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Aortic valve disease: multimodality imaging for risk stratification and evaluation of therapy

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TRANSCATHETER AORTIC VALVE THROMBOSIS: THE RELATION BETWEEN HYPO-ATTENUATED LEAFLET THICKENING, ABNORMAL VALVE HEMODYNAMICS, AND STROKE

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ABSTRACT

AIMS

The presence of hypo-attenuated leaflet thickening (HALT) and/or reduced leaflet motion on multi-detector row computed tomography (MDCT) has been proposed as a possible marker for early transcatheter aortic valve thrombosis. However, its association with abnormal valve hemodynamics on echocardiography (another potential marker of thrombosis) and clinical outcomes (stroke) remains unclear. The present study evaluated the prevalence of HALT on MDCT and abnormal valve hemodynamics on echocardiography. In addition, the occurrence of ischemic stroke and/or transient ischemic attack (TIA) was assessed.

METHODS AND RESULTS

A total of 434 patients (mean age 80 ± 7 years, 51% male) who underwent transcatheter aortic valve replacement (TAVR) were evaluated. Transcatheter valve hemodynamics were assessed on echocardiography at discharge, 6 months, and thereafter yearly (up to 3 years post-TAVR). The presence of HALT and/or reduced leaflet motion was assessed on MDCT performed 35 days [interquartile range 19-210] after TAVR in 128 of these 434 patients. Possible TAVR valve thrombosis was defined by mean transvalvular gradient ≥ 20 mmHg and aortic valve area (AVA) ≤ 1.1 cm² on echocardiography or by the presence of HALT or reduced leaflet motion on MDCT. The occurrence of ischemic stroke/TIA at follow-up was recorded. HALT and/or reduced leaflet motion was present in 12.5% of 128 patients undergoing MDCT, and was associated with a slightly higher mean transvalvular gradient (12.4 ± 8.0 mmHg vs. 9.4 ± 4.3 mmHg; $P=0.026$) and smaller AVA (1.49 ± 0.39 cm² vs. 1.78 ± 0.45 cm², $P=0.017$). Only one patient with HALT on MDCT revealed abnormal valve hemodynamics on echocardiography. At 3-year follow-up, abnormal valve hemodynamics on echocardiography were observed in 3% of patients. HALT on MDCT and abnormal valve hemodynamics on echocardiography were not associated with increased risk of ischemic stroke/TIA.

CONCLUSION

On MDCT, 12.5% of patients showed HALT or reduced leaflet motion, whereas only one of these patients had abnormal valve hemodynamics on echocardiography. Neither HALT nor increased transvalvular gradient were associated with stroke/TIA.

INTRODUCTION

OVER the last decade, transcatheter aortic valve replacement (TAVR) has emerged as an effective alternative to surgical replacement for patients with symptomatic severe aortic stenosis who are at high risk for surgery or are considered inoperable [1, 2]. The promising results of early randomized trials [1–3] have led to the use of this technology in intermediate- to low-risk patients [4–6], with the first large randomized controlled trial showing non-inferiority of TAVR compared with surgical replacement [7]. Since these patients are often younger, valve durability has become an important concern. Recent studies have reported good durability of TAVR prostheses, for both balloon- and self-expandable valves, up to 5 years follow-up using transthoracic echocardiography [8–12]. However, sophisticated 3- and 4-dimensional computed tomography (CT) have described hypo-attenuated leaflet thickening (HALT) with reduced leaflet motion of TAVR prostheses, which could be an early marker of prosthetic valve thrombosis [13–15]. The effects of this leaflet thickening and restrictive motion on valve hemodynamics (assessed with echocardiography) and clinical outcome (transient ischemic attack or stroke) remain unclear and has led to ongoing debate on how to follow-up patients with TAVR valves and which antiplatelet/anticoagulation regime would be more appropriate. The present study aimed at evaluating the occurrence of abnormal valve hemodynamics (suggesting valve thrombosis) in both balloon- and self-expandable TAVR prostheses in a large patient cohort and compared these with the presence of HALT and/or reduced leaflet motion on dynamic multi-detector row CT (MDCT) data in a subpopulation. In addition, the clinical outcome (occurrence of ischemic stroke and/or transient ischemic attack [TIA]) was assessed.

METHODS

PATIENT POPULATION AND DATA COLLECTION

A total of 434 patients who underwent TAVR for severe aortic stenosis or degenerated biological aortic valve prosthesis between November 2007 and June 2015 at the Leiden University Medical Center were analyzed. Severe aortic stenosis was defined according to current recommendations: an aortic valve area $<1.0 \text{ cm}^2$ or indexed aortic valve area $<0.6 \text{ cm}^2/\text{m}^2$ and/or mean transvalvular pressure gradient $>40 \text{ mmHg}$ [16]. The decision of TAVR was based on heart team discussions.

Patients were followed-up clinically at the outpatient clinic at 1–3, 6, and 12 months and thereafter yearly. A subgroup of 128 patients underwent post-procedural MDCT (median 35 days [interquartile range 19–210] after TAVR) in the period of 2008–2013 as per institutional protocol (if there were no contraindications) and at the discretion of the treating cardiologist (see Supplementary Figure 4).

Demographic and clinical data were collected using electronic records (EPD Vision, version 11.4.29.0, EPD Vision, Leiden, The Netherlands). TAVR success and complications were registered as defined by the Valve Academic Research Consortium-2 (VARC-2) [17]. After the procedure, all patients received aspirin life long, whereas clopidogrel was prescribed for 3 months between 2007 and 2011 and thereafter for 1 month. If concomitant oral anticoagulants were used, aspirin was not prescribed.

The institutional review board approved this retrospective analysis of clinically ac-

quired data and waived the need for patient written informed consent.

TRANSCATHETER AORTIC VALVE REPLACEMENT PROCEDURE

TAVR was performed via transfemoral access, if adequate iliofemoral arterial anatomy was present as assessed with pre-procedural MDCT, or via transapical access otherwise. Transcatheter valve size was selected based on MDCT measurements of the aortic annulus, as previously described [18]. Contemporary balloon- and self-expandable valve prostheses were used: Edwards SAPIEN, SAPIEN XT, SAPIEN 3 (Edwards Lifesciences, Irvine, CA, USA), and the Medtronic CoreValve system (Medtronic, MN, Minnesota). Implantation procedures were performed under general anaesthesia with fluoroscopy and transesophageal echocardiography guidance. The hemodynamics of the implanted transcatheter valve were assessed immediately. If significant paravalvular or, less frequently, transvalvular regurgitation were noted, reballoonng of the prosthesis or valve-in-valve implantation were performed, respectively.

ECHOCARDIOGRAPHIC FOLLOW-UP

Transthoracic echocardiography was performed at discharge, 6 and 12 months and yearly thereafter (up to 3 years) to assess the transcatheter valve hemodynamics over time. Commercially available ultrasound systems equipped with 3.5MHz or M5S transducers (Vivid-7 or E9 systems, General Electric Vingmed, Horten, Norway) were used and 2-dimensional, colour, continuous, and pulsed wave Doppler data were acquired from parasternal and apical views with the patient in the left lateral decubitus position. Images were stored digitally on hard disks for offline analysis (EchoPac version BT13; GE Medical Systems). Left ventricular ejection fraction was measured from the apical 2- and 4-chamber views using Simpson's method [19]. Aortic valve peak jet velocity was estimated from the continuous wave Doppler recordings obtained on the 3- or 5-chamber apical views and, if needed, on the right parasternal view using the Pedoff probe [16]. The peak and mean transaortic pressure gradients were calculated according to the Bernoulli equation. The aortic valve area was calculated using the continuity equation.

According to current recommendations, abnormal transcatheter aortic valve hemodynamics indicating valve stenosis caused probably by thrombosis was based on a mean transvalvular gradient ≥ 20 mmHg and an aortic valve area ≤ 1.1 cm² [20]. The presence of paravalvular leakage at follow-up was graded using a multiparametric approach that integrates valve structure and motion, regurgitant flow characteristics including the circumferential extent of the paravalvular leak and left ventricular dimensions, as recommended by the VARC-2 criteria [17].

MULTI-DETECTOR ROW COMPUTED TOMOGRAPHY FOLLOW-UP

Using a 64-row (Aquilion 64; Toshiba Medical Systems, Tochigi-ken, Japan) or a 320-row (AquilionOne; Toshiba Medical Systems, Tochigiken, Japan) CT scanners, electrocardiographic-gated and contrastenhanced data acquisition of the aortic root was performed using previously described protocols [21, 22]. MDCT data were reconstructed at each 10% of RR-interval of the cardiac cycle. All data sets were analysed using dedicated post-processing software (Vitrea FX 6.5; Vital Images, Minnetonka, MN).

The structure and motion of the transcatheter valve leaflets were assessed. Struc-

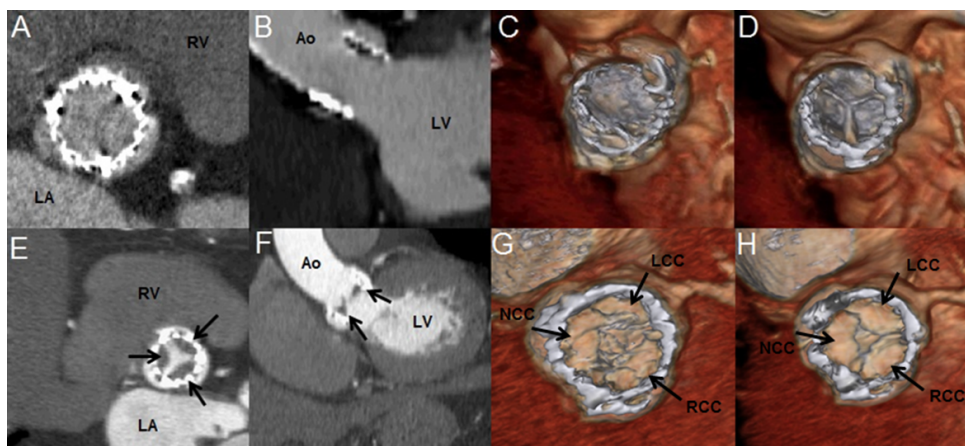


Figure 1: Multi-detector row computed tomography (MDCT) reconstructions after transcatheter aortic valve replacement with examples of normal structure of TAVR prosthesis (*panels A-D*) and transcatheter prosthesis with hypo-attenuated leaflet thickening and reduced leaflet motion (*panels E-H*). The double oblique reconstruction (*panel A*) on diastole of the transcatheter valve shows the stent frame and the leaflets without thickening and the coronal view of the transcatheter valve in systole (*panel B*) where the leaflets opened. The 3D volume renderings in systole (*panel C*) and diastole (*panel D*) show normal opening and closing of the prosthesis leaflets. In *panel E*, thickening of the prosthesis leaflets with hypo-attenuated lesions can be observed on the double oblique reconstruction. During systole, the leaflets remain immobile (*panel F*). *Panels G* and *H* show the 3D volume renderings in systole and diastole, respectively, with thickened leaflets that remain immobile (arrows). Ao, aorta; LA, left atrium; LCC, left coronary cusp of aortic valve; LV, left ventricle; NCC, non-coronary cusp of aortic valve; RCC, right coronary cusp of aortic valve; RV, right ventricle.

tural assessment focused on the presence of HALT, frame eccentricity and expansion, and transcatheter implantation depth. HALT was defined as hypo-attenuated thickening with or without reduced motion of one or more transcatheter valve leaflets and was assessed by 2-dimensional multiplanar reformation planes, and 3- and 4-dimensional volume rendered movies throughout the entire cardiac cycle (Figure 1) [15]. Stent eccentricity and expansion were evaluated at 3 levels (at inflow, mid-portion, and outflow) by using planimetered outer stent area and minimal and maximal diameters as described earlier [13, 15]. An expansion ratio of $\leq 90\%$ of nominal stent dimensions at all three levels was defined as underexpansion. Non-circularity of the transcatheter frame was defined as an eccentricity index >0.1 at all three levels, with eccentricity index calculated as $1 - (\text{minimal diameter} / \text{maximal diameter})$ [13, 15]. In addition, implant depth was measured and defined as the distance between the aortic annular plane and lower transcatheter valve prosthesis rim.

CLINICAL END-POINTS AT FOLLOW-UP

Patients were followed-up prospectively at the outpatient clinic of the Leiden University Medical Centre at 1–3, 6, and 12 months follow-up after TAVR, and yearly thereafter (at the referral centre). Patients with suspected neurologic events were evaluated by a neurologist. For this specific analysis, the occurrence of ischemic stroke (including TIA and ischemic stroke) was recorded.

STATISTICAL ANALYSIS

Continuous variables are presented as mean±standard deviation or as median and interquartile range as appropriate. Categorical variables are expressed as frequencies and percentages. Differences between groups were analyzed using the unpaired Student *t*-test for normally distributed continuous variables and the Mann–Whitney *U* test for non-normally distributed variables. Categorical variables were compared with the χ^2 test. General linear mixed models were used to analyze changes in transcatheter valve hemodynamics over time for the overall population and compared between patients with vs. without HALT and/or reduced leaflet motion on MDCT and between patients with vs. without stroke or TIA. Bonferroni's post-hoc analysis was used to compare the differences between groups over time. Statistical analyses were performed with SPSS software (version 23.0; IBM, Armonk, NY), all analyses were two-sided with *P* values <0.05 considered statistically significant.

RESULTS

PATIENT POPULATION

Baseline clinical, echocardiographic, and procedural characteristics for the overall population (mean age 80±7 years, 51% male) are shown in Table 1. Anticoagulant medication (vitamin K antagonists) was used in 37% of the patients, while 52% used aspirin and 33% clopidogrel. Baseline transthoracic echocardiography showed severe aortic stenosis (mean transvalvular gradient 42.3±18.1 mmHg, aortic valve area 0.78±0.28 cm²) and mean LVEF 53.9±16.1%. The majority of the patients had tricuspid anatomy of the aortic valve, 21 (5%) had a bicuspid aortic valve and 13 (3%) patients underwent valve-in-valve procedure. TAVR access was transfemoral in 52% of the patients and the remaining 48% underwent transapical TAVR. The most frequently implanted prosthesis size was 26 mm (54%). The majority of the patients received a balloon-expandable transcatheter valve (91%), whereas 40 patients received a self-expandable prosthesis. At discharge, moderate and severe paravalvular regurgitation was observed in 7% of the patients. The post-procedural outcomes according to the VARC-2 criteria are summarized in the Supplementary Table 7.

ABNORMAL VALVE HEMODYNAMICS ON ECHOCARDIOGRAPHY AT FOLLOW-UP

During the follow-up period, transthoracic echocardiography was performed in 431 patients at hospital discharge, in 350 patients at 6 months follow-up, in 229 patients at 1-year follow-up and in 116 and 61 patients at 2 and 3 years follow-up, respectively. After TAVR, a significant decrease in transvalvular gradients (peak gradient: from 65.5±26.5 mmHg to 17.1±8.1 mmHg, *P*<0.001; mean gradient: from 42.3±18.1 mmHg to 9.3±4.7 mmHg, *P*<0.001) and an increase in aortic valve area (from 0.78±0.28 cm² to 1.99±0.56 cm², *P*<0.001) were observed. Table 2 and Figure 2 present the hemodynamic changes of TAVR prostheses over time for the overall population. The peak and mean transvalvular gradients remained unchanged. However, the aortic valve area showed a statistically significant decrease after hospital discharge until 1 year follow-up, with a maximum decrease to 1.61±0.51 cm². In addition, a significant increase in LVEF was noted (from

Table 1: Baseline demographic, procedural and echocardiographic characteristics of the entire patient population undergoing transcatheter aortic valve replacement (TAVR).

Variables	Total population (N = 434)
<i>Clinical characteristics</i>	
Female gender, N (%)	212 (49)
Age (years)	80±7
BSA (m ²)	1.85±0.2
Logistic EuroSCORE (%)	21±14
Creatinin level (μmol/ml)	93 [73;115]
Coronary artery disease, N (%)	271 (62)
NYHA classification, N (%)	
I-II	192 (44)
III-IV	242 (56)
Prior myocardial infarction, N (%)	100 (23)
Diabetes, N (%)	125 (29)
Hypertension, N (%)	345 (80)
Hyperlipidaemia, N (%)	319 (74)
Peripheral vascular disease, N (%)	147 (34)
History of smoking, N (%)	134 (31)
Atrial fibrillation, N (%)	94 (22)
Medication, N (%)	
ACE-inhibitors/ARB	239 (55)
Calcium antagonist	116 (27)
Beta-blocker	267 (62)
Diuretics	275 (63)
Spironolactone	68 (16)
Statins	277 (64)
Vitamin K antagonists	162 (37)
Aspirin	224 (52)
Clopidogrel	141 (33)
<i>Baseline echocardiography</i>	
Valve anatomy, N (%)	
Tricuspid	400 (92)
Bicuspid	21 (5)
Biological valve prosthesis, N (%)	13 (3)
Peak transvalvular gradient (mmHg)	65.5±26.5
Mean transvalvular gradient (mmHg)	42.3±18.1
Aortic valve area (cm ²)	0.78±0.28
Left ventricular ejection fraction (%)	53.9±16.1
<i>Procedural variables</i>	
TAVR access route, N (%)	
Transfemoral	224 (52)
Transapical	210 (48)
Valve type, N (%)	
Edwards SAPIEN	117 (27)
Edwards SAPIEN XT	162 (37)
Edwards SAPIEN 3	115 (27)
Medtronic CoreValve	40 (9)
Prosthesis size, N (%)	
23 mm	121 (28)
26 mm	236 (55)
29 mm	77 (18)

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BSA, body surface area; NYHA, New York Heart Association functional classification; TAVR, transcatheter aortic valve replacement.

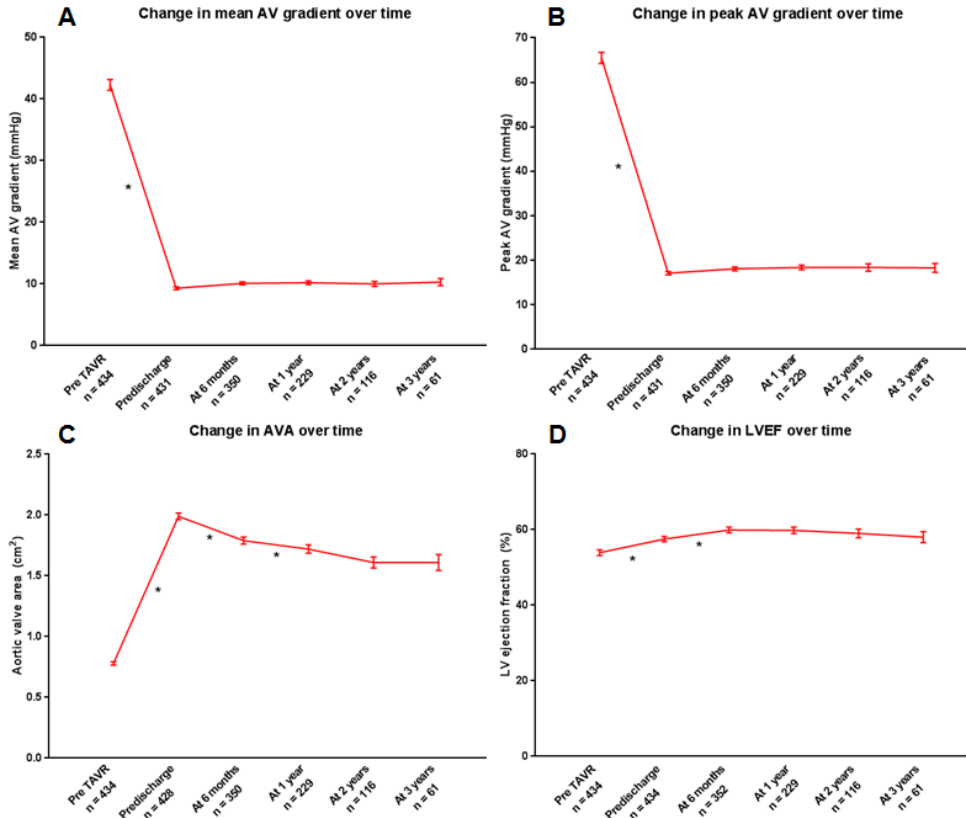


Figure 2: Echocardiographic follow-up for the overall population. Changes in mean and peak aortic valve gradients, aortic valve area and LVEF were analysed with linear mixed models. The means and standard error of the mean are presented. AV, aortic valve; AVA, aortic valve area; LV, left ventricular; LVEF, left ventricular ejection fraction. *Significant changes between time points ($P<0.05$).

Table 2: Echocardiographic characteristics of the entire patient population undergoing transcatheter aortic valve replacement (TAVR) over time.

Variables	Pre-TAVR (N = 434)	Pre-discharge (N = 431)	6 months (N = 350)	1 year (N = 229)
LVOT diameter (cm)	2.1±0.2	2.0±0.2	2.0±0.2	2.0±0.2
Stroke volume (ml)	71.4±22.0	72.5±21.8	76.4±22.4	75.2±22.5
Stroke volume index (ml/m ²)	38.9±11.9	39.4±11.3	41.6±12.1	40.5±11.3
Mean gradient (mmHg)	42.3±18.1	9.3±4.7	10.1±4.9	10.2±4.9
Peak gradient (mmHg)	65.5±26.5	17.1±8.1	18.1±8.2	18.4±8.3
Aortic valve area (cm ²)	0.78±0.28	1.99±0.56	1.79±0.54	1.73±0.52
LV ejection fraction (%)	53.9±16.1	57.5±14.7	59.9±13.9	59.8±12.9

LVOT, left ventricular outflow tract; LV, left ventricular; TAVR, transcatheter aortic valve replacement.

53.9±16.1% to 57.5±14.7%, $P<0.001$) (Figure 2).

According to current recommendations, abnormal valve hemodynamics (mean trans-valvular gradient ≥ 20 mmHg and aortic valve area ≤ 1.1 cm²) indicating possible transcatheter valve thrombosis were observed in 1 (0.2%) patient before discharge, 6 (2%) patients at 6 months, 4 (2%) at 1 year, 0 (0%) patients at 2 years, and 2 (3%) at 3 years follow-up. Worsening of paravalvular or transvalvular regurgitation to moderate regurgitation was observed in 17 (4%) patients at follow-up.

HALT OR REDUCED LEAFLET MOTION ON MDCT AT FOLLOW-UP

In a subgroup of 128 patients with analysable post-TAVR MDCT data, the presence of HALT and/or reduced leaflet motion was evaluated. The MDCT data were acquired at a median interval of 35 [interquartile range 19–210] days after TAVR (see Supplementary Figure 4). The presence of HALT and/or reduced leaflet motion was noted in 16 (12.5%) patients. Baseline clinical, echocardiographic, and procedural characteristics between patients showing HALT and/or reduced leaflet motion and patients without are presented in Tables 3 and 4. There were no statistically significant differences between both groups with the exception of diabetes mellitus which was more prevalent among patients without HALT compared to patients with HALT and/or reduced leaflet motion (32% vs. 6%, respectively; $P=0.033$). Importantly, there were no differences in anticoagulation use prior to MDCT (38 [30%] in the overall group, 35 [31%] in patients without HALT and 3 [19%] patients with HALT and/or reduced leaflet motion, $P=0.603$). Table 5 shows the post-TAVR MDCT characteristics in patients with and without HALT. Both groups were comparable in terms of stent expansion, eccentricity index at the inflow and outflow levels of the stent and valve implantation depth. Patients with HALT and/or reduced leaflet motion showed slightly more circular stent deployment at the mid-portion level as compared with patients without HALT (0.01 [0.01;0.01] vs. 0.01 [0.01;0.02], respectively; $P=0.041$).

CORRELATION BETWEEN ABNORMAL VALVE HEMODYNAMICS AND HALT

Concomitant presence of HALT and/or reduced leaflet motion and abnormal valve hemodynamics (defined by mean transvalvular gradient ≥ 20 mmHg and aortic valve area ≤ 1.1 cm²) suggesting valve thrombosis was observed in only one patient (Figure 1). Figure 3 presents the changes in echocardiographic parameters of transcatheter valve function at follow-up in patients with HALT on MDCT and patients without. Patients showing HALT and/or reduced leaflet motion on post-TAVR MDCT had higher peak and mean transvalvular gradients and smaller aortic valve area at follow-up as compared with patients without, but the difference was statistically significant only for the mean transvalvular gradient at 6 months follow-up (12.4±8.0 mmHg vs. 9.4±4.3 mmHg, respectively; $P=0.026$) and for the aortic valve area at the echocardiogram performed at the time of MDCT (1.49±0.39 cm² vs. 1.78±0.45 cm², respectively; $P=0.017$) and at 6 months (1.32±0.35 cm² vs. 1.76±0.49 cm², respectively; $P<0.001$). LVEF was comparable in both groups without significant differences over time. Similarly, both groups were comparable in terms of paravalvular regurgitation grade over time.

CORRELATION BETWEEN STROKE AND ECHOCARDIOGRAPHIC/MDCT FINDINGS

A total of 14 (3.2%) patients were diagnosed with stroke ($N = 9$)/TIA ($N = 5$) after TAVR. Possible transcatheter aortic valve thrombosis on echocardiography (mean transvalvular gradient ≥ 20 mmHg and aortic valve area ≤ 1.1 cm²) was not present in any of the patients diagnosed with stroke/TIA. Similarly, HALT and/or reduced leaflet motion was not observed on MDCT in any of the patients presenting with stroke/TIA. Table 6 shows the mean and peak transvalvular gradients, aortic valve area, and LVEF over time for patients with vs. without stroke/TIA. There were no differences in valve hemodynamics between patients with and without stroke/TIA (Table 6).

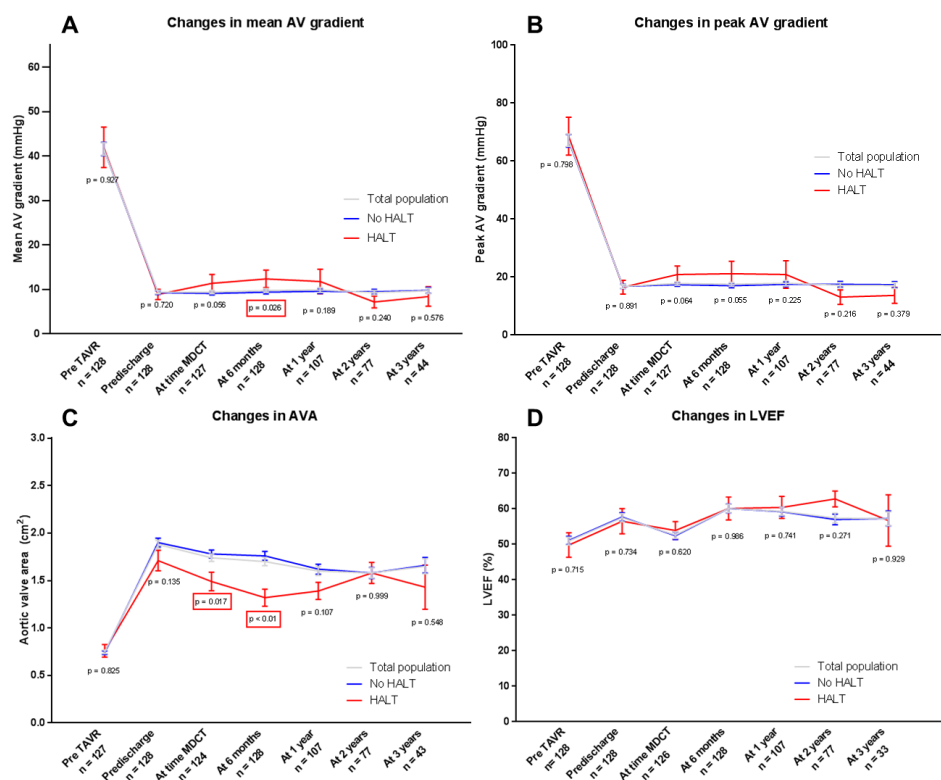


Figure 3: Echocardiographic follow-up of patients with and without evidence of hypo-attenuated leaflet thickening (HALT) and/or reduced leaflet motion on MDCT. Changes in mean and peak aortic valve gradients, aortic valve area and LVEF were analysed with linear mixed models. The means and standard error of the mean are presented. AV, aortic valve; AVA, aortic valve area; HALT, hypo-attenuated leaflet thickening; LVEF, left ventricular ejection fraction; MDCT: multi-detector row computed tomography. *P* values indicate differences between groups (HALT vs. no HALT).

Table 3: Baseline clinical characteristics of patients with and without hypo-attenuated leaflet thickening (HALT) and/or restrictive leaflet motion.

Variables	Patients with			<i>P</i> value
	post-TAVR MDCT (N = 128)	No HALT (N = 112)	HALT (N = 16)	
Female gender, <i>N</i> (%)	62 (48)	54 (48)	8 (50)	0.894
Age (years)	81±7	81±7	81±8	0.968
BSA (m ²)	1.75±0.3	1.77±0.3	1.62±0.3	0.084
Logistic EuroSCORE (%)	23±13	23±13	23±13	0.939
Creatinin level (μmol/ml)	86 [72;103]	88 [73;103]	77 [67; 103]	0.303
Coronary artery disease, <i>N</i> (%)	86 (67)	74 (66)	12 (75)	0.477
NYHA classification, <i>N</i> (%)				0.211
I-II	51 (40)	43 (38)	8 (50)	
III-IV	77 (60)	69 (62)	8 (50)	
Prior MI, <i>N</i> (%)	27 (21)	24 (21)	3 (19)	0.806
PCI within 30 days, <i>N</i> (%)	29 (23)	25 (22)	4 (25)	0.811
Prior thromboembolism, <i>N</i> (%)	4 (3)	4 (4)	0 (0)	0.442
History of cancer, <i>N</i> (%)	30 (24)	26 (23)	4 (25)	0.890
Diabetes, <i>N</i> (%)	37 (29)	36 (32)	1 (6)	0.033
Hypertension, <i>N</i> (%)	98 (77)	87 (78)	11 (69)	0.430
Hyperlipidemia, <i>N</i> (%)	76 (59)	68 (61)	8 (50)	0.414
History of smoking, <i>N</i> (%)	58 (45)	54 (48)	4 (25)	0.081
Previous stroke or TIA, <i>N</i> (%)	27 (21)	21 (19)	6 (38)	0.086
Atrial fibrillation, <i>N</i> (%)	37 (29)	33 (30)	4 (25)	0.713
Only anticoagulation therapy, <i>N</i> (%)	29 (23)	26 (23)	3 (19)	0.603
Anticoagulation + antiplatelet therapy, <i>N</i> (%)	9 (7)	9 (8)	0(0)	

BSA, body surface area; HALT, hypo-attenuated leaflet thickening; MDCT, multi-detector row computed tomography; MI, myocardial infarction; NYHA, New York Heart Association functional classification; PCI, percutaneous coronary intervention; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack.

Table 4: Baseline echocardiographic and procedural characteristics of patients with and without hypo-attenuated leaflet thickening (HALT) and/or reduced leaflet motion.

Variables	Patients with post-TAVR MDCT (N = 128)	No HALT (N = 112)	HALT (N = 16)	P value
<i>Baseline echocardiography</i>				
Valve anatomy, N (%)				0.589
Tricuspid	121 (94)	105 (94)	16 (100)	
Bicuspid	6 (5)	6 (5)	0 (0)	
Biological valve prosthesis	1 (1)	1 (1)	0 (0)	
Peak TV gradient (mmHg)	67.2±24.0	67.0±23.8	68.6±26.2	0.798
Mean TV gradient (mmHg)	41.6±16.1	41.6±15.9	42.0±18.2	0.927
Aortic valve area (cm ²)	0.75±0.22	0.74±0.21	0.76±0.26	0.825
LV ejection fraction (%)	50.9±12.7	51.1±12.6	49.8±13.9	0.715
Stroke volume (ml)	71.6±20.0	72.2±19.3	67.1±24.2	0.361
<i>Procedural variables</i>				
TAVR access route, N (%)				0.399
Transfemoral	44 (34)	37 (33)	7 (44)	
Transapical	84 (66)	75 (67)	9 (56)	
Valve type, N (%)				0.414
Edwards SAPIEN	76 (59)	68 (61)	8 (50)	
Edwards SAPIEN XT	52 (41)	44 (39)	8 (50)	
Edwards SAPIEN3	0 (0)	0 (0)	0 (0)	
Medtronic CoreValve	0 (0)	0 (0)	0 (0)	
Prosthesis size, N (%)				0.689
23 mm	38 (30)	33 (30)	5 (31)	
26 mm	85 (66)	74 (66)	11 (69)	
29 mm	5 (4)	5 (4)	0 (0)	
Post-dilatation performed, N (%)	20 (16)	17 (15)	3 (19)	0.713

HALT, hypo-attenuated leaflet thickening; MDCT, multi-detector row computed tomography; TAVR, transcatheter aortic valve replacement; TV, transvalvular.

Table 5: MDCT characteristics of patients with and without hypo-attenuated leaflet thickening (HALT) and/or reduced leaflet motion.

Variables	Patients with post-TAVR MDCT (N = 128)	No HALT (N = 112)	HALT (N = 16)	P value
Stent expansion (%)				
Inflow	102±7	102±7	98±6	0.060
Mid-portion	106±8	106±9	106±6	0.796
Outflow	109±9	109±9	110±8	0.590
Underexpansion, N (%)	3 (2.3)	3 (2.7)	0 (0)	0.508
Stent eccentricity index				
Inflow	0.01 [0.01;0.02]	0.01[0.01;0.02]	0.01[0.01;0.01]	0.126
Mid-portion	0.01 [0.01;0.02]	0.01[0.01;0.02]	0.01[0.01;0.01]	0.041
Outflow	0.01 [0.01;0.02]	0.01[0.01;0.02]	0.01[0.01;0.01]	0.360
Eccentric, N (%)	1 (0.8)	1 (0.9)	0(0)	0.704
Valve implant depth (mm)	5.1±1.8	5.1±1.8	5.1±2.0	0.947

HALT, hypo-attenuated leaflet thickening; MDCT, multi-detector row computed tomography; TAVR, transcatheter aortic valve replacement.

DISCUSSION

THE present study showed stable, normal hemodynamics and morphological features of transcatheter aortic valves during mid-term follow-up in a large cohort of patients treated with TAVR indicating good mid-term durability of these prosthetic valves. Only a mild, clinically irrelevant, decrease in aortic valve area was observed during the first year post-TAVR, while average transvalvular gradients remained within the normal range. Possible transcatheter valve thrombosis based on abnormal valve hemodynamics on echocardiography was rare (3% of patients at 3 years follow-up). Post-TAVR MDCT showed HALT and/or reduced leaflet motion in 12.5% of patients. In patients with HALT and/or reduced leaflet motion, echocardiographic transvalvular gradients were slightly higher and the aortic valve area was significantly smaller compared with patients without HALT. However, possible TAVR valve thrombosis by MDCT (presence of HALT and/or reduced leaflet motion) was only accompanied by abnormal valve hemodynamics on echocardiography (mean gradient ≥ 20 mmHg and aortic valve area ≤ 1.1 cm²) in one patient. These abnormal findings were not associated with an increased risk of ischemic stroke/TIA.

ECHOCARDIOGRAPHIC VALVE HEMODYNAMICS AFTER TAVR

Since TAVR is increasingly used as an alternative for surgical aortic valve replacement in intermediate- and low-risk patients, valvular prosthesis durability and structural integrity are important issues. Thrombosis of biological surgical aortic valves is a rare complication with a reported incidence ranging between 0.8% and 4% [23, 24]. In transcatheter aortic valve prostheses, the reported incidence of valve dysfunction and specifically thrombosis is low. Five-year follow-up data from the Placement of Aortic Transcatheter Valves (PARTNER) trial have shown stable valve hemodynamics in 348 high-risk patients

Table 6: Valve hemodynamics over time for patients with versus without stroke/TIA.

Variable	Stroke/TIA	Pre-TAVR (N = 434)	Pre-discharge (N = 431)	6 months (N = 350)	1 year (N = 229)	2 years (N = 116)	3 years (N = 61)
Mean gradient (mmHg)	Non stroke	42.4±18.2	9.3±4.7	10.1±4.9	10.2±5.0	10.0±4.7	10.3±4.6
	Stroke/TIA	40.3±17.0	9.1±3.4	11.0±4.5	9.0±3.1	9.6±4.8	11.2±5.2
Peak gradient (mmHg)	Non stroke	65.5±26.5	17.1±8.2	18.0±8.2	18.5±8.4	18.5±8.9	18.3±7.7
	Stroke/TIA	63.6±25.9	16.8±6.4	18.7±8.7	15.9±4.4	17.3±8.7	17.7±8.5
Aortic valve area (cm ²)	Non stroke	0.79±0.28	1.99±0.56	1.79±0.54	1.73±0.52	1.60±0.50	1.61±0.50
	Stroke/TIA	0.72±0.23	2.00±0.60	1.70±0.50	1.73±0.54	1.71±0.63	1.60±0.72
LV ejection fraction (%)	Non stroke	53.9±16.1	57.4±14.6	59.8±13.9	59.8±12.9	59.0±12.3	58.7±11.2
	Stroke/TIA	53.2±17.3	58.5±16.4	62.3±14.2	57.4±15.2	58.9±16.6	48.3±13.7

LV, left ventricular; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack.

(mean transvalvular gradient was 10.7 mmHg and aortic valve area was 1.6 cm²) without occurrence of structural valve deterioration requiring surgical valve replacement [10, 11]. Similarly, Barbanti et al. [8] showed only a slight increase of mean transvalvular gradient (12.8±10.9 mmHg) 5 years after self-expanding transcatheter valve implantation in 353 high-risk patients. Late prosthesis failure occurred in 1.4% and was defined as symptomatic prosthesis stenosis, endocarditis, and severe transvalvular or paravalvular regurgitation. Mild prosthesis stenosis, defined by a mean gradient between 20 and 40 mmHg, was observed in 2.8% of patients [8]. Data from a multicentre study including 1521 patients treated with self-expandable (49.7%) and balloon-expandable prostheses (48.5%) reported an incidence of structural valve degeneration of 4.5% at 2 years of follow-up [25]. The relatively high incidence of valve degeneration in that registry compared with previous studies can be explained by the definition itself: absolute increase in mean transvalvular gradient ≥10 mmHg. An increase in mean transvalvular gradient ≥10 mmHg during follow-up can be caused by changes in loading conditions, stroke volume, or increase in body mass index leading to increased prosthesis–patient mismatch and not necessarily because of valve thrombosis or stenosis. Current recommendations define transcatheter aortic valve stenosis potentially caused by valve thrombosis when the mean transvalvular gradient is ≥20 mmHg and the aortic valve area is ≤1.1 cm² on echocardiography [20]. In the present study, aortic valve area and transvalvular aortic gradients remained stable during 3 years follow-up and 3% of the population showed abnormal valve hemodynamics at 3 years follow-up, consistent with previous studies. Therefore, based on echocardiographic criteria, transcatheter aortic valves appear to have good durability.

HALT AND/OR ABNORMAL LEAFLET MOTION ON MDCT, AND RELATION WITH ECHOCARDIOGRAPHIC VALVE HEMODYNAMICS

The high-spatial resolution of MDCT data has shown that abnormal leaflet motion with apposition of hypo-attenuated masses (HALT) in surgical and transcatheter valves may be more frequent than expected. Leetmaa et al. [13] observed low-attenuation masses attached to prosthetic valve leaflets on post-TAVR MDCT in 4% of patients (5/140). Pache et al. [15] reported a 10.3% (16/156 patients) prevalence of HALT after TAVR. Makkar et al. [14] evaluated the presence of leaflet motion and HALT using 4-dimensional MDCT in a clinical trial including 55 patients undergoing TAVR and two registries with 132 patients undergoing either TAVR or surgical aortic valve replacement. HALT was noted in 40% (22/55) of patients in the clinical trial, while it was only present in 13% (17/132) of patients included in the registries [14]. The factors associated with higher risk of developing HALT are still unclear. Reduced LVEF has been associated with higher prevalence of HALT [13], whereas use of anticoagulation has been associated with lower prevalence of HALT [14]. Importantly, adding anticoagulants to antiplatelet therapy resolved HALT and reduced leaflet motion rapidly [15]. Other procedural factors such as prosthesis frame deployment were not associated with HALT [14, 15]. Nevertheless, the relation between HALT and valve hemodynamics at short- and long-term follow-up remains unclear. The majority of the patients showing HALT did not have increased mean transvalvular gradients ≥20 mmHg or decreased aortic valve area ≤1.1 cm² (the echocardiographic definitions of possible prosthetic valve thrombosis) [13–15, 26]. In the present

study, the incidence of HALT on MDCT was 12.5%, comparable with previous studies [13, 15, 26]. The patients with HALT had a slightly more circular deployment of the transcatheter valve frame compared with those without HALT. The present study provides additional information by reporting transcatheter aortic valve hemodynamics at mid-term follow-up. Although there was a mild change in valve hemodynamics with an increase in both mean and peak transvalvular gradients and a significant decrease in aortic valve area in patients with HALT and/or reduced leaflet motion shortly after TAVR compared with their counterparts, concomitant mean transvalvular gradient ≥ 20 mmHg and aortic valve area ≤ 1.1 cm² was anecdotally observed during the 3 years of follow-up (1 patient). Therefore, the HALT and/or reduced leaflet motion on MDCT was not accompanied by functional echocardiographic criteria of thrombosis.

CLINICAL IMPLICATIONS OF HALT

While surgical prosthetic aortic valve thrombosis is associated with an increased risk of stroke [23, 24], this association is not consistently observed with the presence of HALT on transcatheter aortic valve prostheses [13–15]. The reported rates of stroke and TIA in the Cohort A PARTNER trial ranged from 5.5% to 8.3% at 30 days and 1-year follow-up, respectively, and to 15.9% at 5 years follow-up [3, 11]. In the NOTION (Nordic Aortic Valve Intervention) trial, randomizing low surgical risk patients to TAVR or surgical aortic valve replacement, the rates of stroke and TIA were, respectively, 2.9% and 2.1% at 1-year follow-up [6]. In these trials, no structural valve degeneration was observed and valve hemodynamics remained stable over time. Therefore, these results suggest that the source of stroke/TIA may not primarily be related to the transcatheter valve or that the echocardiographic findings may not be sensitive enough to detect early structural changes of the valve before they present with increased gradients and that can cause embolic events. The use of MDCT showing the presence of HALT and reduced leaflet motion of transcatheter valves has questioned these assumptions. Similar to previous studies, patients in the present study who showed HALT and/or reduced leaflet motion on MDCT did not develop stroke/TIA at follow-up. However, the use of anticoagulation has been shown to restore the normal leaflet aspect and motion in patients who presented with HALT [14, 15] and it could be considered to perform MDCT in these patients for early detection of these structural changes. However, it remains unknown when and in whom the MDCT should be performed and if it should be systematically included in the surveillance of TAVR patients. The important associated risks of MDCT such as renal deterioration associated with the use of contrast and cumulative radiation should be weighed against the risk of stroke/TIA in elderly patients with associated comorbidities and, in the future, in younger patients. Current guidelines recommend transthoracic echocardiography within 6 weeks–3 months after implantation of bioprostheses, when there are changes in the clinical symptoms or signs of valve dysfunction and yearly after 5–10 years of bioprosthesis implantation even if there are no changes in the patient's clinical condition [27, 28]. Specific recommendations for follow-up in patients treated with TAVR have not been defined yet. The cumulative evidence provided by registries and ongoing randomized clinical trials will have an impact on current recommendations [27, 28].

STUDY LIMITATIONS

Several limitations should be acknowledged. This was a retrospective, single-centre study. MDCT after TAVR was performed in a relatively small subgroup of patients. This may have introduced a selection bias. In addition, the findings observed on the MDCT scans relate to previous generations of transcatheter valves and may not be generalizable to newer aortic valve prostheses (Edwards SAPIEN 3 and Medtronic CoreValve Evolut R). Furthermore, the vast majority of patients received a balloon-expandable prosthesis. Patients who deceased during follow-up may have died due to transcatheter valve thrombosis which may underestimate the true incidence of this complication. Assessment of reduced leaflet motion with MDCT may be challenging due to the low temporal resolution of the technique.

CONCLUSION

TRANSCATHETER aortic valves showed good mid-term durability with low rates of abnormal valve hemodynamics at 3 years follow-up. The rate of possible valve thrombosis based on echocardiographic criteria was low (3% at 3 years follow-up). MDCT detected HALT and/or reduced leaflet motion in 12.5% of patients. Only one patient with HALT presented with abnormal valve hemodynamics (the echocardiographic criterium of valve thrombosis). Importantly, both HALT and abnormal valve hemodynamics were not associated with increased risk of ischemic stroke/TIA in the current population.

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SUPPLEMENTARY MATERIAL

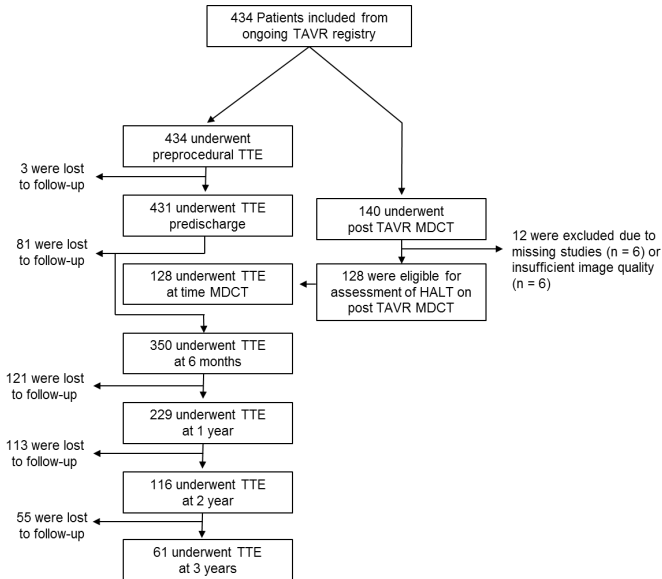


Figure 4: Patient flow chart. HALT, hypo-attenuated leaflet thickening; MDCT, multi-detector row computed tomography; TAVR, transcatheter aortic valve replacement; TTE, transthoracic echocardiogram.

Table 7: Post-procedural outcomes of entire patient population undergoing transcatheter aortic valve replacement (TAVR).

Postprocedural outcomes	Total population (N = 434)
Mortality (within 30 days), N (%)	24(6)
Vascular injury, N (%)	
Minor	34 (8)
Major	20 (5)
Bleeding, N (%)	
Minor	35 (8)
Major	22 (5)
Stroke and TIA, N (%)	
Stroke	9 (2)
TIA	5 (1)
Acute kidney injury (stage 1-3), N (%)	22 (5)
Conduction disturbances and arrhythmias, N (%)	
New high-grade atrioventricular block needing pacemaker implantation	37 (9)
Cardiac tamponade, N (%)	10 (2)
Myocardial infarction (<72 h after the procedure), N (%)	1 (0.2)
Valve migration, N (%)	2 (0.4)
Prosthetic dysfunction, N (%)	
Severe AR needing valve-in-valve procedure	3 (0.7)

AR, aortic regurgitation; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack.

