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경피적 판막 치환술 시행한 환자에서 무증상 판막엽 혈전증이 판막의 혈역학 및 판막 기능 이상에 미치는 영향

Impact of Subclinical Leaflet Thrombosis on Valve Hemodynamic Consequences and Structural Valve Deterioration after Transcatheter Aortic Valve Replacement

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Impact of Subclinical Leaflet Thrombosis on Valve Hemodynamic Consequences and Structural Valve Deterioration after Transcatheter Aortic Valve Replacement

Abstract

BACKGROUND: The effect of subclinical leaflet thrombosis, characterized by hypoattenuated leaflet thickening (HALT), on the valve hemodynamic function and durability of the bioprosthetic valve has not been yet determined.

OBJECTIVES: This study aimed to determine the impact of HALT on valve hemodynamics after transcatheter aortic valve replacement (TAVR) and the predictors of hemodynamic structural valve deterioration (SVD).

METHODS: The ADAPT-TAVR trial is a multicenter, randomized trial that compared edoxaban and dual antiplatelet therapy in patients without an indication for anticoagulation who had undergone successful TAVR. The presence of HALT was evaluated by four-dimensional computed tomography (CT) at 6 months and serial echocardiography performed at baseline, immediately post-TAVR, and after 6 months of follow-up.

RESULTS: At 6 months, HALT was found in 30 of 211 (14.2%) patients. The presence of HALT did not significantly affect aortic valve mean gradients (with vs. without HALT; 14.0 ± 4.8 mmHg vs. 13.7 ± 5.5 mmHg; $p=0.742$) at 6 months. At least moderate hemodynamic SVD was reported in 30 of 206 patients (14.6%) at 6-month follow-up echocardiography. The use of aortic valve size ≤ 23 mm and smaller aortic valve area were independent predictors of hemodynamic SVD; however, the presence of HALT was not identified as a predictor of hemodynamic SVD.

CONCLUSIONS: In patients who had undergone successful TAVR, aortic valve hemodynamic status was not influenced by the presence of HALT. Although HALT was not a predictor of hemodynamic SVD at 6 months, it warrants further longer-term follow-up to evaluate the impact of valve durability.

Key words: aortic stenosis, leaflet thrombosis, transcatheter aortic-valve replacement, valve hemodynamics

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Introduction

For the last few decades, transcatheter aortic valve replacement (TAVR) has been an effective alternative treatment for patients with symptomatic severe aortic stenosis (AS) who are at high or intermediate surgical risk (1-3). Recently, TAVR was also shown to be non-inferior to conventional surgical aortic valve replacement (SAVR) in low-risk patients (4,5). According to updated clinical guideline, TAVR is recommended for patients with symptomatic severe AS who are aged > 65 years (6). Considering the trend of increasing TAVR procedures in relatively younger and low-risk patients, the durability of the bioprosthetic valve after the TAVR procedure remains an important issue, and it is critical to identify risk factors of structural valve deterioration (SVD).

Among patients who underwent TAVR and had follow-up four-dimensional computed tomography (CT) evaluations, subclinical leaflet thrombosis characterized by hypoattenuated leaflet thickening (HALT) was found in approximately 10%–20% of cases (7-11). This imaging phenomenon could be associated with an increased risk of cerebral thromboembolic events, such as stroke or transient ischemic attack (12,13). However, until recently, the effect of HALT on valve hemodynamics and the durability of a bioprosthetic valve have not been clearly determined. Moreover, the key predictors of hemodynamic SVD remain unknown. ADAPT-TAVR(Anticoagulation Versus Dual Antiplatelet Therapy for Prevention of Leaflet Thrombosis and Cerebral Embolization After Transcatheter Aortic Valve Replacement) (ADAPT-TAVR) trial is a randomized trial that compared the effect of edoxaban with dual antiplatelet therapy (DAPT) in patients who underwent successful TAVR (14). As a substudy of the ADAPT trial, this study aimed to determine whether HALT affects valve hemodynamics and to evaluate the frequency of hemodynamic SVD and its predictors via echocardiography at 6 months of follow-up.

Method

Study Design and Patient Population

The design, baseline characteristics, and primary results of the ADAPT-TAVR trial have been published recently (14,15). In brief, the ADAPT-TAVR study is a multinational, multicenter, prospective, randomized, open-label, adjudicator-masked trial that aimed to compare the potential effect of edoxaban vs. DAPT of HALT and the accompanying potential cerebral thromboembolic risk in patients who did not have an indication for oral anticoagulation after undergoing successful TAVR. The trial was conducted at five major centers in three countries (South Korea, Hong Kong, and Taiwan). The protocol was approved by the institutional review board at each site, and all the patients provided written informed consent to participate before trial enrollment.

The inclusion criteria were as follows: severe aortic stenosis; a patient who successfully underwent TAVR, which was defined as a mean aortic valve gradient of <20 mmHg or peak velocity of <3 m/s; no pre-existing indication for anticoagulation; and no contraindication to undergoing a CT scan with contrast. After a successful TAVR procedure, patients were assigned randomly at a 1:1 ratio to receive either edoxaban (60 mg once daily or 30 mg once daily with dose-reduction criteria) or DAPT (aspirin at 100 mg once daily plus clopidogrel at 75 mg once daily) for 6 months.

CT Image and Echocardiography follow up

Randomized patients were routinely scheduled for contrast-enhanced, electrocardiogram-gated cardiac CT scans with full cardiac-cycle coverage (four-dimensional CT) 6 months after the procedures. The detailed CT protocol is described in the ADAPT-TAVR study (14). The presence and degree of HALT (i.e., possible subclinical leaflet thrombosis) were classified according to the standard definition (16,17). All cardiac CT imaging measurements were performed at a central imaging core laboratory (Asan Image Metrics; www. Aimaicro.com) by independent cardiac radiologists who were blinded to the random treatment assignment. Moreover, the treating investigators were blinded to the results of the CT scans.

For all patients, transthoracic echocardiography (TTE) was routinely performed at baseline, immediately post-TAVR, and after 6 months of follow-up to assess the valve hemodynamics. All echocardiographic assessments were performed by independent echocardiographic specialists in each participating center who were blinded to the patients' identities and random treatment assignments and were centrally reviewed by an independent core laboratory (Asan Medical Center, Seoul). All available Core Laboratory–assessed echocardiograms were used in the analysis. When Core Laboratory assessment was not available, clinical site–reported echocardiographic readings were used. The Doppler velocity index was calculated as the ratio of subvalvular velocity obtained on pulsed-wave Doppler and the maximum velocity obtained on continuous wave Doppler across the prosthetic valve.

Study Endpoints and Definitions

The primary objective of the study was to evaluate the prevalence of HALT and the impact of HALT on valve hemodynamics (mean aortic valve gradient, mean aortic valve area, and Doppler velocity index) on serial echocardiography. This effect was further evaluated according to randomized groups of edoxaban and DAPT. HALT was defined as visually identified increased leaflet thickness with a typical meniscal appearance on short and long-axis views (13,18). The secondary objective was to determine the frequency and predictors of hemodynamic SVD at echocardiography after 6 months of follow-up. Moderate or greater hemodynamic SVD was defined as at least one of the following: mean transprosthetic gradient ≥20 mmHg, change in the mean transprosthetic gradient of ≥10 mmHg from baseline, and new or increase in intra-prosthetic aortic regurgitation of ≥1 grade, resulting in moderate or greater valvular regurgitation (19).

Statistical Analysis

Categorical variables are presented as numbers (percentage), and continuous variables are presented as means ± standard deviations. Differences between the two groups were analyzed using Student's t-test for comparison of the continuous variables with normal distributions and using the Wilcoxon rank sum test for continuous variables without normal distribution. Categorical variables were analyzed using the Chi-squared or Fisher exact test, as appropriate.

Predictors of HALT and hemodynamic SVD were assessed using univariable and multivariable logistic regression analysis. Initially, univariable logistic regression models were fit to identify clinical, procedural, echocardiographic, and CT variables associated with HALT and hemodynamic SVD at 6 months. The variables with a probability value <0.10 in the univariate analysis were candidates for building the multivariable regression model. When performing multivariable logistic regression analyses, the three variables, aortic valve area, mean pressure gradient, and peak pressure gradient, were highly correlated with each other, resulting in multicollinearity;

thus, the aortic valve area was chosen to perform a multivariable logistic regression analysis. In addition, when evaluating the predictor of hemodynamic SVD, the valve-in-valve variable was statistically significant in the univariable logistic regression analysis; however, the number of cases was too small to be included in the multivariable logistic regression analysis.

All reported P values are two-sided and have not been adjusted for multiple testing. Results were considered statistically significant at P values < 0.05, and all P values were two-sided. All statistical analyses were performed with SPSS software, version 24.0 (IBM).

Result

Study Population and Baseline characteristics

This study enrolled 235 of 769 randomized patients who underwent successful TAVR from March 2018 to April 2021. Among them, 211 patients who had cardiac CT evaluations after 6 months were included in this study (**Figure 1).** In the study group, the presence of HALT was observed in 30 of 211 (14.2%) patients; in particular, HALT was noted in 10 of 102 patients (9.8%) in the edoxaban group and 20 of 109 patients (18.3%) in the DAPT group.

Baseline demographic and clinical characteristics for groups with and without HALT at 6 months are summarized in **Table 1**. There was no significant difference in clinical risk factors and comorbidities between patients with and without HALT. **Table 2** summarizes the procedural and echocardiographic characteristics at baseline and immediately post-TAVR of the randomized study population according to treatment groups. There were also no significant differences in procedural and echocardiographic characteristics among the groups with and without HALT. A univariable logistic regression analysis of demographic, procedural, and immediate post-TAVR hemodynamic variables, which are considered potential predictors of HALT at 6 months, are shown in **Supplemental Table 1**. No significant baseline predictors were noted for HALT at 6 months.

HALT and Valve Hemodynamic Status

The impact of HALT on valve hemodynamic findings is summarized in **Table**

Table 1. Baseline characteristics of patients according to the presence of HALT on CT after 6 months*

Characteristics	Patients with post-TAVR MDCT (n = 211)	HALT (-) (n = 181)	HALT (+) (n = 30)	P value
Age – years	80.1 ± 5.3	80.0 ± 5.4	80.8 ± 4.7	0.435
Male sex – n (%)	88 (41.7%)	76 (42.0%)	12 (40.0%)	0.838
Body mass index†	25.1 ± 4.1	25.0 ± 3.9	25.6 ± 4.9	0.432
Body surface area – kg/㎡	1.60 ± 0.17	1.60 ± 0.17	1.58 ± 0.18	0.436
STS risk score‡	3.2 ± 1.6	3.0 ± 1.6	3.2 ± 1.4	0.216
EuroSCORE value¶	2.1 ± 1.1	2.1 ± 1.2	2.1 ± 1.0	0.509
NYHA classification – n (%)				0.205
I–II	156 (73.9%)	131 (72.4%)	25 (83.3%)	
III–IV	55 (26.1%)	50 (27.6%)	5 (16.7%)	
Smoking history – n (%)	49 (23.2%)	42 (23.2%)	7 (23.3%)	1.0
Hypertension – n (%)	156 (73.9%)	135 (74.6%)	21 (70.0%)	0.596
Diabetes mellitus – n (%)	64 (30.3%)	55 (30.4%)	9 (30.0%)	0.966

Dyslipidemia – n (%)	157 (74.4%)	133 (73.5%)	24 (80.0%)	0.449
Coronary artery disease – n (%)	58 (27.6%)	48 (26.7%)	10 (33.3%)	0.450
Prior myocardial infarction – n (%)	1 (0.5%)	1 (0.6%)	0 (0%)	> 0.999
Prior PCI – n (%)	30 (14.2%)	26 (14.4%)	4 (13.3%)	> 0.999
Prior CABG – n (%)	4 (1.9%)	3 (1.7%)	1 (3.3%)	0.461
Prior cerebrovascular disease – n (%)	17 (8.1%)	13 (7.2%)	4 (13.3%)	0.274
Peripheral arterial disease – n (%)	18 (8.5%)	16 (8.8%)	2 (6.7%)	> 0.999
Chronic lung disease – n (%)	52 (24.6%)	44 (24.3%)	8 (26.7%)	0.781
Serum Creatinine – mg/dL	0.94 ± 0.27	0.92 ± 0.25	1.03 ± 0.35	0.131

* Values are mean ± SD or n (%). Percentages may not total 100% because of rounding

† The body mass index is the weight in kilograms divided by the square of the height in meters.

‡ STS risk scores use an algorithm that is based on the presence of coexisting illness in order to predict 30-day operative mortality. A score of greater than 8% indicates a high risk, 3 to 8% indicates an intermediate risk, and less than 3% indicates a low risk.

¶ Scores on the European System for Cardiac Operative Risk Evaluation (EuroSCORE) range from 0 to 100, with higher scores indicating a greater risk of death within 30 days after the procedure.

CT, computed tomography; HALT, hypoattenuated leaflet thickening; CABG, Coronary Artery Bypass graft surgery; STS, Society of Thoracic Surgeons; NYHA, New York Heart Association; PCI, Percutaneous Coronary Intervention; STS, Society of Thoracic Surgeons; TAVR, Transcatheter Aortic Valve Replacement

Table 2. Baseline procedural and echocardiographic characteristics of patients according to the presence of HALT on CT after 6 months*

	Patients with post-TAVR MDCT (n = 211)	HALT (-) (n = 181)	HALT (+) (n = 30)	P value
Procedural characteristics				
Pre-TAVR balloon valvuloplasty – n (%)	79 (37.4%)	65 (35.9%)	14 (46.7%)	0.260
Valve type - no. (%)				0.191
Balloon-expandable	190 (90.0%)	165 (91.2%)	25 (83.3%)	
Self-expandable	21 (10.0%)	16 (8.8%)	5 (16.7%)	
Specific valve type				0.147
Sapien 3	188 (89.1%)	163 (90.1%)	25 (83.3%)	
Evolut R	10 (4.7%)	8 (4.4%)	2 (6.7%)	
CoreValve	1 (0.5%)	0 (0.0%)	1 (3.3%)	
Evolut PRO	8 (3.8%)	6 (3.3%)	2 (6.7%)	

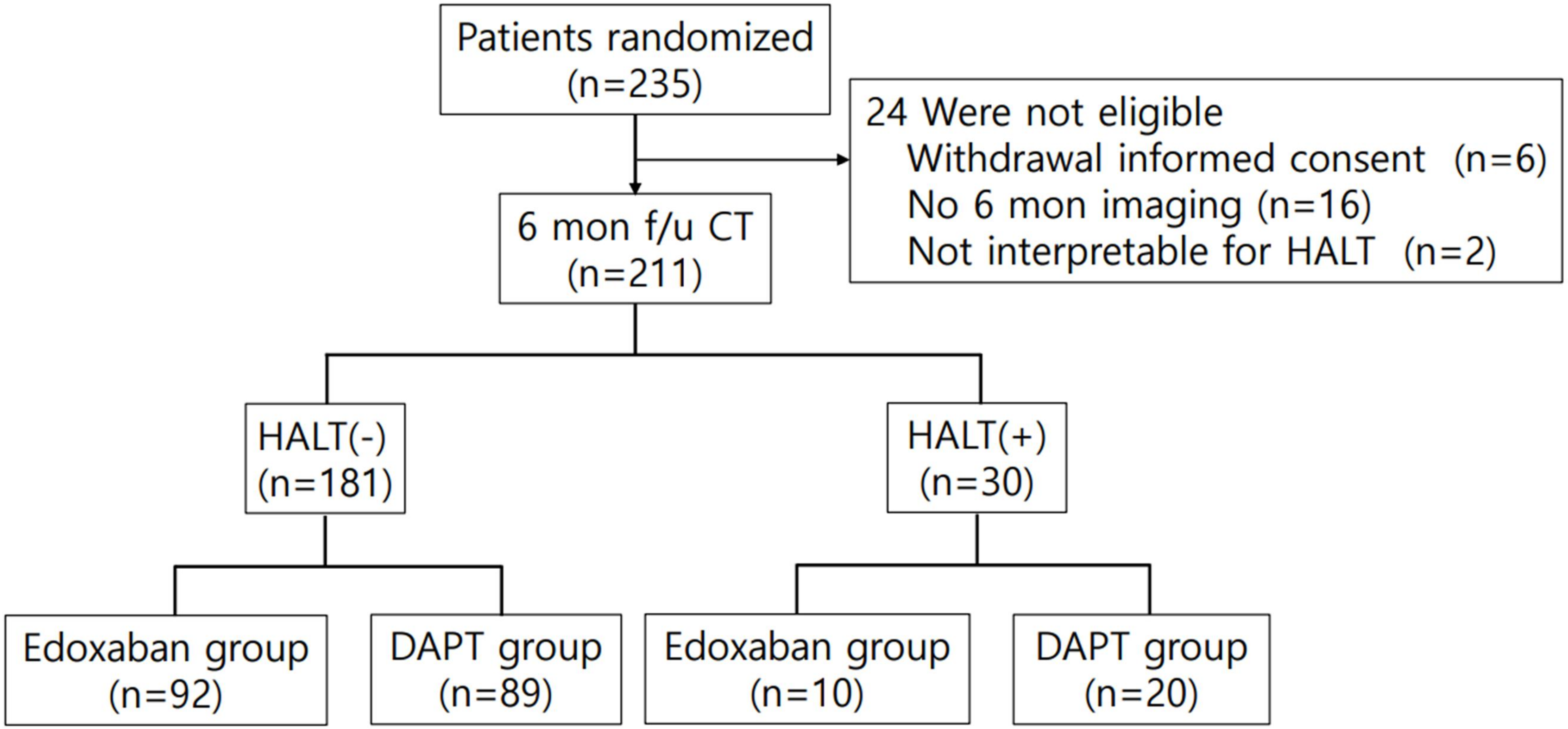
Accurate Neo	4 (1.9%)	4 (2.2%)	0 (0.0%)	
Valve size				0.197
20 mm	10 (4.7%)	10 (5.5%)	0 (0.0%)	
23 mm	72 (34.1%)	63 (34.8%)	9 (30.0%)	
25 mm	1 (0.5%)	1 (0.6%)	0 (0.0%)	
26 mm	96 (45.5%)	83 (45.9%)	13 (43.3%)	
29 mm	30 (14.2%)	23 (12.7%)	7 (23.3%)	
31 mm	1 (0.5%)	0 (0.0%)	1 (3.3%)	
34 mm	1 (0.5%)	1 (0.6%)	0 (0.0%)	
Baseline Echocardiographic characteristics				
Aortic valve area – ㎠	0.58 ± 0.15	0.58 ± 0.15	0.58 ± 0.17	0.972
Aortic valve MG – mmHg	54.5 ± 19.8	54.2 ± 20.0	56.8 ± 19.0	0.504
Aortic valve PG – mmHg	91.0 ± 31.1	90.4 ± 31.4	94.7 ± 29.5	0.484
LVEF – %	61.1 ± 9.2	60.9 ± 9.5	62.0 ± 7.5	0.546
Post-TAVR Echocardiographic characteristics				
Aortic valve area – ㎠	1.55 ± 0.36	1.54 ± 0.36	1.63 ± 0.38	0.277

Aortic valve MG – mmHg	13.9 ± 5.3	14.0 ± 5.5	13.7 ± 4.6	0.754
Aortic valve PG – mmHg	26.9 ± 10.0	27.1 ± 10.2	26.2 ± 9.2	0.648
LVEF – %	64.6 ± 9.3	64.8 ± 9.5	63.4 ± 7.8	0.443
Stroke volume – mL	60.1 ± 14.7	60.1 ± 14.5	60.2 ± 15.9	0.966
Aortic valve DVI	0.44 ± 0.10	0.43 ± 0.10	0.46 ± 0.14	0.356

* Values are mean ± SD or n (%). Percentages may not total 100% because of rounding

CT, computed tomography; HALT, hypoattenuated leaflet thickening; TAVR, transcatheter aortic valve replacement DVI, Doppler velocity index; LVEF, Left ventricular ejection fraction; MG, Mean gradient; PG, Peak gradient; other abbreviations as in Table 1.

Figure 1. Patient flowchart



Supplemental Table 1. Univariable Analysis for Predictors of HALT

	Odds Ratio	95% CI	P value
Clinical characteristics			
Age	1.032	0.958 - 1.119	0.432
Male sex	0.921	0.410 - 2.008	0.838
Body-mass index	1.038	0.944 - 1.137	0.431
STS risk score	1.124	0.853 - 1.356	0.484
EuroSCORE value	1.189	0.695 - 1.380	0.998
NYHA class lll or lV	0.524	0.170 - 1.342	0.212
Smoking history	1.192	0.285 - 4.978	0.857
Hypertension	0.795	0.348 - 1.940	0.597
Diabetes mellitus	0.982	0.405 - 2.222	0.966
Dyslipidemia	1.444	0.588 - 4.086	0.450
Prior CVA	1.988	0.529 - 6.125	0.259
Procedural characteristics			
Pre-TAVR balloon valvuloplasty	1.562	0.709 - 3.409	0.262
Valve type - Balloon expandable	2.062	0.631 - 5.810	0.192

Valve size ≥ 29mm	0.582	0.130 - 2.594	0.477
Baseline echocardiography			
LVEF	1.014	0.972 - 1.064	0.544
Baseline maximal aortic valve velocity	1.159	0.706 - 1.896	0.557
Post-TAVR echocardiography			
Aortic valve MG	0.988	0.916 - 1.062	0.753
Aortic valve PG	0.991	0.952 - 1.030	0.646
Aortic valve area	1.878	0.588 - 5.820	0.277
Aortic valve DVI	8.889	0.222 - 325.608	0.229
Stroke volume	1.001	0.971 - 1.029	0.966
LVEF	0.984	0.945 - 1.026	0.441
Aortic paravalvular leak ≥ moderate	0.639	0.056 - 7.251	0.718

* Analyses were not corrected for multiple comparisons. The odd ratios and corresponding 95% confidence interval (CIs) were calculated by the univariable logistic regression analysis.

CI = confidence interval; CVA = Cerebrovascular Accident; DVI = Doppler velocity index; HALT = hypoattenuated leaflet thickening; LVEF = Left ventricular ejection fraction; MG = Mean gradient; NYHA = New York Heart Association; OR = odd ratio; PG = Peak gradient; STS = Society of Thoracic Surgeons; and TAVR = Transcatheter Aortic Valve Replacement.

3 and Figure 2. The mean and peak aortic valve gradients were not significantly different between patients with and without HALT; the mean aortic valve gradient after TAVR remained consistently low between those who underwent echocardiography immediately post-TAVR and after 6 months of follow-up. The aortic valve area, doppler velocity index, ejection fraction, and frequency of paravalvular leak (at least moderate) were also similar in patients with or without HALT. There was no significant difference in the proportion of patients showing a change in mean pressure gradient ≥10 mmHg (change from baseline in the mean transprosthetic gradient of ≥10 mmHg); 0 (0%) in the HALT group and 4 (2.3%) in the group without HALT. At 6 months, at leastmoderate hemodynamic SVD was reported in 4 of 30 (13.3%) patients with HALT and 26 of 176 (14.8%) patients without HALT (P = 0.836). The analyses of the effect of HALT on hemodynamic significance according to the randomized groups of edoxaban and DAPT are presented in **Supplemental Table 2.** Overall findings were similar regardless of the type of antithrombotic regimen.

Incidence and Predictors of Hemodynamic SVD

Among 211 patients included in this study, five patients without a value of mean transprosthetic gradient by echocardiography immediately post-TAVR or at 6 months of follow-up were excluded from the analysis. At 6 months, the overall incidence of hemodynamic SVD was 14.5% (30 of 206 patients). Baseline demographic and clinical characteristics for groups with and without hemodynamic SVD at 6 months are presented in **Supplement Table 3**. Patients with SVD were older, were more likely to be women, and had a higher mean value of STS score as compared to those without

Table 3. Impact of HALT on valve hemodynamics

	Immediately Post-TAVR			6-Month after TAVR		
	HALT (-) (N =181)	HALT (+) (N =30)	P value	HALT (-) (N =181)	HALT (+) (N = 30)	P value
Mean AV gradient – mmHg	14.0 ± 5.5	13.7 ± 4.6	0.754	13.7 ± 5.5	14.0 ± 4.8	0.742
Peak AV gradient – mmHg	27.1 ± 10.2	26.2 ± 9.2	0.648	26.1 ± 9.7	26.3 ± 9.2	0.911
Aortic valve area – ㎠	1.54 ± 0.36	1.63 ± 0.38	0.277	1.54 ± 0.36	1.64 ± 0.44	0.208
Aortic valve DVI	0.43 ± 0.10	0.46 ± 0.14	0.356	0.44 ± 0.11	0.43 ± 0.09	0.842
Stroke volume	60.1 ± 14.5	60.2 ± 15.9	0.966	57.9 ± 14.5	57.0 ± 8.1	0.685
LVEF – %	64.8 ± 9.5	63.4 ± 7.8	0.443	65.2 ± 7.4	64.1 ± 11.0	0.624
Aortic paravalvular leak ≥ moderate	9 (5.1%)	1 (3.3%)	> 0.999	15 (8.3%)	0 (0.0%)	0.135
Delta gradient* ≥ 10 mmHg	-	-	-	4 (2.3%)	0 (0.0%)	> 0.999
At least moderate hemodynamic valve deterioration†	-	-	-	26/176 (14.8)	4/30 (13.3)	0.836

Values are mean ± SD

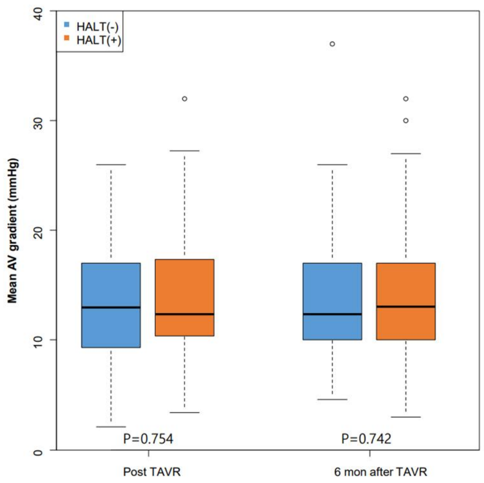
* Delta gradient: increase in mean gradient ≥ 10 mmHg from immediate post-TAVR echocardiography

† Moderate or severe hemodynamic structural valve deterioration (SVD) as assessed by echocardiography after 6 months of follow-up compared to immediately post-TAVR. Definition of hemodynamic SVD was based on a consensus statement from the EAPCI endorsed by ESC and EACTS (2017) (16); AV mean gradient, ≥20 mmHg (moderate) or ≥40 mmHg (severe) or AV mean gradient, ≥ 10 mmHg (moderate) or >20 mmHg (severe) change from baseline, or intra-prosthetic aortic regurgitation, new or worsening (>1/4) from baseline (moderate) or new or worsening (>2/4) from baseline (severe).

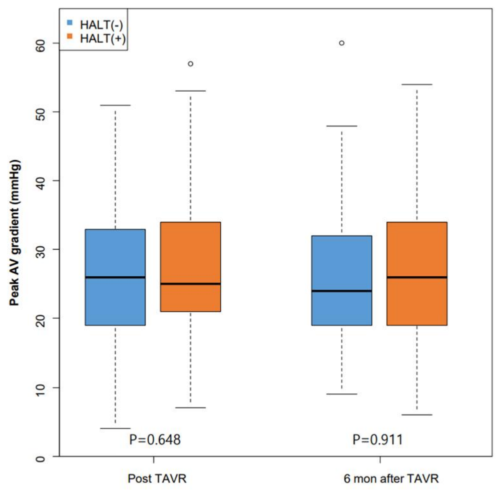
HALT, hypoattenuated leaflet thickening; TAVR, transcatheter aortic valve replacement; AV, aortic valve; DVI, Doppler velocity index; LVEF, Left ventricular ejection fraction; MG, Mean gradient; PG, Peak gradient.

Figure 2. Echocardiographic valve hemodynamics of patients with or without HALT

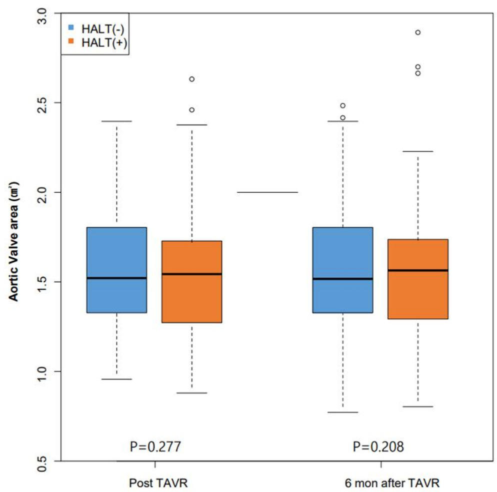
(a) Changes in mean AV gradient



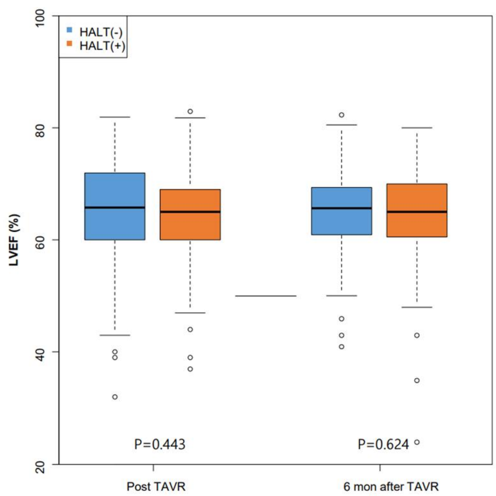
(b) Changes in peak AV gradient



(c) Changes in AVA



(d) Changes in LVEF



Supplemental Table 2. Impact of HALT on Valve hemodynamics According to Type of Antithrombotic Regimens

Edoxaban group	Immediately Post-TAVR			6-Month after TAVR		
	HALT (-) (N =92)	HALT (+) (N = 10)	P value	HALT (-) (N = 92)	HALT (+) (N =10)	P value
Mean gradient – mmHg	13.3 ± 5.1	14.8 ± 4.8	0.356	13.1 ± 5.3	16.4 ± 3.7	0.062
Peak AV gradient – mmHg	25.8 ± 9.9	28.7 ± 10.1	0.369	24.8 ± 9.4	30.7 ± 7.2	0.058
Aortic valve area – ㎠	1.59 ± 0.35	1.51 ± 0.31	0.499	1.60 ± 0.36	1.45 ± 0.30	0.258
Aortic valve DVI	0.44 ± 0.10	0.51 ± 0.21	0.330	0.44 ± 0.13	0.39 ± 0.08	0.196
Stroke volume	59.2 ± 13.9	61.0 ± 6.8	0.724	59.1 ± 17.1	57.3 ± 7.3	0.582
LVEF – %	65.1 ± 9.8	64.1 ± 8.5	0.772	65.7 ± 7.7	65.4 ± 7.2	0.902
Aortic paravalvular leak ≥ moderate	4 (4.4%)	0 (0.0%)	> 0.999	6 (6.7%)	0 (0.0%)	> 0.999
Delta gradient* ≥ 10mmHg	-	-	-	3 (3.4%)	0 (0.0%)	> 0.999
At least moderate hemodynamic valve deterioration†	-	-	-	11 (11.9%)	2 (20.0%)	0.612
DAPT group	Immediately Post-TAVR			6-Month after TAVR		
	HALT (-)	HALT (+)	P value	HALT (-)	HALT (+)	P value

	(N =89)	(N = 20)		(N =89)	(N =20)	
Mean gradient – mmHg	14.7 ± 5.7	13.1 ± 4.5	0.222	14.3 ± 5.7	12.9 ± 4.9	0.314
Peak AV gradient – mmHg	28.4 ± 10.5	24.9 ± 8.6	0.163	27.4 ± 9.9	24.1 ± 9.4	0.177
Aortic valve area – ㎠	1.49 ± 0.36	1.68 ± 0.4	0.052	1.48 ± 0.36	1.73 ± 0.47	0.016
Aortic valve DVI	0.43 ± 0.10	0.43 ± 0.08	0.906	0.43 ± 0.09	0.45 ± 0.09	0.263
Stroke volume	60.9 ± 15.1	59.8 ± 18.9	0.805	56.6 ± 11.4	56.9 ± 8.6	0.916
LVEF – %	64.6 ± 9.2	63.0 ± 7.7	0.500	64.6 ± 7.1	63.5 ± 12.7	0.715
Aortic paravalvular leak ≥ moderate	5 (5.8%)	1 (5.0%)	> 0.999	9 (10.5%)	0 (0.0%)	0.203
Delta gradient* ≥ 10mmHg	-	-	-	1 (1.2%)	0 (0.0%)	> 0.999
At least moderate hemodynamic valve deterioration†	-	-	-	16 (18.0%)	2 (10.0%)	0.517

Values are mean ± SD

* Delta gradient: increase in mean gradient ≥ 10 mmHg from immediate post-TAVR echocardiography

† Moderate or severe hemodynamic structural valve deterioration (SVD) as assessed at the 6-month visit compared to immediate post-TAVR echos. Definition of hemodynamic SVD was based on a consensus statement from the EAPCI endorsed by ESC and EACTS (2017)

(16); AV mean gradient, ≥20 mmHg (moderate) or ≥40 mmHg (severe) or AV mean gradient, ≥ 10 mmHg (moderate) or >20 mmHg (severe) change from baseline, or intra-prosthetic aortic regurgitation, new or worsening (>1/4) from baseline (moderate) or new or worsening (>2/4) from baseline (severe).

AV = aortic valve; DVI = Doppler velocity index; LVEF = Left ventricular ejection fraction; MG = Mean gradient; PG = Peak gradient.

Supplement 3. Baseline Characteristics of Patients According to the Presence or Absence of Hemodynamic SVD*

	SVD (-) (n = 176)	SVD (+) (n = 30)	P value
Age – yr	79.8 ± 5.5	81.5 ± 3.6	0.031
Male sex, n (%)	81 (46.0 %)	4 (13.3 %)	0.001
Body-mass index	25.1 ± 4.1	25.3 ± 3.8	0.755
STS risk score	2.93 ± 1.64	3.38 ± 1.43	0.030
EuroSCORE value	2.00 ± 1.12	2.08 ± 0.91	0.317
NYHA classification – n (%)			0267
I-ll	130 (73.9 %)	25 (83.3 %)	
lll-lV	46 (26.1 %)	5 (16.7 %)	
Smoking history – n (%)	46 (26.2 %)	3 (10.0 %)	0.128
Hypertension – n (%)	131 (74.4 %)	23 (76.7 %)	0.795
Diabetes mellitus – n (%)	54 (30.7 %)	8 (26.7 %)	0.658
Dyslipidemia – n (%)	128 (72.7 %)	26 (86.7 %)	0.104
Coronary artery disease – n (%)	48 (27.3 %)	9 (30.0 %)	0.772
Prior CABG – n (%)	2 (1.1 %)	1 (3.3 %)	0.378

Prior cerebrovascular disease – n (%)	14 (8.0 %)	3 (10.0 %)	0.719
Peripheral arterial disease – n (%)	13 (7.4 %)	4 (13.3 %)	0.282
Chronic lung disease – n (%)	44 (25.0 %)	7 (23.3 %)	0.845
Serum Creatinine – mg/dl	0.95 ± 0.27	0.87 ± 0.22	0.132

CABG = Coronary Artery Bypass graft surgery; NYHA = New York Heart Association; PCI = Percutaneous Coronary Intervention; STS = Society of Thoracic Surgeons; SVD = structural valve deterioration; TAVR = Transcatheter Aortic Valve Replacement.

SVD. Baseline procedural and echocardiographic characteristics according to the presence of SVD are summarized in **Supplement Table 4**. Patients with SVD were more likely to have a valve-in-vale procedure, smaller aortic valve area, higher mean or peak transprosthetic gradient, and lower doppler velocity index on echocardiography immediately post-TAVR compared to those without SVD. The results of univariable and multivariable analysis for predictors of hemodynamic SVD are summarized in **Table 4**. Univariable predictors of SVD included the male sex, pre-TAVR balloon valvuloplasty, TAVR valve size of ≤ 23 mm, baseline LVEF, and aortic valve area measured immediately post-TAVR. By multivariable analysis, the use of a TAVR valve size of ≤ 23mm (p=0.003) and a smaller aortic valve area measured immediately post-TAVR were found to be independent predictors of hemodynamic SVD (p=0.005).

Table 4. Univariable and multivariable analysis identifying predictors of hemodynamic SVD

	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value*
Clinical characteristics				
Age	1.073 (0.991–1.172)	0.100		
Male sex	0.180 (0.052–0.487)	0.002		
Body-mass index	1.015 (0.921–1.113)	0.753		
STS risk score	1.120 (0.933–1.459)	0.157		
EuroSCORE value	1.193 (0.740–1.489)	0.709		
NYHA class lll or lV	0.565 (0.182–1.454)	0.272		
Smoking history	0.066 (0.088–0.566)	0.282		
Hypertension	1.129 (0.473–3.004)	0.795		
Diabetes mellitus	0.822 (0.326–1.897)	0.658		
Dyslipidemia	2.437 (0.892–8.579)	0.114		
Coronary artery disease	1.134 (0.465–2.584)	0.772		

Prior CVA	1.286 (0.283–4.269)	0.707		
Procedural characteristics				
Pre-TAVR balloon valvuloplasty	0.282 (0.092–0.716)	0.014		
Valve type-Balloon expandable	0.285 (0.016–1.460)	0.230		
Valve size ≤ 23mm	0.093 (0.030–0.238)	< 0.001	0.186 (0.056–0.536)	0.003
Valve in valve	19.444 (2.394–400.913)	0.011		
Baseline echocardiographic characteristics				
Aortic valve area	0.594 (0.032–8.348)	0.712		
Aortic valve MG	1.012 (0.993–1.031)	0.224		
Aortic valve PG	1.009 (0.996–1.021)	0.165		
LVEF	1.050 (0.998–1.113)	0.077		
Post-TAVR echocardiographic characteristics				
Aortic valve area	0.014 (0.001–0.089)	< 0.001	0.045 (0.004–0.333)	0.005
Aortic valve MG	1.282 (1.174–1.419)	< 0.001		
Aortic valve PG	1.147 (1.095–1.210)	< 0.001		

LVEF	1.019 (0.975–1.068)	0.419
HALT (+) on 6-month CT	0.888 (0.247–2.516)	0.836
Discharge medication		
Edoxaban	1.278 (0.588–2.836)	0.537

*Moderate or severe hemodynamic structural valve deterioration (SVD) as assessed by echocardiography after 6 months of follow-up compared to immediately post-TAVR. Definition of hemodynamic SVD was based on a consensus statement from the EAPCI endorsed by ESC and EACTS (2017) (16); AV mean gradient, ≥20 mmHg (moderate) or ≥40 mmHg (severe) or AV mean gradient, ≥ 10 mmHg (moderate) or >20 mmHg (severe) change from baseline, or intra-prosthetic aortic regurgitation, new or worsening (>1/4) from baseline (moderate) or new or worsening (>2/4) from baseline (severe).

CI, Confidence interval; other abbreviations as in Table 1 and 2.

Supplement 4. Baseline Procedural and Echocardiographic Characteristics of Patients According to the Presence or Absence of Hemodynamic SVD*

	SVD (-) (n = 176)	SVD (+) (n = 30)	P value
Procedural characteristics			
Pre-TAVR balloon valvuloplasty – n (%)	73 (41.5 %)	5 (16.7 %)	0.010
Valve type – no.(%)			0.320
Balloon-expandable	157 (89.2 %)	29 (96.7 %)	
Self-expandable	19 (10.8 %)	1 (3.3 %)	
Valve size ≤ 23mm	56 (31.8 %)	25 (83.3 %)	< 0.001
Valve in valve	1 (0.6 %)	3 (10.0 %)	0.010
Baseline Echocardiographic characteristics			
Aortic valve area – ㎠	0.59 ± 0.15	0.57 ± 0.19	0.714
Aortic valve MG – mmHg	53.9 ± 20.0	58.7 ± 19.2	0.223
Aortic valve PG – mmHg	89.8 ± 31.4	98.4 ± 28.9	0.164
LVEF – %	61.0 ± 9.0	64.1 ± 6.2	0.025
Post-TAVR Echocardiographic characteristics			

Aortic valve area – ㎠	1.61 ± 0.36	1.27 ± 0.22	< 0.001
Aortic valve MG – mmHg	13.1 ± 4.4	19.5 ± 6.5	< 0.001
Aortic valve PG – mmHg	25.3 ± 8.8	37.7 ± 9.7	< 0.001
LVEF – %	64.7 ± 9.0	66.1 ± 8.4	0.420
Stroke volume – ml	60.9 ± 14.6	56.3 ± 15.1	0.136
Aortic valve DVI	0.45 ± 0.10	0.38 ± 0.08	0.001

*Hemodynamic SVD was defined as at least one of the following: 1) change from baseline in the mean transprosthetic gradient of ≥ 10 mmHg 2) mean transprosthetic gradient ≥ 20 mmHg and 3) new or increase in ≥ 1 grade of intra-prosthetic regurgitation resulting in moderate or greater valvular regurgitation (16).

DVI = Doppler velocity index; LVEF = Left ventricular ejection fraction; MG = Mean gradient; PG = Peak gradient; other abbreviations as in Table 1.

Discussion

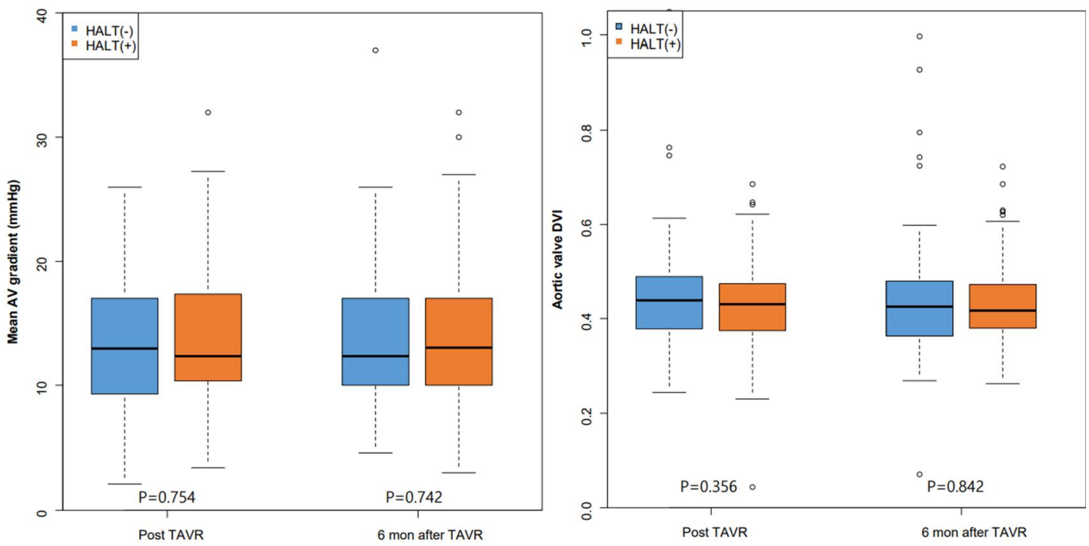
The main findings of our study can be summarized as follows (**Central Illustration**). First, HALT was found in 14.2% of patients who had evaluable 4D cardiac CT scans 6 months after TAVR procedures. Second, we did not find a clear relationship between HALT and valve hemodynamic parameters, and findings were consistent irrespective of antithrombotic groups of edoxaban or DAPT. Third, hemodynamic SVD was observed in 14.5% of patients with serial echocardiography follow-up. Fourth, the use of a TAVR valve size of ≤23 mm and a smaller aortic valve area measured immediately post-TAVR were independent predictors of hemodynamic SVD.

Relationship of HALT and Echocardiographic Valve Hemodynamics

Subclinical leaflet thrombosis has been characterized as HALT or reduced leaflet motion (RLM) using a four-dimensional cardiac CT imaging of the aortic bioprosthesis (20,21). As there is no guideline on routine surveillance of follow-up CT after TAVR, and the timing of follow-up CT is different for each study, the incidence of HALT varied from 10.0% to 30.0% after TAVR (8-11,22,23), which was similar to the 14.2% frequency of HALT in the ADAPT-TAVR trial. However, until recently, it was unclear whether HALT identified on CT scan negatively affects the hemodynamic status of the aortic bioprosthesis. Although the presence of HALT and RLM has been correlated with higher gradients in some studies (7,23,24), our study showed no relationship between the presence or absence of HALT and valve hemodynamic

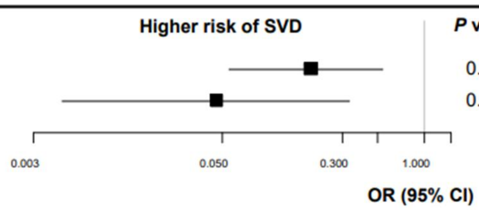
CENTRAL ILLUSTRATION. Impact of HALT on valve hemodynamics and independent predictors of hemodynamic SVD

Impact of HALT on valve hemodynamics



Predictors of SVD

Character	OR (95% CI)	P value
Valve size ≤23mm	0.186 (0.056-0.536)	0.003
Aortic valve area, ㎠	0.045 (0.004-0.333)	0.005



performance at 6 months, as measured by mean gradient or Doppler velocity index. Our findings were similar to the reports from the CT substudy of the PARTNER 3(The Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low-Risk Patients With Aortic Stenosis)(PARTNER 3) trial and the EVOLUT low-risk trial (10,11). In the PARTNER 3 CT substudy (11), the mean aortic valve gradient was not significantly different in patients with and without HALT at 30 days (13.2 ± 0.81 mmHg vs. 11.7 ± 0.24 mmHg; p=0.08) or 1 year (13.7 ± 0.82 mmHg vs. 12.6 ± 0.28 mmHg; p=0.24). The mean aortic valve gradient at 1 year was found to be higher only in patients with HALT both at 30 days and 1 year than in those without HALT at 30 days and 1 year (17.8 ± 2.2 vs. 12.7 ± 0.3; p=0.04). In the EVOLUT low-risk CT substudy (10), the mean aortic valve gradients after TAVR remained consistently low with or without HALT at 30 days and 1 year. The presence and severity of HALT or RLM did not change these findings. Although the follow-up CT duration is different among studies, these findings consistently revealed that HALT did not affect valve hemodynamic status evaluated by mean gradient or doppler velocity index. Considering these hemodynamic results and no definite relationship with potential cerebral thromboembolism (14), performing routine follow-up CT to confirm HALT would not be beneficial for post-TAVR management strategy. Also, in our study, the presence of HALT did not significantly affect the development of hemodynamic SVD at 6 months. Although the relationship between HALT and SVD was not adequately determined in other studies, further larger-sized studies are warranted to determine correlates of long-term bioprosthetic valve durability.

Incidence and Predictors of Hemodynamic SVD

As the age of TAVR candidates becomes younger, an increase in valve durability may have an important influence on the need for subsequent reintervention in younger patients during their lifetime. Accordingly, identifying underlying mechanisms and predictors of SVD is a clinically important issue. Previous studies have suggested potential predictors of SVD with two hypotheses (23,25,26). The first hypothesis was that the factors that could affect the hemodynamic stress of the valve, such as smaller prosthesis size (≤23mm), valve-in-valve procedure, prosthetic and patient mismatch, or HALT might be related to the development of SVD. The second hypothesis is that a lipid-mediated inflammatory mechanism (e.g., greater body mass index or the male sex) might affect SVD by increasing the risk of thrombosis. Similar to previous studies, our study also reported that valve-in-valve procedure, the use of a smaller prosthesis TAVR valve (≤23mm), and a smaller aortic valve area immediately post-TAVR were important predictors of hemodynamic SVD in univariate and multivariate analyses; these factors were likely related to an increased valve hemodynamic stress. Unlike previous studies showing that the absence of anticoagulation therapy at discharge increased SVD risk (25), in our study, antithrombotic regimens were not associated with the development of hemodynamic SVD. Such findings regarding SVD predictors analyzed in this study may help clinicians determine which patients are more vulnerable to SVD and should be monitored more closely. These information are more important if younger and lower-risk patients are treated. Lastly, despite the limited utility of the routine detection of HALT to predict aortic valve hemodynamic status or clinical events, it should be further determined that four-dimensional CT imaging is useful for the detection of patients who develop SVD.

Limitations

Although the ADAPT-TAVR trial was a dedicated imaging surrogate-maker trial designed to study the frequency of HALT in patients who underwent TAVR, it was not powered to detect differences in clinical outcomes. The total number of patients in this substudy was relatively limited, resulting in a small number of patients with HALT or SVD, thus precluding a reliable multivariable analysis. Second, given prior studies reported the transient and dynamic nature of HALT (10,11), it may make it difficult to capture its full spectrum over time using CT assessments at only one time point of 6 months. Third, our study had a relatively short follow-up period of 6 months. Longer follow-up data of up to 5 or 10 years are needed to assess the full impact of this finding, particularly on valve function and SVD. This phenomenon may represent a potential therapeutic target to affect long-term durability of transcatheter bioprosthetic valves.

Conclusion

The presence of HALT did not significantly affect the hemodynamic status of the aortic valve and the development of SVD measured by serial echocardiography. In addition, the use of an aortic valve size of≤23 mm and a smaller aortic valve area measured immediately post-TAVR are independent predictors of SVD. Further studies with a longer-term follow-up are needed to determine the potential impact of HALT more clearly on long-term bioprosthetic valve durability.

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국문초록

서론 : 저감쇠판막비후(HALT)를 특징으로 하는 판막혈전증이 조직판막의 혈역학적 기능 및 내구성에 미치는 영향은 아직 명확하게 밝혀지지 않았습니다.

목적 : 이 연구는 HALT가 경피적 대동맥 판막 교체(TAVR) 후 시행한 심초음파 검사에서 확인된 판막의 혈역학에 미치는 영향을 확인하는 것을 목표로 하였습니다.

방법 : ADAPT-TAVR 연구는 성공적으로 TAVR를 시행한 항응고제 사용의 적응증이 되지 않는 환자들을 대상으로 edoxaban과 이중항혈소판제 요법을 비교한 다기관 무작위 시험입니다. HALT의 존재는 TAVR 6개월 후 4차원 컴퓨터 단층 촬영(CT)로 평가하였으며 시술 전, TAVR 직후, 추적 관찰 6개월 후에 일련의 심초음파를 시행하였습니다.

결과 : 6개월에 HALT는 211명의 환자 중 30명(14.2%)에서 발견되었습니다. HALT의 존재는 6개월 후 대동맥 판막 평균 압력에 유의미한 영향을 주지 않았습니다(HALT 있는 군 vs 없는 군; 14.0 ± 4.8 mmHg vs 13.7 ± 5.5 mmHg; p=0.742). 6개월 후 추적 심초음파에서 206명의 환자 중 30명(14.6%)에서 최소 중등도 이상의 혈역학적 구조적 판막 손상이 보고되었습니다. 23mm 이하 대동맥 판막 크기 또는 더 작은 대동맥 판막 면적을 가진 경우 혈역학적 구조적 판막 손상(SVD)의 독립적인 예측 인자였습니다. 그러나 HALT의 존재는 혈역학적 구조적 판막 손상의 예측 인자로 확인되지 않았습니다.

결론 : 성공적으로 TAVR를 시행한 환자에서 판막의 혈역학적 상태는 HALT의 존재에 영향을 받지 않았습니다. HALT가 6개월 후 구조적 판막 이상의 예측 인자가 아니었지만 판막의 내구성에 대한 영향을 평가하기 위하여 추가적인 장기 추적 조사가 필요합니다.

중심단어 : 대동맥 판막 협착, 무증상 판막엽 혈전증, 경피적 판막 치환술, 판막 혈역학