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Left atrial appendage thrombus and cerebrovascular events post-transcatheter aortic valve implantation

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Aims To elucidate the frequency and clinical impact of left atrial appendage thrombus (LAAT) in patients set for transcatheter aortic valve implantation (TAVI).

Methods and results All patients undergoing TAVI between January 2014 and June 2020 with analysable multislice computed tomography (MSCT) for LAAT were included. Baseline and procedural characteristics were collected, pre-procedural MSCT's were retrospectively analysed for LAAT presence. The primary endpoint was defined as the cumulative incidence of any cerebrovascular event (stroke or transient ischaemic attack) within the first year after TAVI. A Cox proportional hazards model was used to identify predictors.

A total of 1050 cases had analysable MSCT. Median age was 80 [interquartile range (IQR) 74–84], median Society of Thoracic Surgeons' Predicted Risk Of Mortality (STS-PROM) was 3.4% (IQR 2.3–5.5). Thirty-six percent were on oral anticoagulant therapy for atrial fibrillation (AF). LAAT was present in 48 (4.6%) of cases. Patients with LAAT were at higher operative risk [STS-PROM: 4.9% (2.9–7.1) vs. 3.4% (2.3–5.5), $P = 0.01$], had worse systolic left ventricular function [EF 52% (35–60) vs. 55% (45–65), $P = 0.01$] and more permanent pacemakers at baseline (35% vs. 10%, $P < 0.01$). All patients with LAAT had a history of AF and patients with LAAT were more often on vitamin K antagonist-treatment than patients without LAAT [43/47 (91%) vs. 232/329 (71%), $P < 0.01$]. LAAT [hazard ratio (HR) 2.94 (1.39–6.22), $P < 0.01$] and the implantation of more than one valve [HR 4.52 (1.79–11.25), $P < 0.01$] were independent predictors for cerebrovascular events.

Conclusion Patients with MSCT-identified LAAT were at higher risk for cerebrovascular events during the first year after TAVI.

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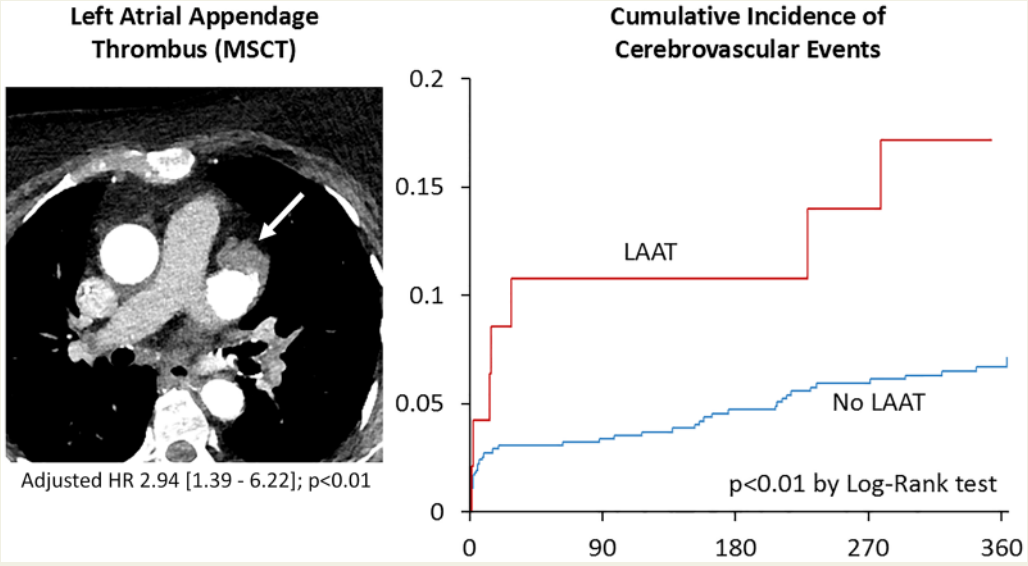
Graphical Abstract



Graphical Abstract Multislice computed tomography detected left atrial appendage thrombus is an independent predictor for cerebrovascular events within the first year after transcatheter aortic valve implantation.

Keywords computed tomography • transcatheter aortic valve implantation • left atrial appendage • stroke • TIA

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is present in over 8% of patients aged 80 years and older.[1] Due to AF there is stasis and reduced contractility in the left atrial appendage (LAA), resulting in thrombi that might migrate to the brain leading to stroke or transient ischaemic attack (TIA). Transoesophageal echocardiography (TOE) studies have shown a 17% prevalence of atrial thrombi in non-valvular AF, of which 91% were located in the LAA.[2,3] Patients undergoing transcatheter aortic valve implantation (TAVI) are typically older with a high prevalence of established AF risk factors, the likes of hypertension, coronary- and peripheral artery disease.[4,5] Consequently, AF is common in patients with severe aortic stenosis ranging from 17% to 30% depending on the profile at risk.[6,7]

Cerebrovascular events within 30 days after TAVI occur in approximately 3% of patients and are associated with increased mortality.[8] Therapies aiming at reducing stroke after TAVI include cerebral embolic protection and optimized antithrombotic strategies; nonetheless, the incidence of periprocedural stroke has remained stable.[9–12]

Multislice computed tomography (MSCT) angiography is standard in the pre TAVI work up and includes a dual phased acquisition of the left atrium. It has been shown that LAA thrombus (LAAT) is present in 11% of TAVI patients with a 100% sensitivity and 98% specificity compared to TOE.[13] The increased risk for stroke in patients with LAAT has been well established, but it is unknown whether it is safe for these patients to undergo TAVI. We aimed to assess the incidence of LAAT and impact on cerebrovascular events in patients undergoing TAVI.

Methods

Study population

All consecutive patients that underwent attempted TAVI from January 2014 until June 2020 at our institution were included in the analysis. Patients in whom the LAA could not be analysed by MSCT were excluded. For repeat procedures (e.g. staged TAVI after balloon aortic valvuloplasty) patients were included upon the second (final) procedure. All patients consented to the procedure and subsequent data analysis for research purposes. All data were prospectively collected and stored in a secured database. The study was conducted in accordance with the declaration of Helsinki and did not fall under the scope of the Medical Research Involving Human Subjects Act per Institutional Review Boards' review.

Study procedures

Standard work-up of patients referred for aortic valve intervention included clinical examination by an interventional cardiologist, electrocardiography, echocardiography, and MSCT analysis of aortic valve, aortic root, and peripheral access. All patients were discussed in the multidisciplinary heart team including a cardiothoracic surgeon, interventional cardiologist, imaging specialist, and a geriatrician. Up to August 2015, all procedures were performed under general anaesthesia, hereafter local anaesthesia became the default approach. Patients received a 300 mg clopidogrel loading dose after the procedure, except for patients who underwent concomitant percutaneous coronary intervention and patients already on clopidogrel therapy. For patients receiving direct oral anticoagulants (DOACs), therapy was interrupted 24 h prior to the procedure. Sentinel embolic protection (Boston Scientific, Marlborough, MA, USA) was inserted when feasible according to manufactures'

instructions for use. Heparin administration during the procedure targeted an activated clotting time of 250 s. Over the years, post-TAVI antithrombotic regimen changed, limiting dual antiplatelet therapy to 3 months and avoiding antiplatelet therapy on oral anticoagulant (OAC). Patients had follow-up visits at 30 days and at 1-, 3-, and 5 years after the procedure and events were adjudicated according to latest valve academic research consortium (VARC) definitions.[14]

Computed tomography scan protocol

MSCT scans were performed with a third-generation dual source computed tomography (CT) scanner (SOMATOM Force, SOMATOM Drive, and SOMATOM Flash Siemens, Erlangen, Germany). The image acquisition included three consecutive scans: (i) a non-enhanced prospectively electrocardiogram (ECG)-triggered scan of the valve region, (ii) a prospectively ECG-triggered sequential CT angiography (CTA) of the heart in systole (20–50% of the cardiac cycle with reconstructions at 5% of the R-R interval), and (iii) a low-dose high-pitch CTA of the entire chest and abdomen (*Figure 1*). All reconstructions were made with an increment of 0.4 mm, slice thickness of 0.75 mm in Bv40 kernel and iterative reconstruction (Admire level 3, Siemens).

A single biphasic contrast administration protocol consisting of 45 mL of contrast (Visipaque 320®, GE Healthcare, Cork, Ireland) was injected at a rate of 3.0 mL/s, followed by 25 mL of contrast at 2.5 mL/s and a saline flush of 30 mL at 2.5 mL/s.

CT image analysis

Assessment of CT examinations was performed on a dedicated PACS workstation (Philips IntelliSpace Enterprise 4.4). The presence of thrombus was defined as a persistent homogeneous filling defect with a well-defined border in both the arterial and delayed acquisition, not caused by artefact or normal cardiac structures (*Figure 2*). All CT's were analysed by a single radiologist with 5 years of experience interpreting cardiac CT. Scans that were equivocal, were double read by another radiologist with 15 years of experience with cardiac CT. All radiologists were blinded for clinical outcomes.

Outcomes and definitions

The primary outcome of the study was the cumulative incidence of cerebrovascular events (including TIA, haemorrhagic, and ischaemic stroke) during the first year after TAVI. The secondary outcome was all-cause mortality. Median aortic valve Agatston scores were determined excluding cases that had a bioprosthesis *in situ*. The first attempted transcatheter heart valve (THV) was reported for patients who had more than one valve implanted.

Statistical analysis

Continuous variables were presented as median with interquartile range (IQR), categorical variables were presented as counts and percentages. Baseline and procedural characteristics were compared using a Mann–Whitney *U* test or Pearson Chi-square/Fisher's exact test. The cumulative incidence of cerebrovascular events and all-cause mortality was stratified according to the presence of LAAT and compared using a log-rank test.

We performed a Cox proportional hazards model to identify predictors for cerebrovascular events during the first year of follow-up. In addition to age, gender, CHA_2DS_2Vasc score, and surgical risk score, we included variables that had a *P*-value < 0.05 on univariate analysis. Variable selection for the univariate analysis was based on clinical perspective. Statistical analyses were performed using Statistical Package for Social Science for Windows version 25.0 (IBM Corporation, Chicago, IL, USA) or R statistical software version 4.0.0 (Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

From January 2014 until June 2020, 1146 patients underwent attempted TAVI. A total of 1050 patients had a CT of sufficient quality to evaluate the presence of LAAT. Median age was 80 (IQR 74–84), median body mass index was 26.4 kg/m^2 (IQR 23.7–30.0), and median Society of Thoracic Surgeons' Predicted Risk Of Mortality (STS-PROM) was 3.4% (IQR 2.3–5.5).

LAAT was present in 48 of 1050 cases (4.6%). Patients with LAAT were at higher operative risk [STS-PROM: 4.9% (2.9–7.1) vs. 3.4% (2.3–5.5), $P = 0.01$], had worse systolic left ventricular function [EF 52% (35–60) vs. 55% (45–65), $P = 0.01$] and more permanent pacemakers at baseline (35% vs. 10%, $P < 0.01$).

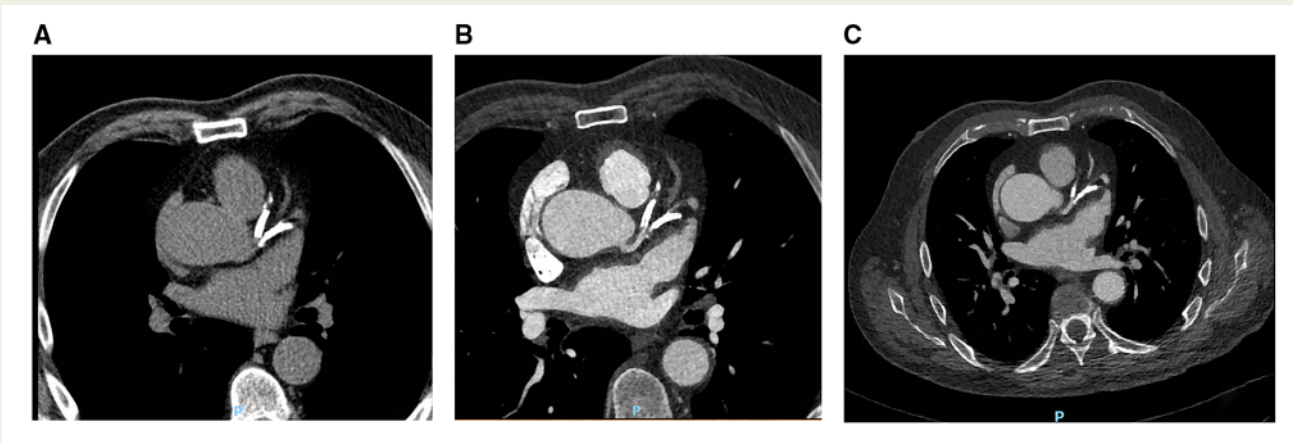


Figure 1 CT image acquisition includes three consecutive scans. Non-enhanced ECG-triggered scan (*A*) and ECG-triggered CT angiography (*B*) of the heart; and a low-dose high-pitch CT angiography oh the entire chest and abdomen (*C*).

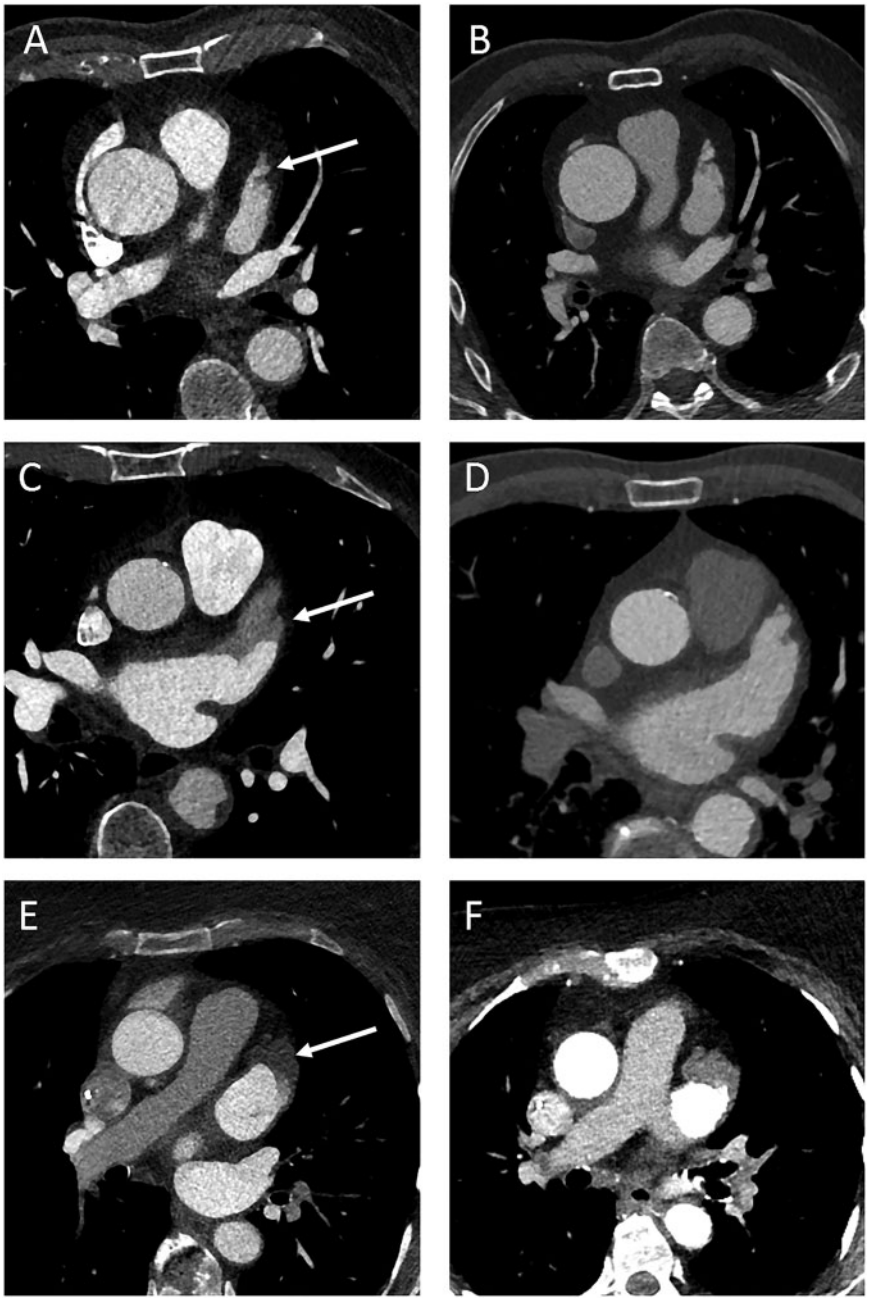


Figure 2 CT analysis. *Upper panel*: patent left atrial appendage in both the arterial (*A*) and delayed acquisition (*B*). *Middle panel*: slow flow/no atrial appendage thrombus with a filling defect in the arterial acquisition (*C*) not persisting in the delayed acquisition (*D*). *Bottom panel*: left atrial appendage thrombus with a filling defect in both the arterial (*E*) and delayed acquisition (*F*).

All patients with LAAT had a history of AF, compared to 29% of patients without LAAT. Patients with LAAT were either receiving OAC monotherapy (90%), OAC and single antiplatelet therapy (6%), or OAC and double antiplatelet therapy (2%). One patient with LAAT only started OAC after TAVI. In patients with a pre-existing indication for OAC therapy, patients with LAAT were more often on vitamin K antagonist (VKA)-treatment than patients without LAAT [43/47 (91%) vs. 232/329 (71%), $P < 0.01$] (*Table 1*).

Procedural characteristics

There were no differences in procedural characteristics between the patients with or without LAAT. The majority of patients were treated with either the Sapien3 (Edwards Lifesciences, Irvine, CA, USA) balloon expandable THV or the self-expanding Evolut R/Pro (Medtronic, Fridley, MN, USA) THV: 37% and 36%, respectively. Two percent of patients required more than one valve. Embolic protection was used in 48% of patients, with no difference between

Table 1 Baseline characteristics

	Overall (n = 1050)	LAAT present (n = 48)	LAAT absent (n = 1002)	P-value
Age (years)	80 (74–84)	83 (73–86)	80 (74–84)	0.21
Male gender	566 (54)	29 (60)	537 (54)	0.44
Body mass index (kg/m^2)	26.4 (23.7–30.0)	25.8 (23.4–28.8)	26.4 (23.7–30.1)	0.24
Society of Thoracic Surgeons' score (%)	3.4 (2.3–5.5)	4.9 (2.9–7.1)	3.4 (2.3–5.5)	0.01
Creatinine (mg/dL)	1.1 (0.9–1.4)	1.2 (1.0–1.5)	1.1 (0.9–1.4)	0.08
Agatston score aortic valve[a]	2702 (1843–3905)	2725 (1902–3669)	2702 (1842–3939)	0.95
LV ejection fraction (%)[b]	55 (45–64)	52 (35–60)	55 (45–65)	0.01
Atrial fibrillation	342 (33)	48 (100)	294 (29)	<0.01
CHA_2DS_2-Vasc score	4 (3–5)	4 (3–5)	4 (3–5)	0.62
Hypertension	794 (76)	35 (73)	759 (76)	0.78
Type 1 or 2 diabetes	329 (31)	14 (29)	315 (31)	0.86
Peripheral artery disease	417 (40)	21 (44)	396 (40)	0.66
Antithrombotic regimen pre-TAVI				
None	237 (23)	1 (2)	236 (24)	
Single antiplatelet	345 (33)	0 (0)	345 (34)	
Double antiplatelet	92 (9)	0 (0)	92 (9)	
OAC + single antiplatelet	70 (7)	3 (6)	67 (7)	
OAC + double antiplatelet	14 (1)	1 (2)	13 (1)	
OAC alone	292 (28)	43 (90)	249 (25)	
VKA/(DOAC+VKA)	275/376 (72)	43/47 (91)	232/329 (71)	<0.01
Permanent pacemaker in place	117 (11)	17 (35)	100 (10)	<0.01
Prior CABG	161 (15)	7 (15)	154 (15)	1.00
Prior PCI	303 (29)	11 (23)	292 (29)	0.44
Prior AVR	53 (5)	2 (4)	51 (5)	1.00
Prior stroke	113 (11)	6 (13)	107 (11)	0.87
Prior TIA	131 (12)	9 (19)	122 (12)	0.26

Categorical variables are presented as numbers (percentage), continuous variables are presented as median (IQR).
AVR, aortic valve implantation; CABG, coronary artery bypass grafting; LAAT, left atrial appendage thrombus; LV, left ventricular; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation; TIA, transient ischaemic attack.
[a]Available in 893/1050 of cases.
[b]Available in 1034/1050 of cases.

LAAT and non-LAAT patients (42% vs. 48%, $P = 0.46$). Total contrast use was 90 mL (IQR 80–120) and total procedural time was 87 min (IQR 59–139) (*Table 2*).

Outcomes

Overall, 61 patients suffered a cerebrovascular event: 14 (23%) disabling stroke, 17 (28%) non-disabling stroke, and 27 (44%) TIA. Three patients (5%) suffered a haemorrhagic stroke. There were 8 cerebrovascular events in the LAAT group vs. 53 in the control group. The cumulative incidence of cerebrovascular events at 12 months of follow-up was higher in the LAAT group compared to control (20.6% vs. 7.1%, $P < 0.01$ by log rank) (*Figure 3A*).

One year all-cause mortality rates were similar in patient with vs. without LAAT (cumulative incidence 15.9% vs. 15.4%, $P = 0.61$ by log rank) (*Figure 3B*).

A total of 20 cerebrovascular events (33%) occurred within 48 h, 15 events (25%) occurred between 48 h and 30 days, and 26 cases (43%) thereafter. Periprocedural stroke (<48 h) occurred in 2 (4.2%) of LAAT patients and in 18 (1.8%) patients without LAAT.

By multivariate Cox regression LAAT and >1 THV implanted were associated with cerebrovascular events during the first year of follow-up [hazard ratio (HR) 2.94 (1.39–6.22), $P < 0.01$ and HR 4.48 (1.79–11.25), $P < 0.01$ respectively], independent of age, gender, STS- and CHA_2DS_2-Vasc scores (*Table 3*).

Five out of the 27 patients (19%) with more than one valve implanted suffered a stroke, all within 48 h after the procedure. Three patients had thrombo-embolic stroke, one patient had a haemorrhagic stroke, and one patient suffered from stroke due to late occlusion of the brachiocephalic trunk by the migrated THV.

Table 2 Procedural characteristics

	Overall (*n* = 1050)	LAAT present (*n* = 48)	LAAT absent (*n* = 1002)	*P*-value
Non-femoral access	82 (8)	3 (6)	82 (8)	1.00
THV implanted				0.14
No valve implanted	5 (1)	1 (4)	4 (0.4)	
Sapien3	386 (37)	26 (53)	360 (36)	
Evolut R	237 (23)	10 (20)	227 (23)	
Evolut Pro	135 (13)	2 (4)	133 (13)	
Acurate NEO	53 (5)	1 (2)	52 (5)	
Lotus Edge	197 (19)	6 (12)	191 (19)	
Other[a]	37 (4)	2 (4)	35 (3)	
Valve size (mm)	26 (25–29)	26 (26–29)	26 (25–29)	0.84
>1 valve implanted	26 (2)	3 (6)	23 (2)	0.11
Embolic protection used	503 (48)	20 (42)	483 (48)	0.46
Total heparin use (IU)[b]	7500 (5000–8500)	7500 (5000–7500)	7500 (5000–8500)	0.52
Total contrast (mL)[c]	90 (80–120)	88 (70–125)	90 (80–120)	0.56
Procedural time (min)	87 (59–139)	109 (61–152)	86 (58–138)	0.19

Categorical variables are presented as numbers (percentage), continuous variables are presented as median (IQR).
BAV, balloon aortic valvuloplasty; THV, transcatheter heart valve.
[a]Including Corevalve, Portico, Jenavalve.
[b]Available in 1039/1050 of cases.
[c]Available in 1019/1050 of cases.

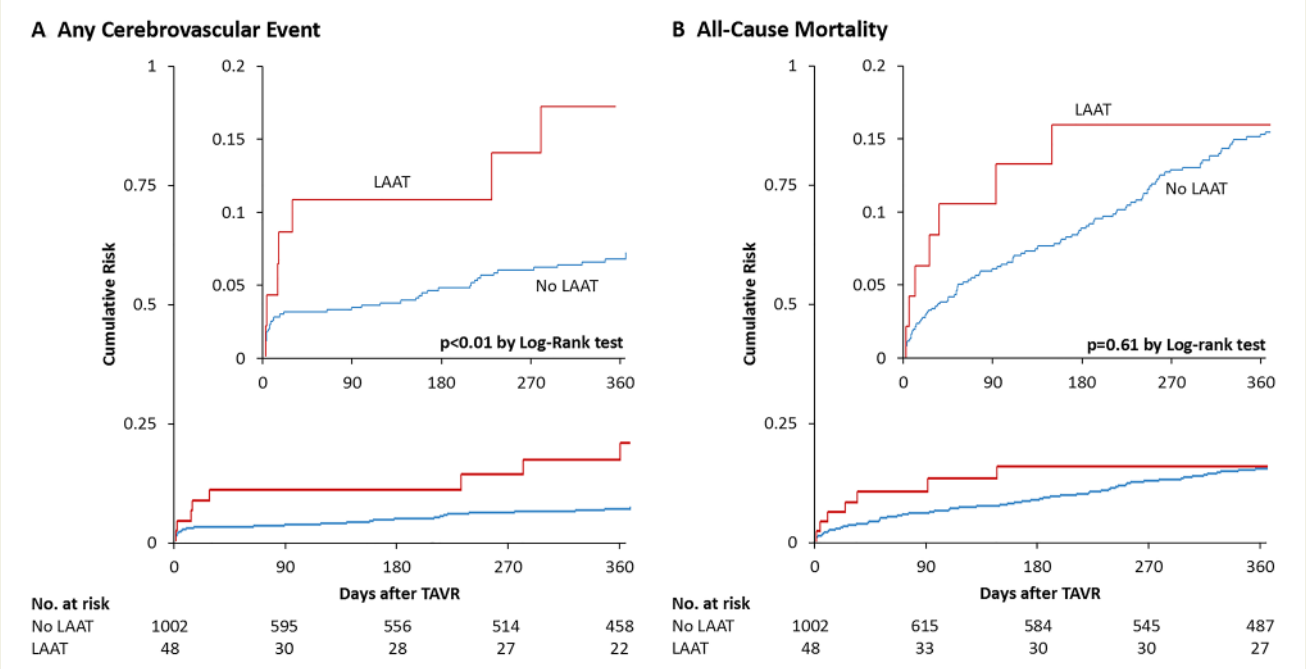


Figure 3 Cumulative risk and time-to-event Kaplan–Meier curves for cerebrovascular events (*A*) and all-cause mortality (*B*) during the first year after TAVI. Insets show the same data on an enlarged *y* axis. LAAT, left atrial appendage thrombus.

A full list and description of cerebrovascular events during the first year of follow up, as well as tables depicting stroke timing and severity stratified by thrombus presence and THV design are available in the supplementary section.

Discussion

To our knowledge, this is the largest study to look at clinical implications of MSCT detected LAAT after TAVI. Our main findings are: (i)

Table 3 Cox proportional hazards model: cerebrovascular events during first year post-TAVI

n = 1050	Unadjusted			Adjusted		
Variable	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Agatston score (per 1000 units increase)	1.12	(0.96–1.31)	0.15			
Age (per year increase)	1.02	(0.98–1.05)	0.29	1.02	(0.98–1.06)	0.42
Atrial fibrillation	1.36	(0.81–2.27)	0.25			
BMI (per kg/m^2 increase)	0.99	(0.94–1.04)	0.74			
CHA_2DS_2-Vasc score (per point increase)	1.05	0.85–1.29)	0.68	1.04	(0.81–1.33)	0.77
Creatinin (per mg/dL increase)	1.01	(0.77–1.32)	0.94			
Ejection fraction (per % increase)	1.00	(0.98–1.02)	0.87			
Embolic protection used	0.81	(0.49–1.34)	0.41			
Hypertension	1.24	(0.66–2.34)	0.50			
LAA thrombus on MSCT	3.11	(1.48–6.55)	<0.01	2.94	(1.39–6.22)	<0.01
Male gender	0.73	(0.43–1.22)	0.22	0.70	(0.40–1.21)	0.70
Non-femoral access	1.35	(0.58–3.14)	0.48			
Peripheral artery disease	1.43	(0.86–2.36)	0.16			
Rapid pacing performed during procedure	0.92	(0.55–1.54)	0.74			
STS-score (per % increase)	1.03	(0.95–1.10)	0.50	1.01	(0.93–1.10)	0.82
≥1 valve implanted	4.64	(1.85–11.58)	<0.01	4.52	(1.79–11.25)	<0.01

Univariate- and multivariate cox regression for cerebrovascular events post-TAVI.
BMI, body mass index; CI, confidence interval; HR, hazard ratio; LAA, left atrial appendage; MSCT, multislice computed tomography; STS, Society of Thoracic Surgeons.

LAAT was present in 4.6% of patients undergoing TAVI, (ii) patients with LAAT were at higher risk for cerebrovascular events within the first year of follow-up, (iii) besides LAAT, the implantation of more than one valve was an independent predictor for cerebrovascular events, and (iv) in patients with LAAT, the proportion of patients on DOAC was lower compared to control.

Previous analyses with LAAT have focused mainly on patients undergoing ablation for AF and found incidences of LAAT on TOE ranging from 0.8% to 5.5%.[15–17] Although our study pertains to a different study population and a different imaging modality, the 4.6% rate of LAAT is well in range with previous findings. There is one study that evaluated pre-TAVI patients and found an 11% incidence of LAAT on MSCT, but this was in a small sample size ($n = 113$) of patients at higher operative risk (EUROscore II 12.3%).[13] Compared to TOE, MSCT is less invasive, has high negative predictive value in excluding LAA thrombi and can adequately assess LAA size and morphology.[2,18] Downside of MSCT in detecting LAAT is that it requires contrast and ECG-synchronized imaging in an arterial and delayed phase and therefore a higher radiation dose (*Figure 4*).

AF is undeniably associated with stroke: the Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT)that enrolled subjects over 65 years old with a history of hypertension, reported subclinical AF in 35% of patients, which was associated with increased stroke risk (HR 2.50, $P = 0.0008$).[19] Besides the 'traditional' pathophysiological mechanism of thrombus formation in the LAA and subsequent migration to the brain causing stroke, mechanisms of atrial cardiomyopathy and LAA dysfunction—independent of AF—have been suggested.[20,21] In this trial, the TAVI procedure was a luxating moment for stroke in patients with LAAT, but it is questionable whether the cerebrovascular events occurred because of mechanical disruption of the thrombus due to wire manipulation, rapid pacing, or dysrhythmias. Unfortunately, the number of events in the LAAT group was too small to perform an additional landmark analysis at 48 h. There is a stroke risk inherent to the procedure itself, but also due to an increased thrombogenic state because of OAC interruption, immobilization, and nosocomial infections. Interestingly, patients with LAAT were more often on VKA-treatment than patients without LAAT [43/47 (91%) vs. 232/329 (71%), $P < 0.01$]. Although prone to selection bias, this might have contributed to the increased stroke rate because of issues around bridging, restarting and time in therapeutic range with coumadin therapy. The cause and effect relation between LAAT and cerebrovascular events remains unclear, that said LAAT at least qualifies as a marker for higher risk of cerebrovascular events. Conceivably, patients on coumadin with LAAT could be switched to DOAC to mitigate the risk for cerebrovascular events at 1 year.

Besides LAAT, patients with more than one THV implanted were at increased risk for cerebrovascular events [adjusted HR 4.49 (1.79–11.25), $P < 0.01$]. Extensive wire and catheter manipulations, frequent post-dilatation and higher incidence of hypo-attenuated leaflet thickening might explain this association.[22] In one patient stroke occurred due to direct obstruction of the brachiocephalic trunk by the migrated THV, but in the other patients, there was no clear obstruction, implying a thromboembolic cause. Previous studies have shown that prior stroke, chronic kidney disease, new-onset AF and centre experience were independent predictors for cerebrovascular events after TAVI and showed no risk increase in patients with multiple-THV

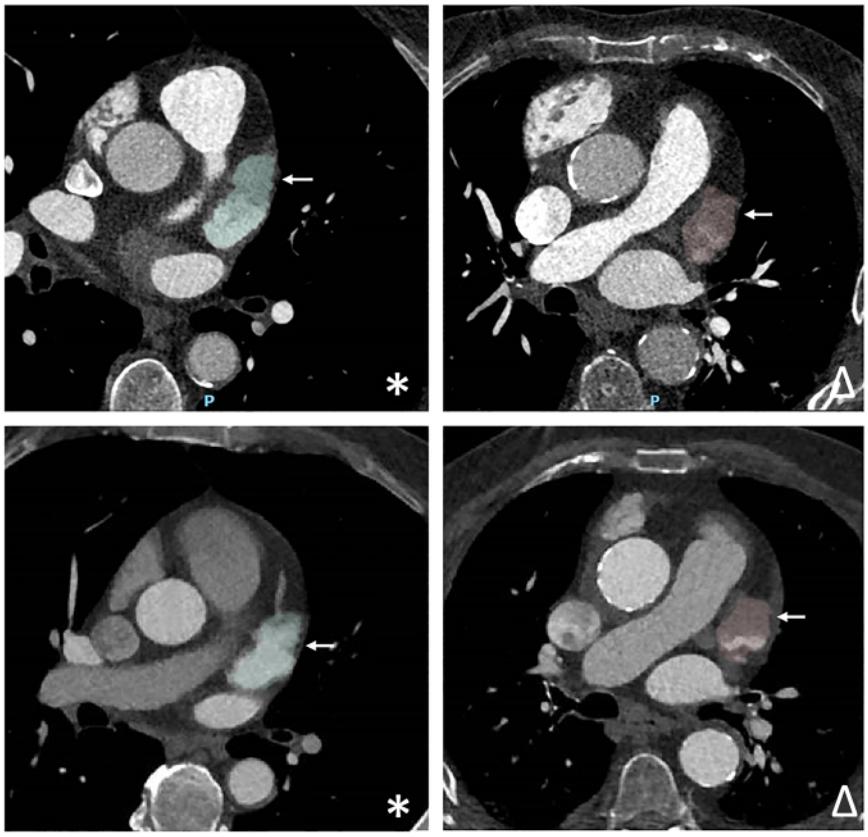


Figure 4 Although delayed acquisition requires a higher radiation dose, it is a prerequisite to differentiate between thrombus and slow flow artefacts. Both patients (asterisk and triangle) have an LAA filling defect, but only one has a persisting filling defect during delayed acquisition, marking true LAA thrombus (triangle).

implants.[23,24] Also, a recent multicentre registry on repeat TAVI procedures showed a low incidence of 30-day stroke of 1.4%.[25]

Limitations

This is a retrospective analysis with inherent selection bias and sample size assumptions. Also, LAAT incidence and event rates were too low to allow for additional analyses of left atrial size, morphology or an additional landmark analysis at 48 h after the procedure. Agatston scores were not available for all patients, for instance the patients with a bioprosthesis *in situ*. Median STS score was 3.4%, although more than 40% of the patients were considered frail and the overall multidisciplinary heart team consensus was that patients were deemed at higher operative risk, therefore our findings apply to patients at higher risk as described here in. Lastly, within the time window of inclusion, several iterations were installed including (i) device iterations, (ii) switch from general to local anaesthesia, and (iii) antithrombotic regimen: this might have influenced the results.

Conclusion

Patients with MSCT-detected LAAT are at increased risk for cerebrovascular events during the first year after TAVI. LAAT finding in the MSCT work-up may trigger efforts to optimize the antithrombotic regime after TAVI.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Data availability

The dataset analyzed during present study is available from the corresponding author on reasonable request.

Conflict of interest: J.D. received institutional research support from Abbott Vascular, Boston Scientific, Medtronic, Pie Medical and PulseCath BV, and consultancy and speaker fees from Boston Scientific, ReCor, Pie Medical, Medtronic and PulseCath BV. N.M.V.M. received research grants from Abbott, Boston Scientific, Edwards, Essential Medical/Teleflex, Medtronic, PulseCath BV. All other authors declared no conflict of interest regarding the publication of this article.

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