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ORIGINAL RESEARCH

Thrombus characterisation and evolution of hypoattenuating leaflet thickening after transcatheter aortic valve implantation

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ABSTRACT

BACKGROUND: Quantifying hypoattenuating leaflet thickening (HALT) on computed tomography angiography (CTA) may provide insights into its clinical implications and guide decisions on oral anticoagulation therapy following transcatheter aortic valve implantation (TAVI).

AIMS: We sought to assess the association between quantitative CTA features of HALT and its evolution over time in a real-world cohort after TAVI.

METHODS: Among 612 patients who underwent CTA 30 days post-TAVI with balloon-expandable bioprostheses, HALT was detected in 118 (19%). We prospectively followed 99 patients who had undergone a second CTA at 1 year to assess HALT progression. Thrombus volume and mean attenuation were quantified using semiautomated software, and various parameters of bioprosthetic deformation were analysed.

RESULTS: Complete resolution of HALT was observed in 43 patients. Multivariate logistic regression showed that lower thrombus attenuation was an independent predictor of HALT resolution (odds ratio [OR] 0.45; p=0.030), along with the eccentricity index (OR 0.42; p=0.003), deformation index (OR 0.53; p=0.005), and implant canting (OR 1.88; p=0.026). In the 56 patients without complete HALT resolution, thrombus evolution was visually categorised as regression (48%), stability (29%), or progression (23%). In a quantitative assessment, regression was associated with a significant decrease in thrombus volume (291 mm³ to 130 mm³; p=0.007), while progression showed an increase (187 mm³ to 667 mm³; p=0.005). The change in thrombus volume between 30 days and 1 year correlated with the magnitude of changes in mean transvalvular gradients over the same period (r=0.462; p<0.001).

CONCLUSIONS: Quantitative thrombus characterisation on CTA is predictive of HALT resolution and correlates with the haemodynamic performance of transcatheter aortic valves.

KEYWORDS: aortic stenosis; hypoattenuating leaflet thickening; quantitative computed tomography angiography; transcatheter aortic valve implantation

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Subclinical leaflet thrombosis after transcatheter aortic valve implantation (TAVI) occurs in up to 25% of patients[1-4]. Thrombus on the surface of the bioprosthetic leaflet is observed on computed tomography (CT) angiography (CTA) as hypoattenuating leaflet thickening (HALT), with or without reduced leaflet motion, as early as in the first postprocedural days[5,6]. HALT is characterised by diverse temporal dynamics, and its clinical significance is not fully understood, with most detected HALT being subclinical[7,8]. The presence of HALT may, however, increase the risk of major adverse cardiovascular and cerebrovascular events and may progress to clinical valve thrombosis[2,9-11]. HALT has also been associated with a slight increase in transvalvular gradients, while its long-term impact on the durability of bioprostheses is yet to be determined[1,12]. Due to these uncertainties, there are no guidelines for managing subclinical leaflet thrombosis[13]. Previous studies have demonstrated that oral anticoagulation is an effective treatment for HALT, leading to its regression in most cases[14]. Nevertheless, complete thrombus regression without any intervention has also been evidenced[1]. Current evidence suggests that non-uniform expansion of transcatheter heart valves contributes to HALT development and may influence its evolution[15-17]. Quantitative HALT characterisation could provide insight into its clinical sequelae as well as its potential progression. Importantly, this could aid challenging clinical decisions regarding oral anticoagulation therapy. Several studies have investigated the history of HALT in transcatheter and surgical cohorts, but there is a limited understanding of the imaging features associated with thrombus evolution over time[1,7,8]. Thus, we sought to examine the association between quantitative HALT features from CTA and its evolution in a real-life population.

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Impact on daily practice

The study highlights the clinical value of quantitative computed tomography angiography (CTA) in evaluating hypoattenuating leaflet thickening (HALT) following transcatheter aortic valve implantation (TAVI). By identifying key factors such as thrombus attenuation and prosthesis deformation, clinicians may more accurately predict HALT resolution and its impact on valve function. This could inform decisions on oral anticoagulation therapy, enabling a more personalised approach based on thrombus evolution. Patients with thrombus progression may benefit from closer monitoring or therapy adjustments. Additionally, serial CTA imaging can aid in the early detection of structural valve deterioration, optimising patient management and improving long-term outcomes post-TAVI.

Methods

PATIENT COHORT

This analysis is based on a prospective observational study conducted at Cedars-Sinai Medical Center. It included patients from the Assessment of TRanscathetEr and Surgical Aortic BiOprosthetic Valve Thrombosis and Its TrEatment With Anticoagulation registry (RESOLVE; ClinicalTrials.gov: NCT02318342) who had undergone TAVI using balloon-expandable prosthetic valves between February 2015 and March 2018, with HALT detected on CTA 30 days post-TAVI, and who completed follow-up CTA 1 year after the procedure **(Central illustration)**. The registry did not consecutively enrol patients treated with TAVI but aimed to include a heterogeneous patient population. Patients with impaired renal function (estimated glomerular filtration rate of <30 mL/min) were excluded from the registry. The institutional review board approved the registry before the study initiation. All patients provided written informed consent.

TRANSCATHETER AORTIC VALVE IMPLANTATION

A multidisciplinary Heart Team at Cedars-Sinai Medical Center discussed the indication for TAVI. Procedural details, including proper device selection and access site, were determined based on preoperative CT imaging and echocardiography. TAVI procedures were conducted under general anaesthesia with fluoroscopic and echocardiographic guidance. Balloon-expandable prostheses, SAPIEN XT and SAPIEN 3 (both Edwards Lifesciences) were used for all TAVI procedures.

CT IMAGING AND EVALUATION

A detailed description of the contrast-enhanced multidetector CTA image acquisition is provided in **Supplementary Appendix 1**. Visually identified HALT is the hallmark of subclinical leaflet thrombosis. The hypoattenuating lesions involve the periphery and base of the leaflet and extend to varying degrees towards the edges of the leaflet in the centre of the bioprosthetic frame. If HALT was identified, a careful assessment of leaflet motion was conducted using four-dimensional (4D) CT imaging. Motion reduction of each leaflet was evaluated using multiphase volume-rendered *en face* cine projection[18]. Hypoattenuation affecting motion (HAM) was defined as >50% reduction in leaflet motion relative to the radius of the bioprosthetic frame.

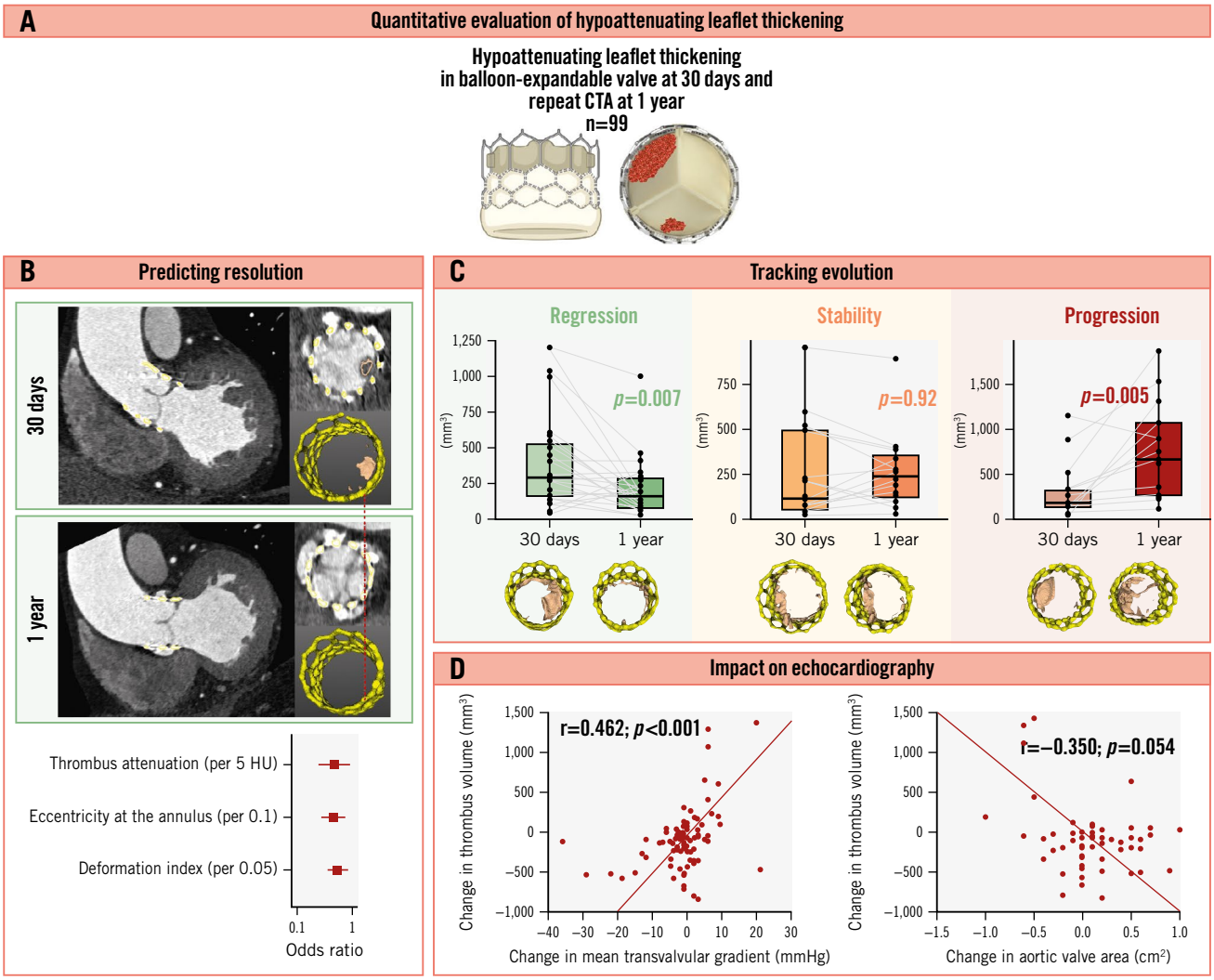
Quantitative analysis of HALT was performed using semiautomated software (ValveQuant module, Autoplaque version 2.5 [Cedars-Sinai Medical Center])[19,20]. The region of interest was manually defined from the base to the top of the bioprosthetic aortic valve. Then, serial multiplanar reformatted images orthogonal to the longitudinal axis of the ascending aorta were rendered to obtain cross-sectional images of the respective region with contouring – comprising 15-20 adjustable points within the inner margin of the stent frame. Leaflet thrombus was defined as voxels between –200

Abbreviations

CTA	computed tomography angiography	**HAM**	hypoattenuation affecting motion
HALT	hypoattenuating leaflet thickening	**TAVI**	transcatheter aortic valve implantation

EuroIntervention — Central Illustration

Temporal changes in hypoattenuating leaflet thickening after TAVI.



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Quantitative thrombus characterisation on computed tomography angiography (CTA) predicts the HALT resolution and correlates with the haemodynamic performance of transcatheter aortic valves. A) Quantitative evaluation of HALT; (B) predicting HALT resolution; (C) tracking the evolution of HALT; (D) impact of HALT on echocardiographic parameters. HALT: hypoattenuating leaflet thickening; HU: Hounsfield units; TAVI: transcatheter aortic valve implantation

Hounsfield units (HU) and 200 HU within the inner margin of the bioprosthetic frame[18,21]. The quantitative thrombus parameters were volume (expressed in mm^3) and mean attenuation (expressed in HU).

For post-implantation evaluation of bioprosthesis geometry, internal and external stent-frame measurements, including the area, major diameter, and minor diameter, were taken at four levels of the prosthesis: the leaflet outflow (corresponding to the three commissural tabs of the prosthetic leaflets, denoted as "a" in the equation below), the prosthesis waist (located at 1/3 of the first cell for SAPIEN XT and at the tip of the outer skirt for SAPIEN 3, "b"), the leaflet inflow (at the nadir of the prosthetic leaflets, "c"), and the native annulus. The postprocedural native annulus level was determined using the preprocedural distance from the annular plane to the sinotubular junction, measured from the pre-TAVI CTA scans. The prosthesis deformation index was then calculated using the internal area measurements at each level, using the following equation[15]:

$$deformation\ index = \frac{(a+c)}{2b}$$

Oversizing at the native annulus level was calculated as follows:

$$\frac{external\ area\ at\ the\ native\ annulus\ level}{native\ annular\ area} - 1$$

Expansion was measured at the four levels:

$$expansion\ (\%) = \frac{external\ area\ at\ the\ respective\ level}{native\ bioprosthetic\ area} * 100$$

The nominal SAPIEN XT prosthetic valve areas used in the calculations were 415 mm^2, 531 mm^2, and 660 mm^2 for 23 mm, 26 mm, and 29 mm devices, respectively. The nominal SAPIEN 3 prosthetic valve areas used in the calculations were 409 mm^2, 519 mm^2, and 649 mm^2 for 23 mm, 26 mm, and 29 mm devices, respectively[22].

Eccentricity was measured at the four levels with the formula:

$$eccentricity = \sqrt{1 - \frac{minor\ diameter^2}{major\ diameter^2}}$$

Eccentricity ranges from 0 to 1, with higher values indicating a more oval shape, while lower values (closer to 0) represent a more circular configuration.

The expansion of each prosthetic leaflet was assessed by measuring the angle between the border stent struts of each leaflet and the transcatheter heart valve (THV) centre point at the coaptation level. Ideally, full leaflet expansion corresponds to 120°, based on the design intent for the frame to expand into a uniform, circular shape with three symmetrical leaflets of equal size and shape. Asymmetric leaflet expansion was determined by summing the difference between 120° and the actual measured angle of each leaflet[17].

The distance between the inflow edge of the THV prosthesis and the basal plane at the centre of each cusp was recorded and averaged to measure implant depth. The degree of canting was determined by calculating the difference between the maximum and minimum implant depths[23].

Commissure alignment was considered misaligned if the coronary ostium was positioned below the inner skirt or directly in front of one of the three bioprosthetic commissural tabs[24].

All tomographic analyses were performed at the Cedars-Sinai Medical Center core laboratory (Los Angeles, CA, USA) by two readers (K. Grodecki and J. Geers, with 7 and 5 years of experience in cardiovascular CT, respectively) blinded to echocardiographic and clinical data. A third observer (H. Jilaihawi) adjudicated any disagreements.

OUTCOMES AND DEFINITIONS

The primary outcome was HALT resolution – defined as the visually evaluated absence of any hypoattenuating material on the bioprosthetic leaflet. The secondary outcome, in patients without complete resolution of HALT, was its evolution, visually defined as regression (significant reduction of hypoattenuating material and/or resolution of reduced leaflet motion), progression (significant increase in hypoattenuating material and/or hypoattenuating material on the new leaflet and/or new presence of reduced leaflet motion) or stability (no regression or progression). Haemodynamic valve deterioration was classified as moderate or severe according to the Valve Academic Research Consortium-3 definitions[25].

Antithrombotic therapy was categorised into oral anticoagulation – comprising both vitamin K antagonists and non-vitamin K antagonists – and compared with no anticoagulation (antiplatelet therapy or no therapy). In patients with HALT, adjustments to antithrombotic therapy were considered if there was an increase in transvalvular pressure gradients and/or the patient experienced significant symptoms.

STATISTICAL ANALYSIS

Categorical patient characteristics are presented as absolute numbers with percentages and were compared between groups of patients with and without HALT resolution using a chi-squared test. Data were tested for normality using the Shapiro-Wilk test. Continuous data are expressed as means±standard deviations (SD) or medians with interquartile ranges (IQR), depending on the distribution, and, for patient characteristics, were compared with the Student's t-test or the Wilcoxon rank-sum test, as appropriate. The Wilcoxon rank-sum test was used for paired sample analysis comparing thrombus volume between the CTAs at 30 days and 1 year. Univariate and multivariate linear regression were performed to examine the association between measures of transcatheter heart valve deformation with the volume of thrombus. The final multivariate model variables were selected based on the univariate results ($p<0.1$) and adjusted for sex, age at the procedure, and oral anticoagulation at the time of the first CTA. Due to high collinearity between variables describing the same deformation measure at different valve levels, the variable with the highest significance was selected. Univariate and multivariate logistic regression were performed to evaluate the predictive value of the quantitative thrombus measure for HALT or HAM resolution. The final multivariate model variables were selected based on the univariate results ($p<0.1$) and adjusted for sex, age at the procedure, and oral anticoagulation at the time of the second CTA. Correlations between continuous variables were assessed using Spearman's rank correlation coefficient: values less than 0.5 indicated poor correlation; between 0.5 and 0.74, moderate correlation; between 0.75 and 0.9, good correlation; and greater than 0.90, excellent correlation. Intra- and interobserver agreement were measured using an intraclass correlation coefficient: values less than 0.5 indicated poor agreement; between 0.5 and 0.74, moderate agreement; between 0.75 and 0.9, good agreement; and greater than 0.90, excellent agreement **(Supplementary Appendix 2)**. Intra- and interobserver variability were measured using Bland-Altman plots with mean bias and limits of agreement. All probability values were 2-tailed, and $p<0.05$ indicated a statistically significant difference. Data were processed using SPSS software, version 25 (IBM) and MedCalc, version 22 (MedCalc Software).

Results

STUDY POPULATION

The study included 612 patients who underwent their first CTA 30 days after TAVI with a balloon-expandable valve; HALT was detected in 118 (19%) of them **(Figure 1)**. Out of 118 patients with HALT, 7 (6%) patients died during the first year of follow-up, 5 (4%) were lost to follow-up, and 3 (2%) had a second CTA postponed for logistical reasons. A second CTA, 1 year after TAVI, was available in 103 (87%) patients, of whom 4 patients were excluded because of suboptimal CTA quality. Of the 99 patients included in the study (mean age 80±9 years; 68 males, 31 females), 21 were receiving oral anticoagulation at baseline for non-valvular reasons, and 78 were diagnosed with HAM on their initial CTA scan.

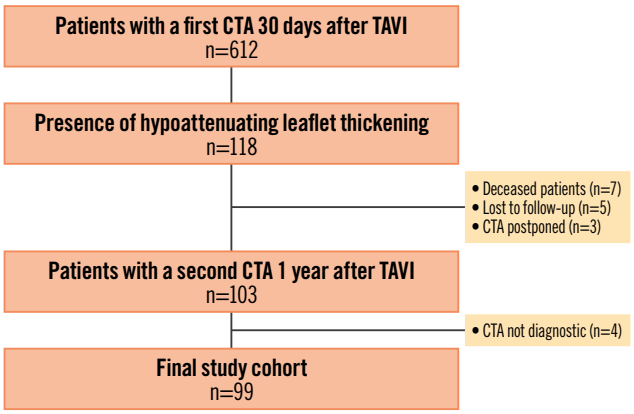

Figure 1. *Study flowchart. CTA: computed tomography angiography; TAVI: transcatheter aortic valve implantation*

Following the first CTA, oral anticoagulation was initiated in 2 additional patients (both with HAM). During the 1-year follow-up, oral anticoagulation was discontinued in a single patient. On the second CTA scan, complete thrombus resolution was observed in 9 of 22 patients receiving oral anticoagulation and 34 of 77 patients not receiving oral anticoagulation (p=0.786) **(Supplementary Figure 1)**. Clinical characteristics are presented in **Table 1**.

QUANTITATIVE THROMBUS MEASUREMENTS AND VALVE DEFORMATION

Patients without HAM had a lower volume of thrombus compared to those with HAM (83 mm^3 vs 303 mm^3; p<0.001) **(Figure 2A)**. These patients also had a higher median thrombus attenuation than patients with HAM (144 HU vs 125 HU; p<0.001) **(Figure 2B)**. Interestingly, deformation parameters did not differ between the groups, except for lower implantation depth and lower eccentricity indices (p<0.001 at all levels) observed in patients without HAM **(Supplementary Table 1)**. In multivariate linear regression adjusted for clinical parameters and oral anticoagulation, the thrombus volume at the first scan was associated with implantation depth (β=75.4; p=0.001) and eccentricity at the waist (β=88.2; p=0.003) **(Table 2)**.

QUANTITATIVE PREDICTORS OF THROMBUS RESOLUTION

Complete resolution of HALT was observed in 43% of all patients. Neither thrombus volume (221 mm^3 [IQR 94-514 mm^3] vs 260 mm^3 [IQR 119-505 mm^3]; p=0.794) nor thrombus attenuation (124 HU [IQR 109-144 HU] vs 131 HU [IQR 109-144 HU]; p=0.178) differed between patients with and without HALT resolution. Univariate analysis of clinical data, quantitative thrombus, and transcatheter valve aortic deformation measures is presented in **Supplementary Table 2**. In multivariate logistic regression adjusted for clinical parameters and oral anticoagulation, lower thrombus attenuation was an independent predictor of HALT resolution (odds ratio [OR] 0.45 per 5 HU increase; p=0.03) as were the eccentricity index at the native annulus (OR 0.42 per 0.1 increase; p=0.003), the deformation index (OR 0.53 per 0.05 increase; p=0.005) and implant canting (OR 1.88 per 1 mm increase; p=0.026) **(Table 3)**. Representative cases are presented in the **Central illustration** and **Supplementary Figure 2**. The sensitivity analysis, including only patients with HAM, showed no difference in thrombus volume in patients with or without HAM resolution (332 mm^3 vs 290 mm^3; p=0.882). However, patients with HAM resolution had lower thrombus attenuation than patients without (122 HU vs 132 HU; p=0.002) **(Supplementary Table 3)**. Univariate analysis of clinical data, quantitative thrombus, and transcatheter valve aortic deformation measures is presented in **Supplementary Table 3**. In multivariate logistic regression adjusted for clinical parameters and oral anticoagulation, lower thrombus attenuation (OR 0.56 per 5 HU increase; p=0.002) and asymmetric leaflet expansion (OR 0.86 per 1 degree increase; p=0.003) independently predicted HAM resolution **(Table 3)**. The sensitivity analysis for predictors of HALT and HAM resolution, excluding patients on oral anticoagulation, is presented in **Supplementary Table 4**.

QUANTITATIVE CTA FOR TRACKING OF THROMBUS EVOLUTION

The temporal dynamics of HALT in a total of 56 patients without complete resolution at 1 year was further visually classified as regression (48%), stability (29%) or progression (23%). A comparison of thrombus volume from quantitative CTA at 30 days and 1 year showed a decrease in the regression group (291 mm^3 vs 130 mm^3; p=0.007), no change in the stability group (130 mm^3 vs 255 mm^3; p=0.921), and an increase in the progression group (187 mm^3 vs 667 mm^3; p=0.005) **(Central illustration)**.

THROMBUS VOLUME AND ECHOCARDIOGRAPHIC PARAMETERS

There was no difference in echocardiographic parameters at 30 days or 1 year between patients with and without HALT resolution (p>0.05) **(Supplementary Table 5)**. However, patients with HALT resolution had greater decreases in the mean (–1.0 mmHg vs –1.0 mmHg; p=0.014) and maximum (–1.5 mmHg vs –0.5 mmHg; p=0.032) transvalvular pressure gradients on echocardiography at 30 days and 1 year **(Supplementary Table 5)**. Thrombus volume at 30 days did not correlate with echocardiographic parameters (p>0.05 for all) **(Supplementary Table 6)**. Similarly, no correlation between thrombus volume at 1 year and echocardiographic parameters at 1 year was found (p>0.05 for all) **(Supplementary Table 6)**. However, the change in thrombus volume correlated with the magnitude of change in the mean transvalvular pressure gradient (r=0.462; p<0.001) and maximal transvalvular pressure gradient (r=0.380; p<0.001) between echocardiography at 30 days and 1 year **(Table 4)**. Seven patients met the criteria of haemodynamic valve deterioration 3 years after TAVI: two moderate and five severe. None of the patients received oral anticoagulation at the time of the first CTA; however, it was initiated in two of them following the imaging results. Among patients with haemodynamic valve deterioration, one died of pneumonia during the second year of follow-up, while another required redo-TAVI in the third year. Patients with valve deterioration had a higher thrombus volume at 1 year than the remaining patients (400 mm^3 [IQR 98-1,269 mm^3] vs 62 mm^3 [IQR 0-249 mm^3]; p=0.018).

Table 1. Baseline clinical characteristics and procedural data.

	Resolution of HALT		*p*-value
	Yes (n=43)	No (n=56)	
Baseline characteristics			
Male	27 (63)	41 (73)	0.283
Age at procedure, years	78±9	83±8	0.006
Body mass index, kg/m^2	28.6±8.6	25.8±4.1	0.070
Arterial hypertension	31 (72)	54 (96)	0.142
Diabetes	7 (16)	18 (32)	0.143
Atrial fibrillation	6 (14)	13 (23)	0.405
Coronary artery disease	24 (56)	34 (61)	0.814
Previous myocardial infarction	4 (9)	10 (18)	0.371
Glomerular filtration rate, ml/min/1.73 m^2	73 (57-85)	51 (41-65)	0.061
STS-PROM	2.5 (1.9-4.7)	4.7 (2.3-6.5)	0.042
Preprocedural echocardiographic data			
Aortic valve area, cm^2	0.7 (0.5-0.8)	0.7 (0.5-0.75)	0.046
Mean transvalvular gradient, mmHg	41.0 (28.5-44.5)	46.0 (41.0-54.0)	0.024
Maximal transvalvular gradient, mmHg	70.0 (47.0-78.0)	76.0 (67.0-87.0)	0.081
Peak velocity, m/s	3.9±0.6	4.3±0.8	0.174
Left ventricular ejection fraction, %	60 (45-66)	61 (51-69)	0.565
Moderate or greater aortic regurgitation	2 (4)	4 (7)	0.606
Preprocedural tomographic data			
Aortic annulus area, mm^3	532 (450-567)	477 (416-516)	0.062
Aortic valve calcium score	2,227 (1,445-4,332)	2,884 (1,807-3,804)	0.269
Procedural data			
Non-transfemoral access	1 (2)	1 (2)	1.000
SAPIEN XT[a]	2 (5)	9 (16)	0.073
SAPIEN 3[a]	41 (95)	47 (84)	
Valve size, mm			
23	7 (16)	12 (21)	0.344
26	16 (37)	26 (46)	
29	20 (47)	18 (32)	
Predilatation	0 (0)	1 (2)	1.000
Post-dilatation	0 (0)	1 (2)	1.000
Medications at the first CTA			
Oral anticoagulation	11 (26)	10 (18)	0.663
Aspirin	41 (95)	48 (86)	0.114
$P2Y_{12}$ inhibitor	9 (21)	16 (29)	0.385
Medications at the second CTA			
Oral anticoagulation	9 (21)	13 (23)	0.894
Aspirin	42 (98)	52 (93)	0.277
$P2Y_{12}$ inhibitor	12 (28)	13 (23)	0.594

Data are presented as n (%), mean±SD or median (IQR). [a]by Edwards Lifesciences. CTA: computed tomography angiography; HALT: hypoattenuating leaflet thickening; IQR: interquartile range; SD: standard deviation; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality

Discussion

Quantitative characterisation of HALT in relation to valve deformation could provide mechanistic insight into its clinical sequelae and aid decisions about oral anticoagulation therapy. Several studies have investigated the history of HALT in transcatheter and surgical cohorts, but there is a limited understanding of how imaging features influence thrombus evolution over time[1,7,8]. Thus, we sought to examine the association of quantitative HALT features from CTA with its progression in a real-life population. We found that (1)

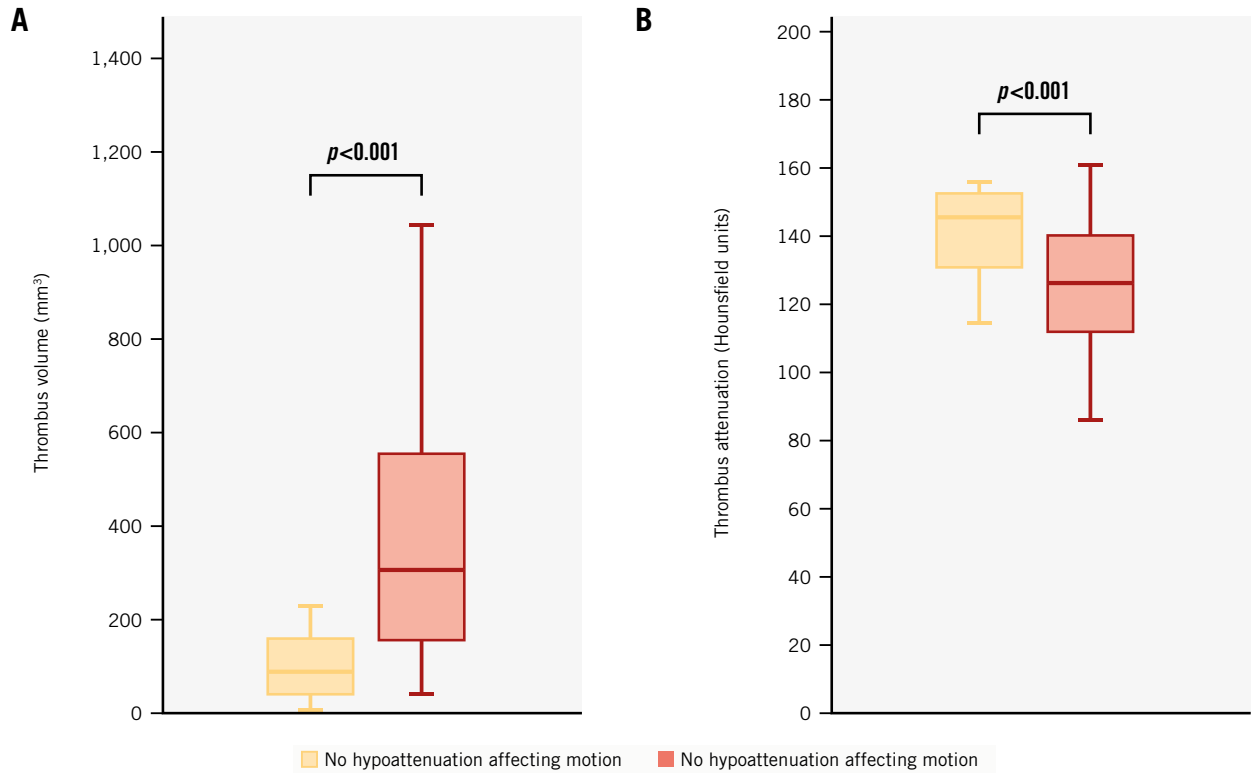

Figure 2. *Differences in thrombus volume and attenuation in patients without and with hypoattenuation affecting motion. A) Differences in thrombus volume; (B) differences in thrombus attenuation.*

Table 2. Univariate and multivariate associations of clinical variables and transcatheter aortic valve deformation measures with thrombus volume (mm³).

	Univariate			Multivariate		
	β coefficient	95% CI	*p*-value	β coefficient	95% CI	*p*-value
Male sex	210.1	76.7 to 343.4	0.002	93.2	–50.6 to 237.1	0.201
Age at procedure (per 1 year)	–1.0	–8.2 to 6.2	0.784	–0.6	–7.0 to 5.9	0.860
Oral anticoagulation at the time of the first CTA	–109.9	–444.5 to 224.5	0.515	–69.4	–352.9 to 213.9	0.627
Valve size	210.1	133.4 to 288.3	<0.001	97.1	–4.8 to 199.1	0.062
Asymmetric leaflet expansion (per 1 degree)	–0.3	–5.4 to 4.9	0.925	-	-	-
Implant depth (per 1 mm)	97.5	–55.9 to 1.19	<0.001	75.4	30.4 to 120.5	0.001
Canting (per 1 mm)	39.5	–10.1 to 89.2	0.158	-	-	-
Commissure malalignment						
Right coronary	–202.3	–529.2 to 124.5	0.222	-	-	-
Left coronary	151.5	–44.8 to 347.9	0.129	-	-	-
Post-implant oversizing (per 1%)	1.5	–17.6 to 20.6	0.875	-	-	-
Expansion (per 1%)						
Leaflet outflow	–0.2	–7.3 to 7.0	0.958	-	-	-
Prosthesis waist	–0.1	–7.1 to 7.2	0.998	-	-	-
Leaflet inflow	1.1	–5.3 to 7.6	0.724	-	-	-
Native annulus	–5.3	–12.8 to 2.1	0.156	-	-	-
Eccentricity (per 0.1)						
Leaflet outflow	100.3	40.6 to 160.0	0.001	-	-	-
Prosthesis waist	106.6	49.6 to 163.6	<0.001	88.2	31.1 to 145.4	0.003
Leaflet inflow	53.3	70.7 to 99.6	0.024	-	-	-
Native annulus	64.8	16.1 to 113.0	0.009	-	-	-
Prosthesis deformation index (per 0.05)	–28.6	–68.3 to 11.1	0.156	-	-	-

*Indicates statistical significance. CI: confidence interval; CTA: computed tomography angiography

Table 3. Multivariate association of clinical variables, thrombus quantitative parameters, and transcatheter aortic valve deformation measures with resolution of hypoattenuating leaflet thickening or hypoattenuation affecting motion.

	Resolution of hypoattenuating leaflet thickening			Resolution of hypoattenuation affecting motion		
	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
Male sex	0.69	0.18-2.63	0.591	0.59	0.11-3.97	0.121
Age at procedure (per 1 year)	0.91	0.85-0.98	0.010	0.93	0.85-1.02	0.121
Oral anticoagulation at the time of the second CTA	0.67	0.20-2.28	0.512	1.21	0.25-5.8	0.815
Thrombus volume (per 100 mm^3)	0.99	0.97-1.01	0.314	0.99	0.96-1.01	0.341
Thrombus attenuation (per 5 HU)	0.45	0.21-0.92	0.030	0.56	0.39-0.81	0.002
Asymmetric leaflet expansion (per 1 degree)	-	-	-	0.86	0.78-0.95	0.003
Eccentricity at the native annulus (per 0.1)	0.42	0.24-0.74	0.003	-	-	-
Deformation index (per 0.05)	0.53	0.33-0.83	0.005	0.60	0.33-1.09	0.096
Implant canting (per 1 mm)	1.88	1.08-3.30	0.026	-	-	-

CI: confidence interval; CTA: computed tomography angiography; HU: Hounsfield unit

Table 4. Correlation between the change in the thrombus volume and echocardiographic parameters.

Change in echocardiographic parameters	Change in thrombus volume, mm^3
Δ aortic valve area, cm^2	r=–0.350 p=0.054
Δ mean transvalvular gradient, mmHg	r=0.462 p<0.001
Δ maximal transvalvular gradient, mmHg	r=0.380 p<0.001
Δ peak velocity, m/s	r=0.201 p=0.161

lower thrombus attenuation predicts HALT resolution, independently of clinical characteristics and non-uniform expansion of the prosthesis; (2) volumetric evaluation of thrombus allows precise tracking of HALT evolution; and (3) an increase in thrombus volume is associated with higher transvalvular pressure gradients.

Multiple clinical risk factors, including the absence of anticoagulation therapy, renal impairment, and reduced left ventricular function, have been associated with HALT[26]. Additionally, the post-implant geometry of transcatheter aortic valves plays a significant role in thrombus formation[15]. Several studies have identified deformation of the bioprosthetic midsegment and asymmetric leaflet expansion as independent predictors of HALT[16,17]. Indeed, we show that increased thrombus volume is associated with implantation depth (β=75.4, 95% confidence interval [CI]: 30.4-120.5; p=0.001) and eccentricity at the waist (β=88.2, 95% CI: 31.1-145.4; p=0.003) of balloon-expandable valves. These findings are in line with our previous study on transcatheter valve deformation in bicuspid aortic valves, which showed that suboptimal expansion affects the incidence of HALT. Deep valve implantation and deformation, particularly eccentric configurations, may disturb blood flow and negatively affect the microstructure of the leaflets, thus promoting thrombus formation[27].

Thrombus incidence and volume are likely influenced by the size of the bioprosthetic valve, as demonstrated in previous studies on fluid mechanics and other large multicentre registries. Indeed, we observed a trend suggesting an association between thrombus volume and valve size, but no association was found between thrombus volume and the resolution of the thrombus. Additionally, we extend the evidence on the role of bioprosthetic valve deformation in HALT by showing an association of eccentricity at the native annulus level and deformation index with thrombus resolution.

While semiquantitative visual grading of HALT remains the clinical standard, the quantitative approach objectifies the evaluation of thrombus. One study by Karády and colleagues measured HALT volume by extracting low-density voxels (between –200 HU and +200 HU) within a bioprosthetic frame using an open-source platform for multipurpose medical image analysis 3D Slicer (https://www.slicer.org/) and described a HALT prevalence of 79% with a median volume of 72 mm^3[3,21]. A high prevalence of small thrombus volumes suggests that quantification was likely affected by photon starvation artefacts adjacent to the high-density bioprosthetic frame. For this reason, we used HALT quantification supplementary to visual detection rather than as a substitute. Moreover, our software is dedicated to aortic valve tissue characterisation and has been previously validated against histology[20].

Our volumetric quantification of thrombus is therefore a precise method for accurately tracking HALT evolution between CTA scans. Presented results demonstrate that the difference in thrombus volume between the two scans corresponds closely with visual assessment. Moreover, the magnitude of change

in thrombus volume correlated with haemodynamic changes. Whereas the presence of HALT may slightly decrease short-term haemodynamic performance, its impact on the long-term durability of the transcatheter aortic valve remains uncertain[1,12]. Volumetric quantification of thrombus allows the detection of visually indescribable HALT evolution in serial imaging that reflects the subtle changes in echocardiographic indices. While quantitative thrombus characterisation requires little additional labour (2-3 minutes per case), the trajectory of changes in thrombus volume could potentially inform decisions on starting oral anticoagulation and refine risk stratification of long-term structural deterioration of bioprostheses.

Our quantitative measures of HALT also included the attenuation. For the first time, we have shown that lower thrombus attenuation independently predicts HALT resolution (OR 0.45 [95% CI: 0.21 - 0.92] per 5 HU increase; p=0.03). Differences in attenuation have been shown to discriminate between thrombosis and pannus formation in mechanical heart valve dysfunction[28]. Although an optimal threshold of >145 HU was determined for differentiating pannus from thrombus (sensitivity 88%; specificity 96%), the best response to thrombolysis was seen in the lowest attenuation masses (complete resolution in all cases <90 HU and only in 42% at 90-145 HU). Increasing thrombus attenuation may reflect the replacement of cellular material by collagen during its maturation, which could increase the resistance to thrombolytic pathways[29,30].

The findings of our study may help optimise TAVI procedures by highlighting the role of valve deformation and implantation depth in HALT formation. Both deformation and implantation depth contribute to the risk of HALT formation by affecting neo-sinus characteristics. Greater prosthesis deformation has been linked to a lower sinus volume, which promotes HALT formation[15]. Similarly, a lower implantation depth has been shown to impair neo-sinus washout, potentially further increasing the risk[31]. The deformation of the bioprosthesis depends on the anatomy and calcification of the aortic valve complex. While the opportunity to control this aspect is limited, identifying anatomical features associated with HALT can be valuable during the planning stage. On the other hand, high implantation techniques in balloon-expandable valves have been shown to decrease conduction abnormalities and permanent pacemaker implantation rates. Current results suggest that higher implantation may decrease thrombus volume and potentially improve the durability of the bioprosthetic valve.

Limitations

Our study has several limitations. First, we included only balloon-expandable transcatheter aortic valves, which limited the generalisability of the presented findings. Second, long-term clinical outcomes were unavailable; therefore, their association with thrombus characteristics could not be studied. Finally, patients receiving oral anticoagulation were included; thus, the results might not represent the natural history of thrombus, but they do reflect current clinical practice.

Conclusions

In conclusion, quantitative thrombus characterisation on CTA is predictive of HALT resolution and correlates with the haemodynamic performance of transcatheter aortic valves. Quantitative thrombus characterisation may improve risk stratification in patients with HALT and inform therapeutic decisions.

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Conflict of interest statement

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References

1. Makkar RR, Blanke P, Leipsic J, Thourani V, Chakravarty T, Brown D, Trento A, Guyton R, Babaliaros V, Williams M, Jilaihawi H, Kodali S, George I, Lu M, McCabe JM, Friedman J, Smalling R, Wong SC, Yazdani S, Bhatt DL, Bax J, Kapadia S, Herrmann HC, Mack M, Leon MB. Subclinical Leaflet Thrombosis in Transcatheter and Surgical Bioprosthetic Valves: PARTNER 3 Cardiac Computed Tomography Substudy. *J Am Coll Cardiol.* 2020;75:3003-15.

2. Blanke P, Leipsic JA, Popma JJ, Yakubov SJ, Deeb GM, Gada H, Mumtaz M, Ramlawi B, Kleiman NS, Sorajja P, Askew J, Meduri CU, Kauten J, Melnitchouk S, Inglessis I, Huang J, Boulware M, Reardon MJ; Evolut Low Risk LTI Substudy Investigators. Bioprosthetic Aortic Valve Leaflet Thickening in the Evolut Low Risk Sub-Study. *J Am Coll Cardiol.* 2020;75:2430-42.

3. Garcia S, Fukui M, Dworak MW, Okeson BK, Garberich R, Hashimoto G, Sato H, Cavalcante JL, Bapat VN, Lesser J, Cheng V, Newell MC, Goessl M, Elmariah S, Bradley SM, Sorajja P. Clinical Impact of Hypoattenuating Leaflet Thickening After Transcatheter Aortic Valve Replacement. *Circ Cardiovasc Interv.* 2022;15:e011480.

4. Chakravarty T, Søndergaard L, Friedman J, De Backer O, Berman D, Kofoed KF, Jilaihawi H, Shiota T, Abramowitz Y, Jørgensen TH, Rami T, Israr S, Fontana G, de Knegt M, Fuchs A, Lyden P, Trento A, Bhatt DL,

Leon MB, Makkar RR; RESOLVE; SAVORY Investigators. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet*. 2017;389:2383-92.

5. Yanagisawa R, Tanaka M, Yashima F, Arai T, Jinzaki M, Shimizu H, Fukuda K, Watanabe Y, Naganuma T, Higashimori A, Mizutani K, Araki M, Tada N, Yamanaka F, Otsuka T, Yamamoto M, Hayashida K. Early and Late Leaflet Thrombosis After Transcatheter Aortic Valve Replacement. *Circ Cardiovasc Interv*. 2019;12:e007349.

6. Ruile P, Minners J, Breitbart P, Schoechlin S, Gick M, Pache G, Neumann FJ, Hein M. Medium-Term Follow-Up of Early Leaflet Thrombosis After Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv*. 2018;11:1164-71.

7. Sondergaard L, De Backer O, Kofoed KF, Jilaihawi H, Fuchs A, Chakravarty T, Kashif M, Kazuno Y, Kawamori H, Maeno Y, Bieliauskas G, Guo H, Stone GW, Makkar R. Natural history of subclinical leaflet thrombosis affecting motion in bioprosthetic aortic valves. *Eur Heart J*. 2017;38:2201-7.

8. Imaeda S, Inohara T, Yoshijima N, Kobari Y, Myojin S, Ryuzaki T, Hattori O, Shinada K, Tsuruta H, Takahashi T, Yamazaki M, Kato J, Yamada Y, Jinzaki M, Shimizu H, Fukuda K, Hayashida K. Natural History of Leaflet Thrombosis After Transcatheter Aortic Valve Replacement: A 5-Year Follow-Up Study. *J Am Heart Assoc*. 2022;11:e026334.

9. Leetmaa T, Hansson NC, Leipsic J, Jensen K, Poulsen SH, Andersen HR, Jensen JM, Webb J, Blanke P, Tang M, Nørgaard BL. Early aortic transcatheter heart valve thrombosis: diagnostic value of contrast-enhanced multidetector computed tomography. *Circ Cardiovasc Interv*. 2015;8:e001596.

10. Pache G, Schoechlin S, Blanke P, Dorfs S, Jander N, Arepalli CD, Gick M, Buettner HJ, Leipsic J, Langer M, Neumann FJ, Ruile P. Early hypo-attenuated leaflet thickening in balloon-expandable transcatheter aortic heart valves. *Eur Heart J*. 2016;37:2263-71.

11. Chitturi KR, Aladin AI, Braun R, Al-Qaraghuli AK, Banerjee A, Reddy P, Merdler I, Chaturvedi A, Abusnina W, Haberman D, Lupu L, Rodriguez-Weisson FJ, Case BC, Wermers JP, Ben-Dor I, Satler LF, Waksman R, Rogers T. Bioprosthetic Aortic Valve Thrombosis: Definitions, Clinical Impact, and Management: A State-of-the-Art Review. *Circ Cardiovasc Interv*. 2024;17:e014143.

12. Khan JM, Rogers T, Waksman R, Torguson R, Weissman G, Medvedofsky D, Craig PE, Zhang C, Gordon P, Ehsan A, Wilson SR, Goncalves J, Levitt R, Hahn C, Parikh P, Bilfinger T, Butzel D, Buchanan S, Hanna N, Garrett R, Shults C, Garcia-Garcia HM, Kolm P, Satler LF, Buchbinder M, Ben-Dor I, Asch FM. Hemodynamics and Subclinical Leaflet Thrombosis in Low-Risk Patients Undergoing Transcatheter Aortic Valve Replacement. *Circ Cardiovasc Imaging*. 2019;12:e009608.

13. Adrichem R, Rodes Cabau J, Mehran R, Park DW, Ten Berg JM, de Backer O, Hengstenberg C, Budde RPJ, Dangas GD, Makkar R, Van Mieghem NM. Treatment of Transcatheter Aortic Valve Thrombosis: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2024;84:848-61.

14. Ferstl P, Achenbach S, Marwan M, Bittner DO. Comparison of oral anticoagulation by vitamin-K antagonists and non-vitamin-K antagonists for treatment of leaflet thickening after transcatheter aortic valve implantation (TAVI). *Int J Cardiol*. 2023;386:104-8.

15. Fukui M, Bapat VN, Garcia S, Dworak MW, Hashimoto G, Sato H, Gössl M, Enriquez-Sarano M, Lesser JR, Cavalcante JL, Sorajja P. Deformation of Transcatheter Aortic Valve Prostheses: Implications for Hypoattenuating Leaflet Thickening and Clinical Outcomes. *Circulation*. 2022;146:480-93.

16. Jung S, Ammon F, Smolka S, Moshage M, Marwan M, Achenbach S. Commissural misalignment independently predicts leaflet thrombosis after transcatheter aortic valve implantation. *Clin Res Cardiol*. 2024;113:29-37.

17. Fuchs A, De Backer O, Brooks M, de Knegt MC, Bieliauskas G, Yamamoto M, Yanagisawa R, Hayashida K, Søndergaard L, Kofoed KF. Subclinical leaflet thickening and stent frame geometry in self-expanding transcatheter heart valves. *EuroIntervention*. 2017;13:e1067-75.

18. Jilaihawi H, Asch FM, Manasse E, Ruiz CE, Jelnin V, Kashif M, Kawamori H, Maeno Y, Kazuno Y, Takahashi N, Olson R, Alkhatib J, Berman D, Friedman J, Gellada N, Chakravarty T, Makkar RR. Systematic CT Methodology for the Evaluation of Subclinical Leaflet Thrombosis. *JACC Cardiovasc Imaging*. 2017;10:461-70.

19. Grodecki K, Tamarappoo BK, Huczek Z, Jedrzejczyk S, Cadet S, Kwiecinski J, Rymuza B, Parma R, Olasinska-Wisniewska A, Fijalkowska J, Protasiewicz M, Walczak A, Nowak A, Gocol R, Slomka PJ, Reczuch K, Jagielak D, Grygier M, Wojakowski W, Filipiak KJ, Dey D. Non-calcific aortic tissue quantified from computed tomography angiography improves diagnosis and prognostication of patients referred for transcatheter aortic valve implantation. *Eur Heart J Cardiovasc Imaging*. 2021;22:626-35.

20. Grodecki K, Olasińska-Wiśniewska A, Cyran A, Urbanowicz T, Kwieciński J, Geers J, Tamarappoo BK, Perek B, Gocoł R, Nawara-Skipirzepa J, Jemielity M, Kochman J, Wojakowski W, Górnicka B, Slomka PJ, Jilaihawi H, Makkar RR, Huczek Z, Dey D. Quantification of Aortic Valve Fibrotic and Calcific Tissue from CTA: Prospective Comparison with Histology. *Radiology*. 2024;312:e240229.

21. Karády J, Apor A, Nagy AI, Kolossváry M, Bartykowszki A, Szilveszter B, Simon J, Molnár L, Jermendy ÁL, Panajotu A, Suhai FI, Varga A, Rajani R, Maurovich-Horvat P, Merkely B. Quantification of hypo-attenuated leaflet thickening after transcatheter aortic valve implantation: clinical relevance of hypo-attenuated leaflet thickening volume. *Eur Heart J Cardiovasc Imaging*. 2020;21:1395-404.

22. Kazuno Y, Maeno Y, Kawamori H, Takahashi N, Abramowitz Y, Babak H, Kashif M, Chakravarty T, Nakamura M, Cheng W, Friedman J, Berman D, Makkar RR, Jilaihawi H. Comparison of SAPIEN 3 and SAPIEN XT transcatheter heart valve stent-frame expansion: evaluation using multi-slice computed tomography. *Eur Heart J Cardiovasc Imaging*. 2016;17:1054-62.

23. Vora AN, Tang GHL, Reardon MJ, Deeb GM, Yakubov SJ, Huang J, Spencer J, Gada H. Transcatheter Aortic Valve Implant Depth Measurements Differ by Aortography Versus Computed Tomography. *JACC Cardiovasc Interv*. 2021;14:1045-7.

24. Ochiai T, Chakravarty T, Yoon SH, Kaewkes D, Flint N, Patel V, Mahani S, Tiwana R, Sekhon N, Nakamura M, Cheng W, Makkar R. Coronary Access After TAVR. *JACC Cardiovasc Interv*. 2020;13:693-705.

25. VARC-3 WRITING COMMITTEE; Généreux P, Piazza N, Alu MC, Nazif T, Hahn RT, Pibarot P, Bax JJ, Leipsic JA, Blanke P, Blackstone EH, Finn MT, Kapadia S, Linke A, Mack MJ, Makkar R, Mehran R, Popma JJ, Reardon M, Rodes-Cabau J, Van Mieghem NM, Webb JG, Cohen DJ, Leon MB. Valve Academic Research Consortium 3: Updated Endpoint Definitions for Aortic Valve Clinical Research. *J Am Coll Cardiol*. 2021;77:2717-46.

26. Pieniak K, Jędrzejczyk S, Domaszk O, Grodecki K, Rymuza B, Huczek Z, Kochman J, Filipiak KJ, Gąsecka A. Predictors and Biomarkers of Subclinical Leaflet Thrombosis after Transcatheter Aortic Valve Implantation. *J Clin Med*. 2020;9:3742.

27. Midha PA, Raghav V, Sharma R, Condado JF, Okafor IU, Rami T, Kumar G, Thourani VH, Jilaihawi H, Babaliaros V, Makkar RR, Yoganathan AP. The Fluid Mechanics of Transcatheter Heart Valve Leaflet Thrombosis in the Neosinus. *Circulation*. 2017;136:1598-609.

28. Bonnichsen CR, Pellikka PA. Prosthetic Valve Thrombus Versus Pannus: Progress With Imaging. *Circ Cardiovasc Imaging*. 2015;8:e004283.

29. Nosaka M, Ishida Y, Kimura A, Kondo T. Time-dependent appearance of intrathrombus neutrophils and macrophages in a stasis-induced deep vein thrombosis model and its application to thrombus age determination. *Int J Legal Med*. 2009;123:235-40.

30. Stanford SN, Sabra A, D'Silva L, Lawrence M, Morris RH, Storton S, Brown MR, Evans V, Hawkins K, Williams PR, Davidson SJ, Wani M, Potter JF, Evans PA. The changes in clot microstructure in patients with ischaemic stroke and the effects of therapeutic intervention: a prospective observational study. *BMC Neurol*. 2015;15:35.

31. Pott D, Sedaghat A, Schmitz C, Werner N, Schmitz-Rode T, Steinseifer U, Jansen SV. Hemodynamics inside the neo- and native sinus after TAVR: Effects of implant depth and cardiac output on flow field and coronary flow. *Artif Organs*. 2021;45:68-78.

Supplementary data

Supplementary Appendix 1. Computed tomography angiography image acquisition and analysis.

Supplementary Appendix 2. Reproducibility of thrombus quantitative characterisation.

Supplementary Table 1. Transcatheter aortic valve deformation measures in patients without and with hypoattenuation affection motion.

Supplementary Table 2. Univariate association of clinical variables, thrombus quantitative parameters and transcatheter aortic valve deformation measures with resolution of HALT.

Supplementary Table 3. Univariate association of clinical variables, thrombus quantitative parameters and transcatheter aortic valve deformation measures with resolution of hypoattenuation affecting motion.

Supplementary Table 4. Multivariate association of clinical variables, thrombus quantitative parameters, and transcatheter aortic valve deformation measures with resolution of HALT or hypoattenuation affecting motion in patients not receiving oral anticoagulation.

Supplementary Table 5. Comparison of echocardiographic data between patients with and without HALT.

Supplementary Table 6. Correlation between thrombus volume and echocardiographic data.

Supplementary Figure 1. The evolution of HALT and hypoattenuation affecting motion between the first computed tomography angiography at 30 days and the second at 1 year.

Supplementary Figure 2. Examples of imaging predictors for the resolution of HALT.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-01043

Supplementary data

Supplementary Appendix 1. Computed tomography angiography image acquisition and analysis.

We utilized electrocardiogram (ECG)-gated CTA examinations conducted on a second-generation dual-source CT system (Siemens Somatom Definition Flash; Siemens Healthcare, Erlangen, Germany). Contrast enhancement was achieved using a commercial contrast medium (Omnipaque, GE Healthcare, Little Chalfont, Buckinghamshire, United Kingdom), administered at a standardized dose of 100 mL per patient. CTA acquisition was performed in the cranio-caudal direction, covering the area from the aortic arch to the diaphragm. CTA scans were obtained with a collimation of 128 × 0.625 mm, and the maximum tube current was automatically adjusted for each patient using Caredose (Siemens Healthcare, Erlangen, Germany). The tube potential was fixed at 100–120 kV. Images were reconstructed with a slice thickness of 0.6 mm and a 0.3-mm overlap using iterative reconstruction, allowing evaluation at 10% intervals within the 0%–90% RR range. CTA images were reconstructed using 3mensio Valves Version 9.0 (3mensio Medical Imaging BV, Bilthoven, The Netherlands) and reviewed by experts in a dedicated CT core laboratory at our institution.

Supplementary Appendix 2. Reproducibility of thrombus quantitative characterisation.

There was excellent interobserver repeatability for thrombus volume measurement, with an ICC of 0.99 (95% CI: 0.98, 0.99; $p<0.001$). Additionally, Bland-Altman analysis showed that the two readers achieved a coefficient of repeatability of 31.9 and a mean bias of 5.1 mm^3 (95% limits of agreement: −25.9 mm^3, 36.0mm^3) for the assessment of thrombus volume. Interobserver repeatability for thrombus attenuation was also excellent, with an ICC of 0.99 (95% CI: 0.99, 0.99; $p<0.001$), and Bland-Altman analysis showed that the two readers achieved a coefficient of repeatability of 3.7 and mean bias of 0.1 HU (95% limits of agreement: −3.7HU, 3.8HU

Supplementary Table 1. Transcatheter aortic valve deformation measures in patients without and with hypoattenuation affection motion.

	Hypoattenuation affecting motion		P value
	NO (n = 21)	**YES (n = 78)**	
Asymmetric leaflet expansion (degree)	8 (4 - 20)	9 (4 – 24)	0.942
<10°	11 (52)	39 (50)	0.652
10°–15°	2 (10)	11 (14)	
15°–20°	0 (0)	4 (5)	
>20°	8 (38)	24 (31)	
Implant depth (mm)	4.2 (3.3 – 5.0)	4.7 (2.8 – 6.2)	0.027
Canting (mm)	1.1 (0.5 – 2.3)	1.3 (0.6 – 2.1)	0.552
Commissure malalignment			
Right coronary, n (%)	3 (14)	1 (1)	0.029
Left coronary, n (%)	1 (5)	11 (14)	0.452
Postimplant oversizing (%)	-0.4 (-1 – 1.1)	0.6 (-1.7 – 3.1)	0.216
Expansion (%)			
Leaflet outflow	105.4 (97.8 – 110.4)	103.4 (97.8 – 109.3)	0.993
Prosthesis waist	95.2 (95.1 – 100.9)	94.2 (88.2 – 101.6)	0.791
Leaflet inflow	101.5 (96.3 – 105.9)	99.3 (95.2 – 104.3)	0.300
Native annulus	98.0 (91.8 – 1.0)	93.3 (88.8 – 100.0)	0.128
Eccentricity			
Leaflet outflow	0.24 (0.14 – 0.28)	0.31 (0.23 – 0.39)	0.001
Prosthesis waist	0.21 (0.16 – 0.27)	0.36 (0.27 – 0.41)	<0.001
Leaflet inflow	0.17 (0.11 – 0.24)	0.33 (0.22 – 0.38)	<0.001
Native annulus	0.22 (0.18 – 0.27)	0.32 (0.23 – 0.39)	0.002
Prosthesis deformation index	1.10 (1.07 – 1.14)	1.10 (1.04 – 1.15)	0.824

Supplementary Table 2. Univariate association of clinical variables, thrombus quantitative parameters and transcatheter aortic valve deformation measures with resolution of HALT.

	Univariable		
	Odds ratio	95% Confidence Interval	P value
Male sex	0.61	0.26 – 1.45	0.269
Age at procedure	0.94	0.89 – 0.98	**0.008**
Oral anticoagulation at the time of the second CTA	1.05	0.39 – 2.82	0.919
Thrombus volume (per 100mm^3)	0.99	0.98 – 1.01	0.749
Thrombus attenuation (per 5HU)	0.92	0.84 – 1.01	0.092
Valve size	1.44	0.83 – 2.51	0.192
Asymmetric leaflet expansion (per 1 degree)	0.99	0.96 – 1.03	0.877
Implant depth (per 1 mm)	0.98	0.74 – 1.29	0.871
Canting (per 1 mm)	1.43	1.02 – 1.99	**0.038**
Commissure malalignment			
Right coronary, n (%)	4.12	0.41 – 41.12	0.227
Left coronary, n (%)	0.92	0.27 – 3.13	0.895
Postimplant oversizing (per 1%)	0.92	0.81 – 1.04	0.193
Expansion (per 1%)			
Leaflet outflow	0.99	0.95 – 1.04	0.908
Prosthesis waist	0.87	0.54 – 1.40	0.555
Leaflet inflow	0.99	0.96 – 1.04	0.895
Native annulus	1.02	0.97 – 1.06	0.510
Eccentricity (per 0.1 increase)			
Leaflet outflow	0.50	0.32 – 0.78	**0.002**
Prosthesis waist	0.97	0.62 – 1.51	0.141
Leaflet inflow	0.61	0.43 – 0.87	**0.005**
Native annulus	0.56	0.41 – 0.87	**0.005**
Deformation index (per 0.05)	0.66	0.49 – 0.89	**0.007**

Supplementary Table 3. Univariate association of clinical variables, thrombus quantitative parameters and transcatheter aortic valve deformation measures with resolution of hypoattenuation affecting motion.

	Univariable		
	Odds ratio	95% Confidence Interval	P value
Male sex	0.49	0.16 – 1.52	0.218
Age at procedure	0.95	0.89 – 1.01	0.065
Oral anticoagulation at the time of the second CTA	1.45	0.47 – 4.45	0.518
Thrombus volume (per 100mm^3)	1.00	0.99 – 1.01	0.966
Thrombus attenuation (per 5HU)	0.81	0.70 – 0.94	**0.005**
Valve size	1.00	0.52 – 1.91	1.000
Asymmetric leaflet expansion (per 1 degree)	0.93	0.89 – 0.97	**0.002**
Implant depth (per 1 mm)	0.81	0.58 – 1.13	0.216
Canting (per 1 mm)	1.07	0.73 – 1.57	0.723
Commissure malalignment			
Right coronary, n (%)	-	-	-
Left coronary, n (%)	0.36	0.10 – 1.30	0.117
Postimplant oversizing (per 1%)	0.94	0.83 – 1.07	0.371
Expansion (per 1%)			
Leaflet outflow	0.98	0.93 – 1.03	0.436
Prosthesis waist	0.99	0.95 – 1.05	0.958
Leaflet inflow	0.99	0.94 – 1.04	0.629
Native annulus	1.06	0.99 – 1.13	0.064
Eccentricity (per 0.1 increase)			
Leaflet outflow	0.79	4.49 – 1.28	0.339
Prosthesis waist	0.99	0.58 – 1.66	0.958
Leaflet inflow	0.76	0.52 – 1.10	0.139
Native annulus	0.98	0.68 – 1.39	0.892
Deformation index (per 0.05)	0.60	0.44 – 0.81	**0.001**

Supplementary Table 4. Multivariate association of clinical variables, thrombus quantitative parameters, and transcatheter aortic valve deformation measures with resolution of HALT or hypoattenuation affecting motion in patients not receiving oral anticoagulation.

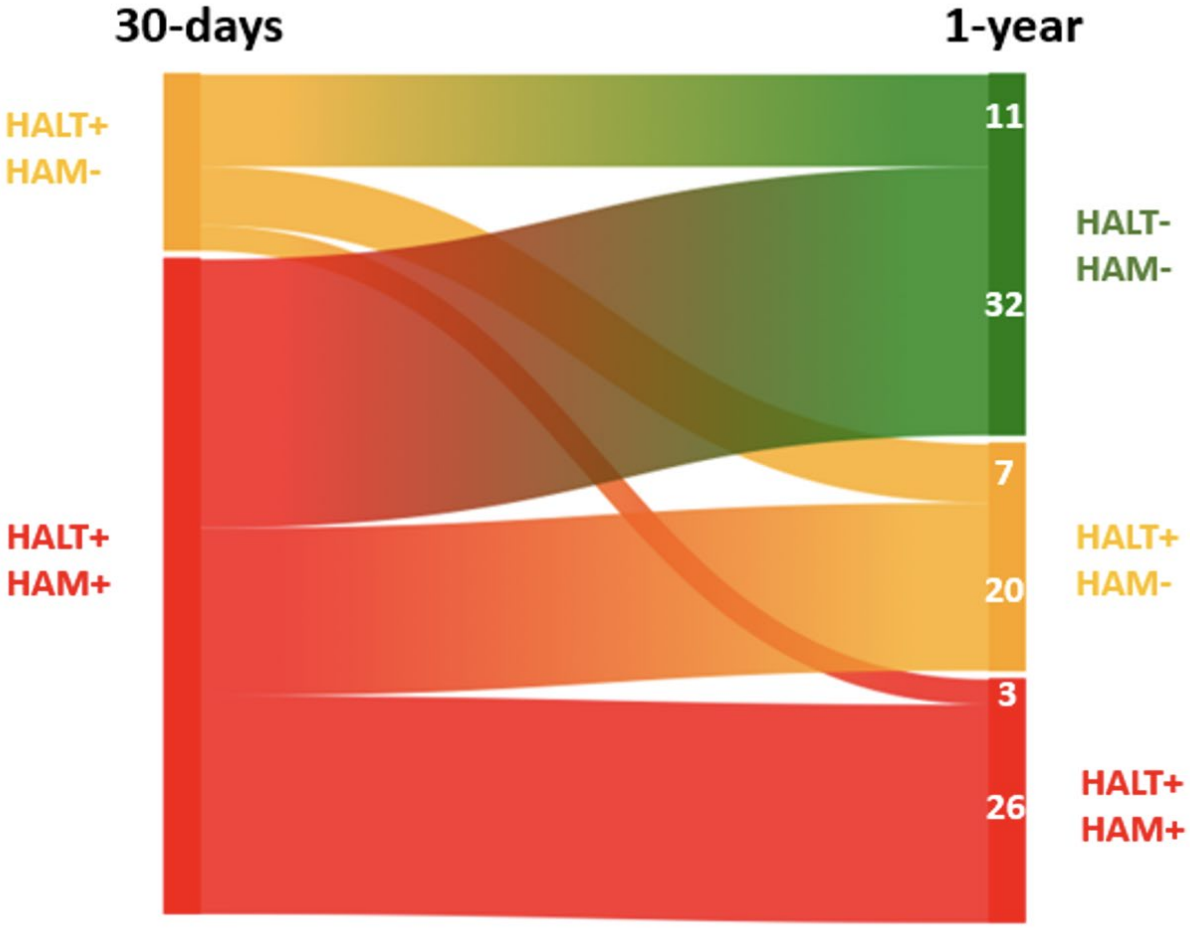
	Resolution of Hypoattenuating Leaflet Thickening			**Resolution of Hypoattenuation Affecting Motion**		
	Odds ratio	95% Confidence Interval	P value	**Odds ratio**	95% Confidence Interval	P value
Male sex	0.21	0.03 – 1.37	0.103	0.22	0.01 – 3.70	0.293
Age at procedure (per 1 year)	0.91	0.83 – 1.01	0.066	0.94	0.83 – 1.05	0.254
Thrombus volume (per 100mm^3)	0.80	0.62 – 1.05	0.103	0.85	0.62 – 1.15	0.292
Thrombus attenuation (per 5HU)	0.77	0.59 – 0.99	0.045	0.38	0.19 – 0.76	0.006
Asymmetric leaflet expansion (per 1 degree)	-	-	-	0.79	0.65 – 0.95	0.014
Eccentricity at the native annulus (per 0.1)	0.42	0.21 – 0.89	0.022	-	-	-
Deformation index (per 0.05)	0.30	0.13 – 0.67	0.003	0.28	0.07 – 1.07	0.062
Implant canting (per 1 mm)	2.71	1.22 – 6.00	0.014	-	-	-

Supplementary Table 5. Comparison of echocardiographic data between patients with and without HALT.

	Resolution of Hypoattenuating Leaflet Thickening		
	YES (n = 21)	**NO (n = 78)**	P value
Echocardiographic data at 30 days			
Aortic valve area (cm^2)	1.30 (1.15 – 1.50)	1.20 (1.00 – 1.40)	0.552
Mean transvalvular gradient (mmHg)	11.0 (9.5 – 15.5)	14.0 (10.0 – 18.0)	0.422
Maximal transvalvular gradient (mmHg)	21.0 (16.0 – 26.0)	26.0 (18.0 – 29.0)	0.670
Peak velocity (m/s)	2.35 ± 0.56	2.50 ± 0.65	0.958
Left ventricular ejection fraction (%)	64 (55 – 66)	60 (50 – 65)	0.155
Aortic regurgitation moderate or greater	0 (0)	0 (0)	1.000
Echocardiographic data at 1 year			
Aortic valve area (cm^2)	1.3 (1.0 – 1.5)	1.4 (1.2 – 1.6)	0.429
Mean transvalvular gradient (mmHg)	11.0 (9.0 -14.0	11.0 (8.0 – 17.2)	0.352
Maximal transvalvular gradient (mmHg)	21.0 (17.0 – 26.0)	21.5 (16.0 – 31.2)	0.357
Peak velocity (m/s)	2.31 ± 0.38	2.38 ± 0.52	0.452
Left ventricular ejection fraction (%)	65 (59 – 70)	62 (54 – 68)	0.681
Aortic regurgitation moderate or greater	0 (0)	0 (0)	1.000
Change in echocardiographic data			
Δ Aortic valve area (cm^2)	0.0 (-0.18 – 0.18)	0.20 (-0.22 – 0.52)	0.147
Δ Mean transvalvular gradient (mmHg)	-1.0 (-4.5 – 1.7)	-1.0 (-4.0 – 6.0)	0.014
Δ Maximal transvalvular gradient (mmHg)	-1.5 (-5.0 – 3.8)	-0.5 (-6.0 – 7.0)	0.032
Δ Peak velocity (m/s)	-0.05 (-0.4 – 0.28)	-0.07 (-0.41 – 0.39)	0.109

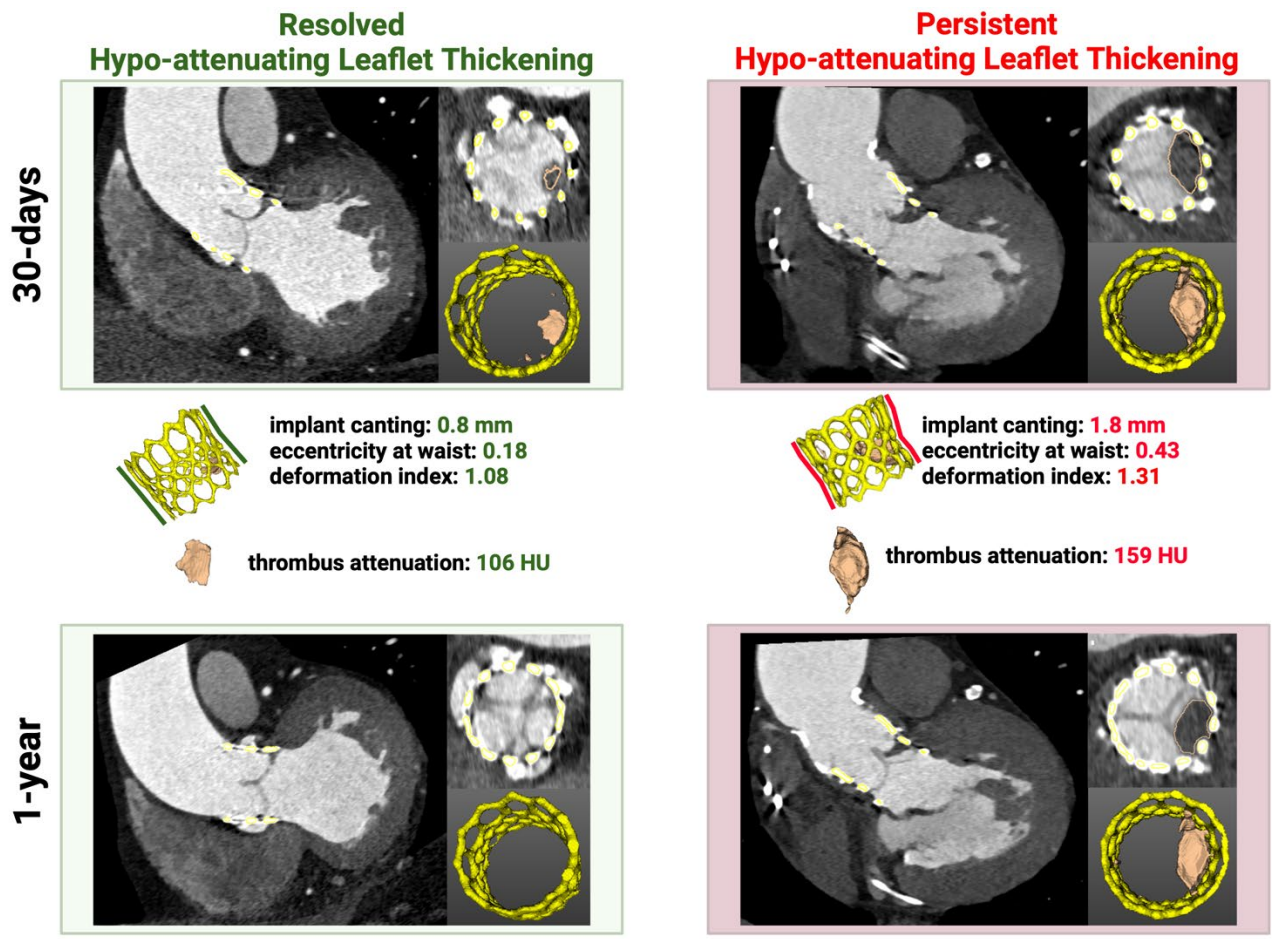
Supplementary Table 6. Correlation between thrombus volume and echocardiographic data.

	Thrombus volume at 30 days (mm^3)
Echocardiographic data at 30 days	
Aortic valve area (cm^2)	r=-0.015 p=0.898
Mean transvalvular gradient (mmHg)	r=-0.006 p=0.952
Maximal transvalvular gradient (mmHg)	r= 0.005 p=0.963
Peak velocity (m/s)	r=-0.014 p=0.894
	Thrombus volume at 1 year (mm^3)
Echocardiographic data at 1 year	
Aortic valve area (cm^2)	r=-0.029 p=0.804
Mean transvalvular gradient (mmHg)	r=-0.008 p=0.936
Maximal transvalvular gradient (mmHg)	r=-0.022 p=0.826
Peak velocity (m/s)	r=0.026 p=0.808



Supplementary Figure 1. The evolution of HALT and hypoattenuation affecting motion between the first computed tomography angiography at 30 days and the second at 1 year.

The width of the lines between timepoints is proportional to the number of reclassified lesions.



Supplementary Figure 2. Examples of imaging predictors for the resolution of HALT.