4%)	0.75
Any warfarin or direct oral anticoagulant	104 (36.2%)	9 (34.6%)	95 (36.4%)	0.86
Any warfarin	83 (28.9%)	9 (34.6%)	74 (28.4%)	0.50
Warfarin only	0	0	0	1.00
Warfarin + Aspirin	64 (22.3%)	8 (30.8%)	56 (21.5%)	0.28
Warfarin + Clopidogrel	15 (5.2%)	1 (3.8%)	14 (5.4%)	1.00
Warfarin + Aspirin + Clopidogrel	4 (1.4%)	0	4 (1.5%)	1.00
Subtherapeutic international normalized ratio	23 (27.7%)	6 (66.7%)	17 (23.0%)	0.012
Any direct oral anticoagulant	21 (7.3%)	0	21 (8.0%)	0.24
Direct oral anticoagulant only	1 (0.3%)	0	1 (0.4%)	1.00
Direct oral anticoagulant + Aspirin	15 (5.2%)	0	15 (5.7%)	0.38
Direct oral anticoagulant + Clopidogrel	5 (1.7%)	0	5 (1.9%)	1.00
Direct oral anticoagulant + Aspirin + Clopidogrel	0	0	0	1.00

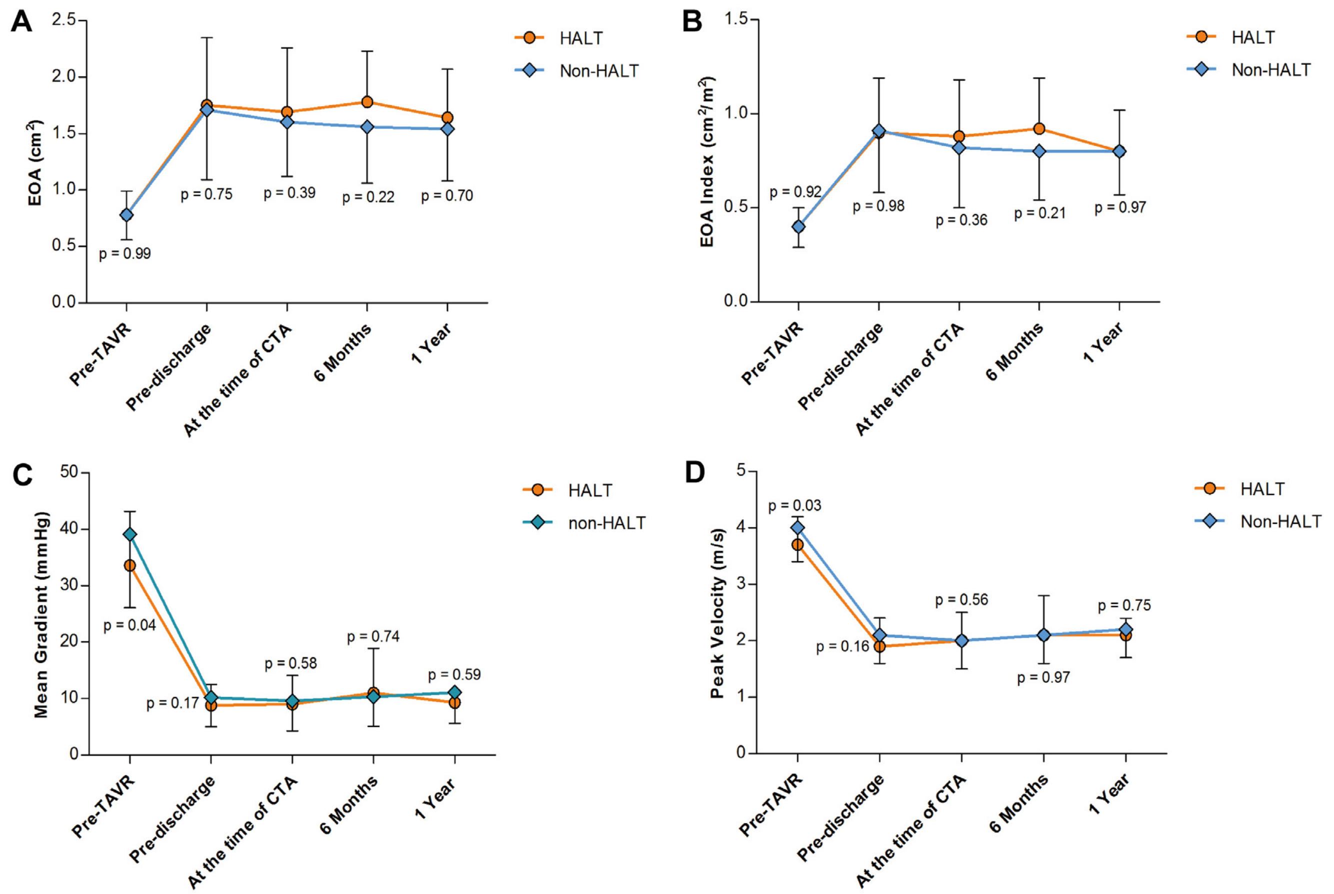

Figure 1. **Echocardiographic follow-up for the overall study population.** Changes in *(A)* EOA, *(B)* EOA index, *(C)* mean gradient, and *(D)* peak velocity between the 2 groups during follow-up. EOA, effective orifice area.

complete resolution of HALT, as confirmed by the follow-up MDCT scanning. During follow-up, ischemic stroke occurred in 2 patients with HALT (7.7%) (10 days after TAVI and 3 weeks after HALT diagnosis), and 4 patients (1.5%) without HALT (p = 0.09). A statistical trend (p = 0.09) was present for worse survival free of major adverse clinical events among patients who were found to have HALT on MDCT imaging (Figure 3).

Discussion

The present investigation was a prospective evaluation for the frequency and clinical factors associated with HALT in patients undergoing commercial TAVI. The key findings are: (1) Early HALT was detected in 9.1% of TAVI patients; (2) HALT occurred more commonly in patients with balloon-expandable valves than those who received self-expanding valves, and in those who received larger prostheses; (3) Most patients with HALT had no evidence of hemodynamic compromise on echocardiography, and thus otherwise likely would have gone undetected without advanced cardiac imaging. (4) A trend for a higher incidence of major adverse clinical events was present for patients with HALT.

Whereas HALT has been the subject of previous publications in TAVI patients, most of these reports have been heavily influenced either by their retrospective nature,[8–10,22–25] and thus subjected to clinical indications for the evaluation for leaflet thrombosis in the contemporary era. Our screening program is prospective for all patients who underwent TAVI with commercial valves. The incidence of HALT was 9.1%, and we believe this is a considerable number, especially given that nearly all patients were asymptomatic and without abnormal echocardiographic findings. Our incidence rate is in line with other studies on the frequency of HALT early after TAVI (i.e., 4% to 13%).[8–10,22–24] Of note, the current practice guidelines for the management of patients with valvular heart disease have strongly endorsed serial echocardiography in patients with prosthetic valves, only when there is a change in clinical symptoms or signs suggesting valve dysfunction or annually beginning at 10 years after the procedure.[26] However, our findings, in concert with other previous studies,[27] demonstrate the possibility of early leaflet thrombosis after TAVI can precede the onset of clinical symptoms or hemodynamic derangement on echocardiography. Thus, early prospective screening with MDCT may be of incremental clinical utility, and should be considered for detection of HALT in patients who undergo TAVI.

In the present investigation, HALT was identified more commonly in patients with balloon-expandable than in those received self-expandable valves, similar to previous studies.[8,13,28,29] The cause of different thrombosis rates is uncertain, but might be attributable to greater interaction of the balloon with the prosthetic leaflets, potentially leading

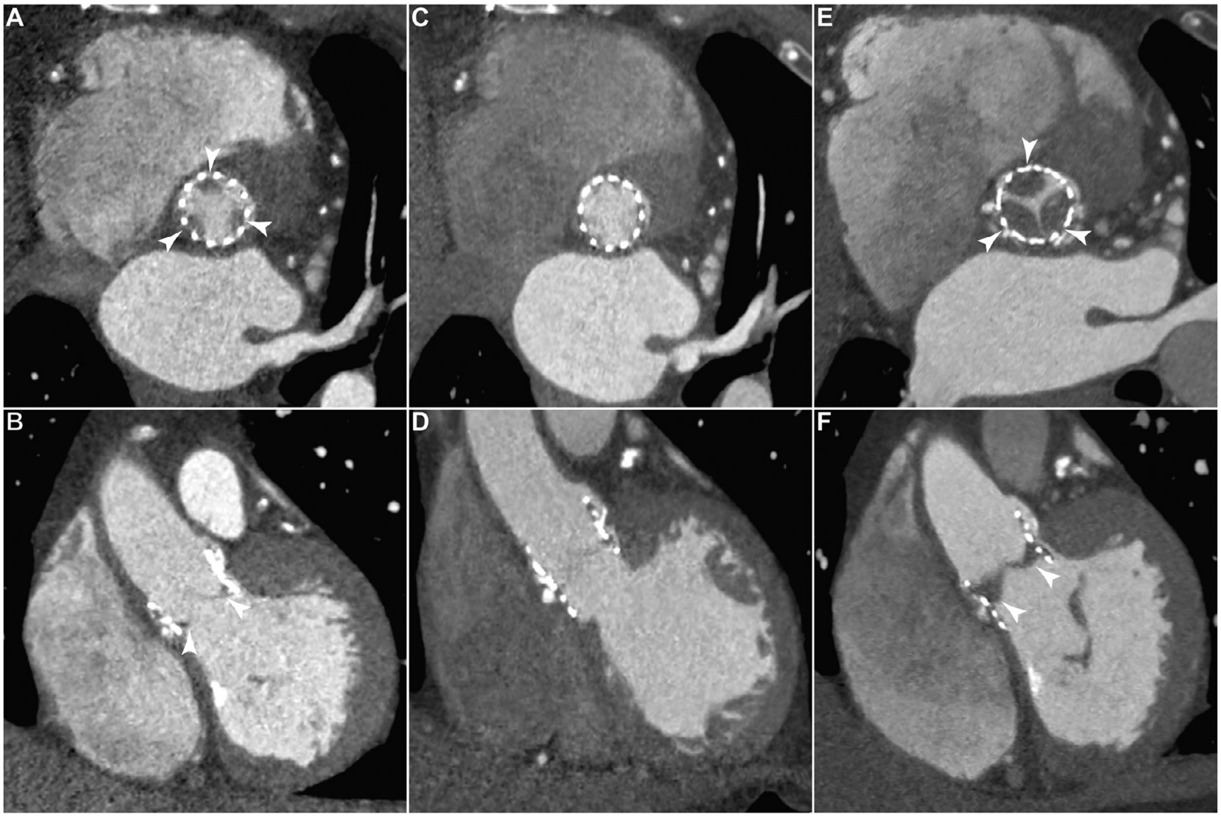

Figure 2. **Serial contrast-enhanced multidetector computed tomography images in a patient with recurrent hypoattenuated leaflet thickening (HALT) after transcatheter aortic valve implantation with Sapien 3 valve.** Diastolic computed tomography angiography (CTA) images performed 1 month after procedure in a *(A)* short-axis and *(B)* coronal long-axis view revealed hypoattenuated thickening at the bases of all 3 leaflets *(arrowhead). (C and D)* Follow-up CTA images showing HALT resolution after 3 months of warfarin therapy. The patient was advised continue his warfarin for a total treatment duration of 6 months. *(E and F)* After discontinuation of warfarin for 3 months, follow-up CTA revealed marked hypoattenuated thickening involving all 3 leaflets with noncoronary and right coronary leaflets immobile *(arrowhead)*.

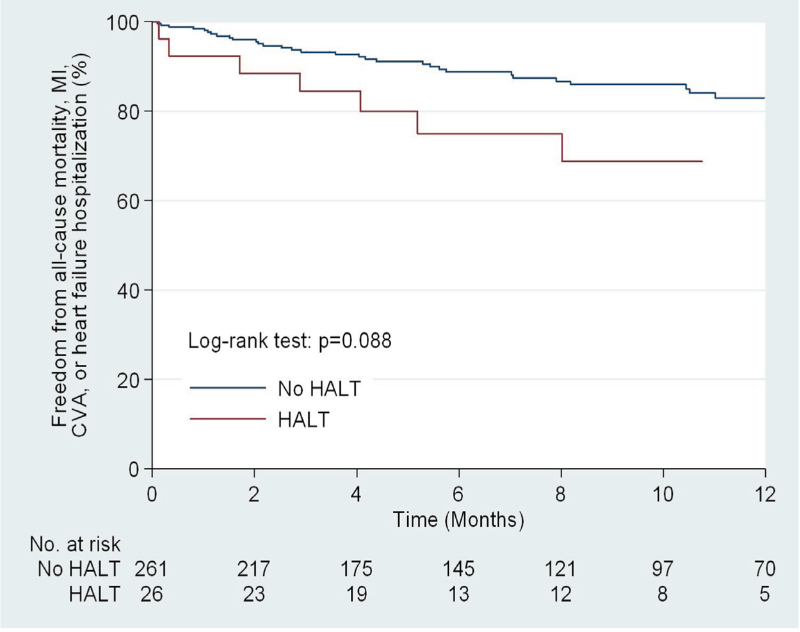

Figure 3. **Survival for the study patients**. Kaplan−Meier curve for survival free of all-cause mortality, myocardial infarction, ischemia stroke, transient ischemia attack, or heart failure rehospitalization.

to more extensive surface injury during the procedure. Such balloon interaction may occur either during prosthesis deployment or from postdilation, which is also more commonly undertaken with the Portico system than in other self-expanding valves such as the CoreValve or Evolut R. The relation of a relatively larger aortic annular area or a larger prosthesis to HALT also was notable, and has been reported previously.[23,24] Furthermore, HALT was more common in patients with lower stroke volume and lower aortic valve gradients. Whether a large annular size reflects the potential for more balloon-leaflet interaction, serves as a nidus for retention of blood flow in a large sinus of Valsalva, or is coincidental, deserves further study.

The association of HALT with major adverse clinical events has been a concern in TAVI patients. In our study, we observed a trend toward worse major adverse clinical events during 1-year follow-up. The RESOLVE and SAVORY registries showed HALT to be significantly associated with increased rate of stroke,[8] but such an association has not been observed in all reports. Nonetheless, early detection of HALT does present an opportunity for timely intervention, and potentially averting worsening thrombosis. In a recent study by Hansson et al.,[24] 18% of patients with HALT developed clinically overt obstructive THV thrombosis during 1-year follow-up. In our program, where patients were identified prospectively and then initiated on anticoagulation, complete resolution was achieved in all but 2 patients. Moreover, comparable hemodynamics with management guided by the presence of HALT on MDCT was maintained through extended follow-up. Importantly, 9 of our 26 patients with HALT were already on anticoagulation, which previously had been described to be a negative predictor,[8,24,28] though some patients had subtherapeutic INR. The optimal antithrombotic therapy after TAVI has not been well established. A recent large observational study confirmed that anticoagulation with DOAC or warfarin, but not the current guidelines recommend dual antiplatelet therapy (DAPT), was the only effective strategy in prevention or treatment of leaflet thrombosis.[8,26] Of note, in our study, warfarin was prescribed for all HALT patients. However, the use of warfarin for this treatment was not randomized. The effect of DOAC therapy on leaflet thrombosis and associated clinical events is the subject of several ongoing randomized clinical trials. The ADAPT-TAVR (Anticoagulant vs. Dual Antiplatelet Therapy for Preventing Leaflet Thrombosis and Cerebral Embolization after Transcatheter Aortic Valve Replacement; NCT03284827) and GALILEO (Global Study Comparing a rivAroxaban-based Antithrombotic Strategy to an antipLatelet-based Strategy After Transcatheter aortIc vaLve rEplacement to Optimize Clinical Outcomes; NCT02556203) studies aim to assess the superiority of anticoagulation with Edoxaban or Rivaroxaban, respectively, vs. DAPT for reducing leaflet thrombosis and thromboembolic events after successful TAVI are underway. Results from these trials may provide new evidence for this issue.

The present study is a single-center investigation with the initial MDCT screening performed only at 30-day follow-up. Although most incidences of HALT or thrombosis have been reported to occur within 3 months after the index procedure, there is evidence that the risk of leaflet thrombosis may persist beyond 1 year after procedure. Thus, our reported incidence of HALT might be an underestimation. Further investigation with an expanded cohort is needed to determine the incidence and clinical burden of HALT in extended follow-up.

In conclusion, HALT was prospectively detected in 9% of TAVI cases among patients without clinical evidence of thrombosis. HALT occurred more commonly in patients treated with large, balloon-expandable prosthesis. Such prospective screening may be considered as early HALT is reversible by timely management with therapeutic anticoagulation.

Disclosures

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