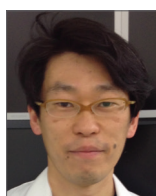# Aortic atheroma burden predicts acute cerebrovascular events after transcatheter aortic valve implantation: insights from volumetric multislice computed tomography analysis

Yu Kataoka[1], MD; Rishi Puri[2], MBBS, PhD; Anthony D. Pisaniello[1], MBBS; Muhammad Hammadah[3], MD; Mohammed Qintar[3], MD; Kiyoko Uno[4], MD, PhD; Joseph K. Montarello[5], MBBS; Stephen J. Nicholls[1,5], MBBS, PhD; Stephen G. Worthley[1,5]*, MBBS, PhD

1. South Australian Health & Medical Research Institute, University of Adelaide, Adelaide, Australia; 2. Interventional Cardiology & Structural Heart Disease, Quebec Heart & Lung Institute, Laval University, Quebec City, Canada; 3. Department of Internal Medicine, Heart & Vascular Institute, Cleveland Clinic, Cleveland, OH, USA; 4. Department of Cardiovascular Medicine, Heart & Vascular Institute, Cleveland Clinic, Cleveland, OH, USA; 5. Cardiovascular Investigation Unit, University of Adelaide, Royal Adelaide Hospital, Adelaide, Australia

This paper also includes supplementary data published online at: http://www.pcronline.com/eurointervention/103rd_issue/127

Abstract

Aims: Embolisation of atheromatous debris during catheter manipulation is considered to underlie acute cerebrovascular events (CVE) after transcatheter aortic valve implantation (TAVI). However, the relationship between aorta atheroma burden and acute CVE after TAVI has not been established. We investigated the impact of aorta atheroma burden on acute CVE.

Methods and results: Preoperative multislice computed tomographic (MSCT) images in 278 patients receiving TAVI were analysed. Total atheroma volume (TAV) was calculated by measuring aorta vessel and lumen areas in every 1 mm cross-sectional image. Acute CVE was observed in 16 patients. Patients having acute CVE were more likely to have a prior CVE (p=0.002), and to exhibit greater TAV in the ascending aorta (12.8 ± 3.5 vs. 7.0 ± 2.1 cm^3, p<0.001) and the aortic arch (3.1 ± 1.6 vs. 1.2 ± 0.2 cm^3, p<0.001). TAV in the ascending aorta >10.3 cm^3 and in the aortic arch >2.9 cm^3 predicted acute CVE. The incidence of acute CVE was highest (36.4%) if patients had a prior CVE and TAV in the ascending aorta and the aortic arch above cut-offs.

Conclusions: Patients with acute CVE after TAVI had greater aorta atheroma burden. Our findings might underscore preoperative MSCT analysis of aorta atherosclerosis to identify high-risk patients for acute CVE, who might require an embolic protection device during TAVI.

Corresponding author: Cardiovascular Investigation Unit, University of Adelaide, Royal Adelaide Hospital, North Terrace, Adelaide, SA, 5000, Australia. E-mail: stephen.worthley@adelaide.edu.au

Abbreviations

CVE	cerebrovascular events
MSCT	multislice computed tomography
TAV	total atheroma volume
TAV$_{arch}$	total atheroma volume in the aortic arch
TAV$_{ascending}$	total atheroma volume in the ascending aorta
TAVI	transcatheter aortic valve implantation

Introduction

Despite the clinical efficacy of transcatheter aortic valve implantation (TAVI) in inoperable or high surgical risk patients with severe symptomatic aortic valve disease[1], the PARTNER (Placement of Aortic Transcatheter Valves) trial has raised safety concerns by showing a 30-day stroke rate of 6.7% in inoperable patients treated with a balloon-expandable bovine pericardial valve[2]. These cerebrovascular events (CVE) were more frequent after TAVI compared to surgical procedure in high-risk patients (5.5 vs. 2.4%, p=0.04)[3]. In another clinical trial comparing a self-expanding porcine pericardial valve with surgical aortic valve replacement, the stroke rate was 4.9% and 6.2% at 30 days (p=0.46) in the TAVI and surgical groups, respectively[4]. Given the morbidity and mortality associated with CVE, it is necessary to establish better pre-procedural assessment and use of effective risk reduction strategies.

CVE after TAVI have been shown to occur most frequently in the first 24 hours[5,6]. The interventional procedure, through the manipulation of guidewires and catheters for example, is considered to induce embolism of debris from the aortic wall or aortic valve. Additionally, it has been reported that scraping of aortic plaques occurs in >50% of percutaneous cardiac interventions and is more frequent when larger catheters are used[7,8]. Since large diameter devices (≥18 Fr) are currently required for TAVI, we hypothesised that the presence of a larger amount of atheroma within the aorta might be associated with acute CVE after the procedure.

Preoperative multislice computed tomography (MSCT) imaging has become an important tool in the workup of patients who are being considered for TAVI[9]. This modality also enables visualisation of the burden of aortic atherosclerosis. The purpose of this analysis was to quantify aortic atheroma burden in patients with severe aortic stenosis undergoing TAVI and its association with periprocedural CVE.

Methods

STUDY POPULATION

Two hundred and seventy-eight (278) consecutive patients with symptomatic severe aortic valve stenosis undergoing TAVI at the Royal Adelaide Hospital between August 2009 and July 2015 were analysed. Eligibility for TAVI was based on the consensus of a multidisciplinary team composed of interventional cardiologists and cardiac surgeons. The current study was approved by the institutional review committee. All patients consented to the performance and analysis of the CT data set prior to the TAVI procedure and gave informed consent.

TAVI PROCEDURES

Technical aspects of TAVI procedures with the use of a balloon-expandable or a self-expanding stent valve have been described in detail previously[10,11]. After conducting valvuloplasty of the aortic valve with a 20 to 23 mm balloon catheter under right ventricular pacing, one of the following four TAVI systems was utilised: CoreValve® (Medtronic, Minneapolis, MN, USA), SAPIEN XT (Edwards Lifesciences, Irvine, CA, USA), Lotus™ (Boston Scientific, Marlborough, MA, USA) or Portico™ (St. Jude Medical, St. Paul, MN, USA).

Patients were treated with aspirin and clopidogrel the day before TAVI. Patients receiving oral anticoagulation therapy were instructed to stop three days before the procedure, and were switched to continuous intravenous unfractionated heparin administration. During the procedure, intravenous unfractionated heparin was administered to achieve an activated clotting time >250 seconds. After the procedure, aspirin was continued indefinitely, whereas clopidogrel was discontinued after six months.

PREOPERATIVE MSCT IMAGING

A plain and contrast-enhanced MSCT was performed in all patients by using a 128 detector system (Siemens Definition AS+; Siemens Medical Solutions, Erlangen, Germany). Sublingual nitroglycerine and a beta-blocker were administered prior to MSCT imaging. After plain MSCT images were obtained, contrast-enhanced ones were acquired during injection of non-ionic iodinated contrast agent (Ultravist 370™; Bayer Healthcare, New York, NY, USA). Retrospectively, ECG-gated data acquisition was used with 128×0.6 mm collimation, scan pitch of 0.18 and a gantry rotation time of 300 ms.

MEASUREMENTS OF AORTA ATHEROMA BURDEN AND CALCIUM VOLUME AT AORTIC VALVE COMPLEX

Acquired MSCT images were analysed by a commercially available software (3mensio Structural Heart, version 5.1; Pie Medical Imaging BV, Maastricht, The Netherlands). This software automatically draws a centreline across the aortic lumen. After manual adjustment of the centreline, the software displays the short-axis view of the aortic root. Manual planimetry was used to trace the leading edges of the luminal and outer wall boundaries at 1 mm intervals of cross-sectional images. The plaque area was defined as the difference in area occupied by lumen area and vessel area. The entire aorta was divided into four segments: 1) the ascending aorta between the sinotubular junction and the origin of the brachiocephalic artery, 2) the aortic arch between the brachiocephalic artery and the left subclavian artery, 3) the descending aorta between the left subclavian artery and the diaphragm, and 4) the abdominal aorta below the diaphragm and above the bifurcation of the common iliac artery **(Figure 1)**.

In each segment, total atheroma volume (TAV) was calculated by summation of the plaque area and subsequently normalised to account for difference in segment length between subjects **(Figure 2)**:

$$\text{Total atheroma volume (cm}^3) = \frac{\Sigma \text{ (vessel area} - \text{lumen area)}}{\text{Number of images in segment}} \times \frac{\text{Median number of images}}{\text{in segment of study subjects}}$$

Vessel and lumen volumes were calculated in a similar fashion.

Figure 1. *Analysed segments of aorta. The aorta was divided into four segments: (1) the ascending aorta, (2) the aortic arch, (3) the descending aorta, and (4) the abdominal aorta.*

Calcium volume at the aortic valve complex and each cusp was also measured as previously published[12]. Since the average measurement of Hounsfield units in the lumen of the aorta was 500±100, a threshold of ≥700 Hounsfield units (=averaged value+2SD) was used to detect areas of calcium in the aortic valve complex.

ACUTE CVE

A neurologist was prospectively involved to identify CVE after TAVI, and to conduct cerebral CT scanning and appropriate therapeutic management. Acute CVE were defined as transient ischaemic attack or stroke within 24 hours after TAVI[5,13]. Transient ischaemic attack was defined as an acute focal neurological deficit lasting <24 hours without any evidence of cerebral infarction on imaging. Stroke was defined as an acute focal neurological deficit lasting >24 hours and/or with evidence of cerebral infarction on imaging. Stroke was classified as major stroke or minor stroke according to the modified Rankin Scale (major stroke: modified Rankin Scale score ≥2 at 30 days, minor stroke: modified Rankin Scale score <2 at 30 days).

STATISTICAL ANALYSIS

Continuous variables are expressed as mean±SD or median, and categorical variables as percentages. The chi-square test was used to test for differences in categorical variables between groups and continuous data were compared using unpaired t-tests, or Mann-Whitney log-rank tests when the variable was not normally distributed. Variables with a value of p<0.10 in the univariate logistic regression analysis were entered into a multivariate analysis to determine the independent predictors of acute CVE after TAVI. Receiver-operating characteristic analyses, and calculations of sensitivity and specificity were performed to analyse the predictive ability of TAV for acute CVE. The best cut-off value of $TAV_{ascending}$ and TAV_{arch} was determined by selecting the value which maximised the sum of sensitivity and specificity. A value of p<0.05 was considered significant. All statistical analyses were performed using JMP software, version 11.0.1 (SAS Institute, Cary, NC, USA).

Results

CLINICAL DEMOGRAPHICS

Sixteen patients had an acute CVE after TAVI (10 major and six minor stroke). Clinical characteristics are summarised in **Table 1**. Patients having acute CVE were more likely to have a history of cerebrovascular disease (p=0.002). There were no significant differences in other clinical demographics. The distribution and the detailed characteristics of CVE are summarised in **Online Figure 1** and **Online Table 1**, respectively.
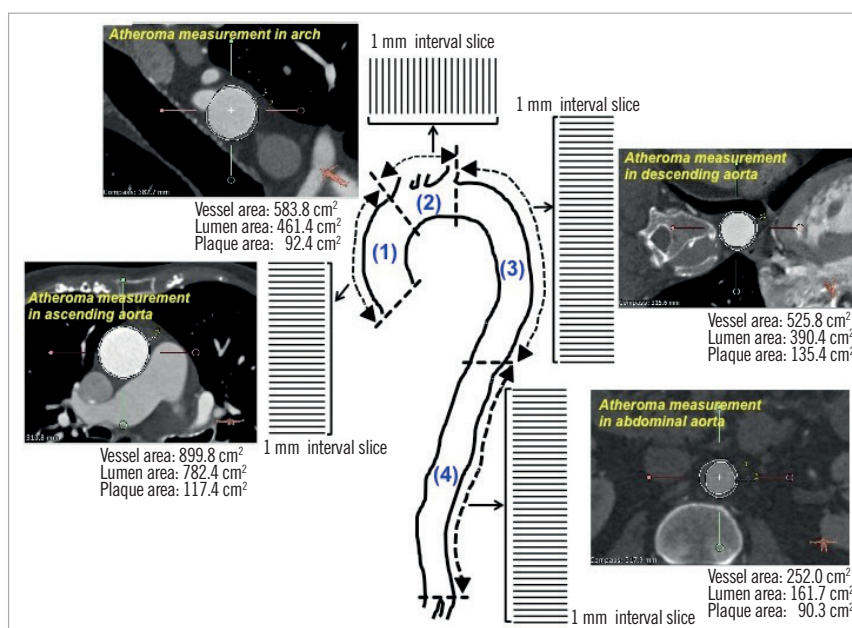

Figure 2. *Volumetric analysis of aorta plaque burden. Lumen and outer wall boundaries were traced in every cross-sectional image at 1 mm intervals.*

Table 1. Baseline clinical characteristics.

	No stroke (n=262)	Stroke (n=16)	p-value
Clinical characteristics			
Age (years)	80.6±6.5	82.7±5.0	0.22
Female, n (%)	112 (42.7)	5 (31.2)	0.11
BMI (kg/m²)	27.4±6.0	27.7±3.8	0.95
Hypertension, n (%)	154 (58.7)	11 (68.7)	0.44
Diabetes, n (%)	114 (43.5)	7 (43.7)	0.95
Insulin user, n (%)	62 (23.6)	4 (25.0)	0.90
Dyslipidaemia, n (%)	109 (41.6)	7 (43.7)	0.69
NYHA functional class	2.9±0.4	3.0±0.5	0.61
Chronic atrial fibrillation, n (%)	89 (33.9)	7 (43.7)	0.10
Coronary artery disease, n (%)	176 (67.1)	10 (63.0)	0.61
Prior myocardial infarction, n (%)	105 (40.1)	7 (43.7)	0.64
Prior PCI, n (%)	161 (61.4)	9 (56.2)	0.59
Prior CABG, n (%)	101 (38.5)	5 (31.2)	0.52
Prior cerebrovascular event, n (%)	31 (11.8)	10 (62.5)	0.002
Peripheral artery disease, n (%)	32 (12.2)	2 (12.5)	0.94
COPD, n (%)	105 (40.1)	7 (43.7)	0.65
eGFR (mL/min/1.73 m²)	51.2±18.3	52.3±24.4	0.84
STS score (%) *	8.1 (7.8-13.5)	7.3 (6.4-18.4)	0.37
Echocardiography data			
Mean aortic gradient (mmHg)	52.1±12.9	47.0±9.3	0.31
Aortic valve area (cm²)	0.66±0.14	0.74±0.15	0.15
LVEF (%)	54.1±10.8	58.5±10.4	0.71
Aortic annulus diameter (TEE, mm)	25.2±2.3	26.6±2.5	0.22
Antithrombotic therapy			
Aspirin use prior to TAVI			0.70
No use, n (%)	42 (16.0)	4 (22.2)	
Continued use of stable dose, n (%)	218 (83.2)	14 (77.8)	
Loading before TAVI, n (%)	2 (0.8)	0 (0.0)	
Clopidogrel use prior to TAVI			0.45
No use, n (%)	73 (27.9)	6 (33.3)	
Continued use of stable dose, n (%)	187 (71.4)	12 (66.6)	
Loading before TAVI, n (%)	2 (0.7)	0 (0.0)	
Anticoagulant use prior to TAVI, n (%)	57 (21.7)	6 (33.3)	0.47
Statin use, n (%)	194 (74.0)	11 (68.7)	0.55
LDL-C level (mg/dl)	102±18	107±21	0.98

*Median (interquartile range). BMI: body mass index; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; LDL-C: low-density lipoprotein; LVEF: left ventricular ejection fraction; STS: Society of Thoracic Surgeons; TAVI: transcatheter aortic valve implantation; TEE: transoesophageal echocardiography

Table 2. Procedural characteristics.

		No stroke (n=262)	Stroke (n=16)	p-value
Procedural time (min)		161±47	162±70	0.91
Approach	Transfemoral, n (%)	200 (76.3)	14 (87.6)	
	Transapical, n (%)	19 (7.3)	1 (6.2)	0.20
	Subclavian, n (%)	43 (16.4)	1 (6.2)	
Prosthesis diameter (mm)	23, n (%)	34 (13.0)	4 (25.0)	
	26, n (%)	94 (35.9)	3 (18.7)	
	27, n (%)	13 (5.0)	2 (12.5)	0.61
	29, n (%)	111 (42.3)	7 (43.8)	
	31, n (%)	10 (3.8)	0 (0.0)	
Prosthesis type	CoreValve, n (%)	116 (44.4)	6 (37.5)	
	SAPIEN XT, n (%)	82 (31.3)	6 (37.5)	0.58
	Lotus, n (%)	33 (12.5)	3 (18.7)	
	Portico, n (%)	31 (11.8)	1 (6.3)	
Ratio of prosthesis to annulus size		1.20±0.33	1.25±0.25	0.76
Balloon post-dilation, n (%)		24 (9.2)	0 (0.0)	0.50
Valve embolisation, n (%)		0 (0.0)	2 (12.5)	0.14
Need for a second valve, n (%)		8 (3.1)	0 (0.0)	0.63
Intra-aortic balloon pump, n (%)		24 (9.2)	1 (6.3)	0.66
New-onset atrial fibrillation, n (%)		23 (8.7)	2 (12.5)	0.81
Permanent pacemaker insertion, n (%)		53 (20.2)	3 (18.7)	0.63
Activated clotting time (sec)		245.1±4.1	243.8±12.1	0.79

VOLUMETRIC MSCT ANALYSIS

Table 3 summarises MSCT measures in the two groups. On volumetric plaque analysis, greater $TAV_{ascending}$ and TAV_{arch} were observed in patients with acute CVE (12.8±3.5 vs. 7.0±2.1 cm³, p<0.001, 3.1±1.6 vs. 1.2±0.2 cm³, p<0.001), whereas there were no significant differences in TAV within the descending and abdominal aorta (29.5±11.8 vs. 29.3±11.0 cm³, p=0.75; 10.2±2.5 vs. 9.8±2.4 cm³, p=0.60). Vessel and lumen volumes were comparable in each segment between the two groups.

Of patients who did not experience acute CVE, late CVE (>24 hours after TAVI) were observed in six cases (6/262 [2.2%]). There were no significant differences in TAV between patients with and without late CVE **(Online Table 2)**.

The calcification volume within the aortic valve complex and each cusp was also comparable (26.5±5.1 vs. 24.2±4.7 cm³, p=0.88; right cusp: 3.5±3.0 vs. 2.2±1.7 cm³, p=0.91, left cusp: 14.8±6.2 vs. 14.0±5.1 cm³, p=0.98, non-coronary cusp: 6.7±4.9 vs. 5.9±3.3 cm³, p=0.94).

OBSERVER VARIABILITY

Analysis of intra-observer variability was determined in 25,221 images acquired from 50 patients. The mean (±SD) differences were negligible for vessel wall (–0.10 cm² [0.53 cm²]) and lumen areas (–0.04 cm² [0.35 cm²]). Linear regression analysis showed close correlations between the original analysis and re-analysis (r=0.99 for vessel area, r=0.99 for lumen area). For inter-observer variability determination, the mean (±SD) differences were negligible for vessel wall (–0.18 cm² [0.60 cm²]) and lumen areas (–0.14 cm² [0.48 cm²]) in 25,221 images of 50 patients. Close correlations

TAVI procedural data are summarised in **Table 2**. The femoral access was used in the majority of patients with and without acute CVE (p=0.20). The size and the type of prosthesis were similar between the two groups (p=0.61 and 0.58, respectively). There were no significant differences in stroke rate among four different valves (CoreValve 4.9% [6/122] vs. SAPIEN XT 6.8% [6/88] vs. Lotus 8.3% [3/36] vs. Portico 3.1% [1/32], p=0.39) and in self-expanding (CoreValve, Lotus and Portico) vs. balloon-expandable valves (SAPIEN XT) (5.2 vs. 5.6%, p=0.80), and Lotus valve vs. other valves (4.6 vs. 4.1%, p=0.77).

Table 3. Atheroma volume in patients with and without acute cerebrovascular events.

		No stroke (n=262)	Stroke (n=16)	*p*-value
Ascending aorta	TAV (cm³) *	7.0±2.1	12.8±3.5	<0.001
	Vessel volume (cm³)	63.8±11.4	72.3±12.9	0.11
	Lumen volume (cm³)	54.1±10.9	60.2±10.6	0.20
	Analysed length (mm)	70.2±14.2	69.5±18.2	0.58
Aortic arch	TAV (cm³) *	1.2±0.2	3.1±1.6	<0.001
	Vessel volume (cm³)	12.4±1.8	13.6±2.2	0.10
	Lumen volume (cm³)	9.6±1.2	10.5±1.6	0.22
	Analysed length (mm)	32.5±6.1	30.5±6.2	0.27
Descending aorta	TAV (cm³) *	29.3±11.0	29.5±11.8	0.75
	Vessel volume (cm³)	117.6±24.2	119.4±25.2	0.87
	Lumen volume (cm³)	86.5±18.9	86.7±18.7	0.82
	Analysed length (mm)	243.3±20.1	233.7±21.9	0.38
Abdominal aorta	TAV (cm³) *	9.8±2.4	10.2±2.5	0.60
	Vessel volume (cm³)	31.5±10.1	32.2±9.0	0.94
	Lumen volume (cm³)	21.0±7.2	21.7±6.7	0.83
	Analysed length (mm)	112.5±12.0	106.5±14.3	0.19
*adjusted for BMI and analysed length. TAV: total atheroma volume				

between the original analysis and subsequent analysis (r=0.97 for vessel area, r=0.97 for lumen area) were similarly observed.

PREDICTORS OF ACUTE CVE AFTER TAVI

Factors associated with acute CVE are shown in **Table 4**. A history of prior cerebrovascular disease (p=0.01), $TAV_{ascending}$ (p=0.008) and TAV_{arch} (p=0.009) were independent predictors of acute CVE. By receiver-operating curve analysis, the optimal cut-off value of $TAV_{ascending}$ and TAV_{arch} for predicting an acute CVE was 10.3 cm³ and 2.9 cm³, respectively **(Figure 3)**.

The incidence of acute CVE was compared in patients stratified into three groups according to the number of predictive features,
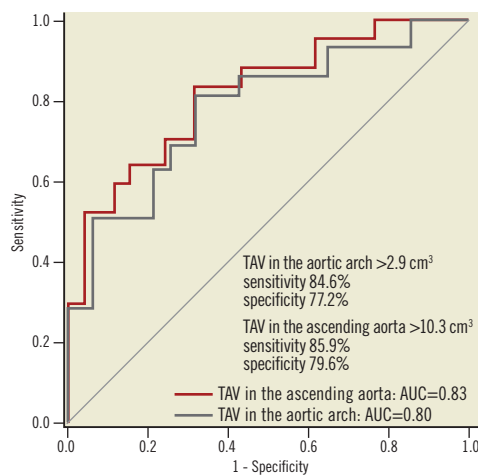

Figure 3. *Receiver-operating characteristic analysis of $TAV_{ascending}$ and TAV_{arch} for predicting acute CVE after TAVI.*
CVE: cerebrovascular events; TAV_{arch}: total atheroma volume in the aortic arch; $TAV_{ascending}$: total atheroma volume in the ascending aorta; TAVI: transcatheter aortic valve implantation

Table 4. Univariate and multivariate analysis for predictors of acute CVE.

Variable		Univariate analysis		Multivariate analysis	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age		0.93 (0.81-1.07)	0.45	–	–
Female		1.15 (0.44-1.36)	0.32	–	–
Diabetes		1.11 (0.77-1.38)	0.36	–	–
Chronic atrial fibrillation		1.19 (0.88-1.62)	0.21	–	–
New-onset atrial fibrillation		1.22 (0.94-1.71)	0.22	–	–
Prior cerebrovascular disease		1.34 (1.11-1.97)	0.01	1.24 (1.10-1.90)	0.01
eGFR <60 mL/min/1.73 m²		1.01 (0.96-1.10)	0.72	–	–
Aortic valve area		1.20 (0.84-1.49)	0.73	–	–
LVEF <40%		1.02 (0.95-1.08)	0.95	–	–
Transfemoral approach		1.04 (0.87-1.23)	0.56	–	–
Balloon post-dilation		1.22 (0.81-1.54)	0.20	–	–
Aspirin use		0.89 (0.63-1.08)	0.35	–	–
Clopidogrel use		0.85 (0.69-1.09)	0.21	–	–
Anticoagulant use		0.92 (0.67-1.26)	0.37	–	–
TAV	Ascending aorta	1.98 (1.49–2.32)	0.002	1.81 (1.34-2.21)	0.008
	Aortic arch	1.92 (1.41-2.23)	0.004	1.76 (1.29-2.10)	0.009
	Descending aorta	1.03 (0.92-1.15)	0.94	–	–
	Abdominal aorta	1.02 (0.87-1.25)	0.78	–	–

CVE: cerebrovascular events; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; TAV: total atheroma volume; TAVI: transcatheter aortic valve implantation

including a history of cerebrovascular disease, $TAV_{ascending}$ >10.3 cm³ and TAV_{arch} >2.9 cm³ **(Figure 4)**. While the incidence of acute CVE was 2.0% (4/196) in patients who had zero or one predictive feature, it was 6.7% (4/60) if patients had two predictive features. Moreover, patients having all three predictive features exhibited the highest incidence of acute CVE (36.4% [8/22], p<0.0001).

CLINICAL CHARACTERISTICS ASSOCIATED WITH $TAV_{ascending}$ AND TAV_{arch}

Further analysis was conducted to investigate clinical demographics associated with greater $TAV_{ascending}$ and TAV_{arch} **(Online Table 3, Online Table 4)**. Patients with $TAV_{ascending}$ above 10.3 cm³ were less likely to be female (p=0.04) and more likely to have a history of cerebrovascular disease (p=0.04). There was a lower proportion of females (p=0.009) and a higher prevalence of dyslipidaemia (p=0.04) in patients having TAV_{arch} above 2.9 cm³.

Discussion

Dislodgement of debris from aorta atheroma burden during the passage of large-bore valve delivery catheters has been considered as a possible mechanism for acute CVE after TAVI. Our volumetric MSCT analysis showed that the occurrence of acute CVE was predicted by greater $TAV_{ascending}$ and TAV_{arch}. This finding is consistent with previous reports from transoesophageal echocardiography, showing a higher incidence of embolism after cardiac catheterisation in patients with evidence of aorta atherosclerosis[14,15]. Moreover, this incidence was higher in patients receiving intra-aortic balloon pump placement, which required the use of a larger size of
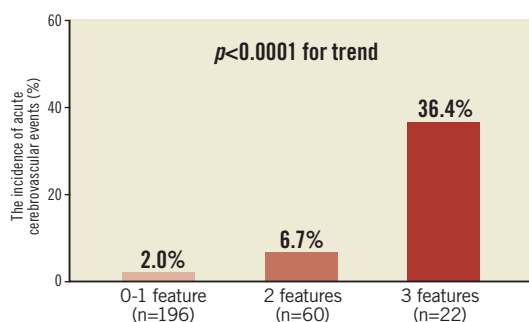
Figure 4. *The incidence of acute CVE in patients having predictive features. The incidence of acute CVE was shown according to the number of predictive features: a history of cerebrovascular disease, $TAV_{ascending} > 10.2\ cm^3$ and $TAV_{arch} > 2.8\ cm^3$. CVE: cerebrovascular events; TAV_{arch}: total atheroma volume in the aortic arch; $TAV_{ascending}$: total atheroma volume in the ascending aorta*

catheter[14]. These observations support our hypothesis that patients receiving TAVI are at an increased risk of acute CVE if they have more $TAV_{ascending}$ and TAV_{arch}. As detached debris from the aortic wall between the ascending aorta and the aortic arch can travel to the brain through the brachiocephalic and left common carotid arteries, our MSCT findings may suggest an important distribution of aorta atherosclerosis associated with acute CVE after TAVI.

To date, there has been no study which has conducted volumetric MSCT analysis of aorta atherosclerosis. We sought to acquire cross-sectional images of the whole aorta to measure atheroma volume, as previously employed with intravascular ultrasound imaging of coronary atherosclerosis[16]. Inter- and intra-observer variability indicates that the current MSCT measurement approach is highly reproducible. A recent large cohort study reported balloon redilation and valve embolisation as independent predictors of acute CVE after TAVI[5]. However, it is hard to predict these procedural situations prior to TAVI. Therefore, evaluating atheroma burden might be a useful preoperative risk estimation of stroke after the procedure.

A history of cerebrovascular disease was identified as an independent predictor of acute CVE in the current study and in another recent article[6]. Patients having a prior cerebrovascular disease may harbour fragile atheroma in carotid arteries, potentially contributing to periprocedural stroke after TAVI. We could not delineate characteristics of carotid atherosclerosis as the number of patients who had baseline carotid imaging was limited.

A recent clinical trial has demonstrated the ability of cerebral protection devices to reduce ischaemic brain lesions and neurologic deficits after the procedure[17]. While this finding suggests the potential benefit of cerebral embolic protection devices, the appropriate indications for the use of this device have not yet been established. Our findings might suggest the ability of preoperative MSCT imaging of aorta atherosclerosis to identify patients who warrant cerebral embolic protection device use during TAVI.

The acute CVE rate in our study was higher compared to other recent studies[4,5]. One possibility is the learning curve effect. Twelve acute CVE were observed from 2009 to 2012, whereas there were

four acute CVE from 2013 to 2015 **(Online Figure 1)**. Less experience in procedure and post-procedural management, and the use of a catheter with a larger size might have contributed to a higher incidence of acute CVE in the early observational period.

Limitations

A number of caveats should be noted. The possibility of selection bias cannot be excluded, although consecutive subjects were included in the current analysis. The current study did not conduct MRI scans. This might have underestimated the incidence of CVE after the procedure. Quantification of atheroma burden by MSCT is affected by calcium blooming artefacts, potentially leading to the overestimation of calcified plaques. Plaque mobility and complexity and its composition may affect CVE, but its assessment is limited with MSCT. The small study population makes the analysis underpowered and a beta error cannot be ruled out with certainty. The ability of multivariate analysis to elucidate predictors with only 16 acute CVE is limited. The relationship of TAV with acute CVE should be further investigated in future studies with larger sample populations.

Conclusion

In summary, MSCT-derived aorta atheroma volume predicted acute CVE after TAVI in patients with severe symptomatic aortic valve stenosis. Our findings may underscore preoperative assessment of aorta atherosclerosis for risk estimation of acute CVE. Furthermore, this may have implications for the use of cerebral embolic protection devices in patients undergoing TAVI.

Impact on daily practice

CVE after TAVI are associated with morbidity and mortality. The interventional procedure is considered to induce embolism of atheromatous debris from the aortic wall. Volumetric MSCT analysis elucidated the association of $TAV_{ascending}$ and TAV_{arch} with acute CVE. Preoperative assessment of aorta atherosclerosis on MSCT might be useful to estimate the risk of acute CVE and identify patients requiring a cerebral embolic protection device during TAVI.

Acknowledgements

Conflict of interest statement

has received research grants and honoraria from St. Jude Medical and Medtronic. The other authors have no conflicts of interest to declare.

References

1. Rodés-Cabau J. Transcatheter aortic valve implantation: current and future approaches. *Nat Rev Cardiol.* 2011;9:15-29.

2. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med.* 2010;363:1597-607.

3. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med.* 2011;364:2187-98.

4. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J Jr, Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK; U.S. CoreValve Clinical Investigators. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med.* 2014;370:1790-8.

5. Nombela-Franco L, Webb JG, de Jaegere PP, Toggweiler S, Nuis RJ, Dager AE, Amat-Santos IJ, Cheung A, Ye J, Binder RK, van der Boon RM, Van Mieghem N, Benitez LM, Pérez S, Lopez J, San Roman JA, Doyle D, Delarochellière R, Urena M, Leipsic J, Dumont E, Rodés-Cabau J. Timing, predictive factors, and prognostic value of cerebrovascular events in a large cohort of patients undergoing transcatheter aortic valve implantation. *Circulation.* 2012;126:3041-53.

6. Tay EL, Gurvitch R, Wijesinghe N, Nietlispach F, Wood D, Cheung A, Ye J, Lichtenstein SV, Carere R, Thompson C, Webb JG. A high-risk period for cerebrovascular events exists after transcatheter aortic valve implantation. *JACC Cardiovasc Interv.* 2011;4:1290-7.

7. Keeley EC, Grines CL. Scraping of aortic debris by coronary guiding catheters: a prospective evaluation of 1,000 cases. *J Am Coll Cardiol.* 1998;32:1861-5.

8. Eggebrecht H, Oldenburg O, Dirsch O, Haude M, Baumgart D, Welge D, Herrmann J, Arnold G, Schmid KW, Erbel R. Potential embolization by atherosclerotic debris dislodged from aortic wall during cardiac catheterization: histological and clinical findings in 7,621 patients. *Catheter Cardiovasc Interv.* 2000;49:389-94.

9. Zamorano JL, Gonçalves A, Lang R. Imaging to select and guide transcatheter aortic valve implantation. *Eur Heart J.* 2014;35:1578-87.

10. Webb JG, Pasupati S, Humphries K, Thompson C, Altwegg L, Moss R, Sinhal A, Carere RG, Munt B, Ricci D, Ye J, Cheung A,

Lichtenstein SV. Percutaneous transarterial aortic valve replacement in selected high-risk patients with aortic stenosis. *Circulation.* 2007;116:755-63.

11. Webb JG, Chandavimol M, Thompson CR, Ricci DR, Carere RG, Munt BI, Buller CE, Pasupati S, Lichtenstein S. Percutaneous aortic valve implantation retrograde from the femoral artery. *Circulation.* 2006;113:842-50.

12. Ewe SH, Ng AC, Schuijf JD, van der Kley F, Colli A, Palmen M, de Weger A, Marsan NA, Holman ER, de Roos A, Schalij MJ, Bax JJ, Delgado V. Location and severity of aortic valve calcium and implications for aortic regurgitation after transcatheter aortic valve implantation. *Am J Cardiol.* 2011;108:1470-7.

13. Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, Krucoff MW, Mack M, Mehran R, Miller C, Morel MA, Petersen J, Popma JJ, Takkenberg JJ, Vahanian A, van Es GA, Vranckx P, Webb JG, Windecker S, Serruys PW. Standardized endpoint definitions for Transcatheter Aortic Valve Implantation clinical trials: a consensus report from the Valve Academic Research Consortium. *J Am Coll Cardiol.* 2011;57:253-69.

14. Karalis DG, Quinn V, Victor MF, Ross JJ, Polansky M, Spratt KA, Chandrasekaran K. Risk of catheter-related emboli in patients with atherosclerotic debris in the thoracic aorta. *Am Heart J.* 1996;131:1149-55.

15. Sugioka K, Matsumura Y, Hozumi T, Fujita S, Ito A, Kataoka T, Takagi M, Mizutani K, Naruko T, Hosono M, Hirai H, Sasaki Y, Ueda M, Suehiro S, Yoshiyama M. Relation of aortic arch complex plaques to risk of cerebral infarction in patients with aortic stenosis. *Am J Cardiol.* 2011;108:1002-7.

16. Nicholls SJ, Tuzcu EM, Sipahi I, Schoenhagen P, Nissen SE. Intravascular ultrasound in cardiovascular medicine. *Circulation.* 2006;114:e55-9.

17. Lansky AJ, Schofer J, Tchetche D, Stella P, Pietras CG, Parise H, Abrams K, Forrest JK, Cleman M, Reinöhl J, Cuisset T, Blackman D, Bolotin G, Spitzer S, Kappert U, Gilard M, Modine T, Hildick-Smith D, Haude M, Margolis P, Brickman AM, Voros S, Baumbach A. A prospective randomized evaluation of the TriGuard™ HDH embolic DEFLECTion device during transcatheter aortic valve implantation: results from the DEFLECT III trial. *Eur Heart J.* 2015;36:2070-2078.

Supplementary data

Online Table 1. Timing and characteristics of stroke event.
Online Table 2. Total atheroma volume in patients with and without late CVE.
Online Table 3. Clinical characteristics associated with TAV in the ascending aorta.
Online Table 4. Clinical characteristics associated with TAV in the aortic arch.
Online Figure 1. Distribution of acute CVE.

The supplementary data are published online at:
http://www.pcronline.com/
eurointervention/103rd_issue/127

Supplementary data

Online Table 1. Timing and characteristics of acute CVE.

	Age/gender	Valve*	Timing	Type of stroke	Symptoms	Infarct type	TAV: ascending aorta (cm³)	TAV: aortic arch (cm³)	NIHSS	Rankin	Therapy
1	94/M	C	7 hrs 31 min	Major	Rt hemiparesis	New cortical (territorial)	12.9	4.1	12	3	Aspirin
2	89/M	S	3 hrs 10 min	Major	Lt hemiparesis dysarthria	New cortical (territorial) Old lacunar (multiple)	12.6	4.3	16	4	Aspirin
3	83/M	C	14 hrs 52 min	Major	Lt hemiparesis	Lacunar type (new multifocal spots)	10.0	2.8	11	3	Aspirin, clopidogrel
4	83/M	S	2 hrs 58 min	Major	Lt hemiparesis	Lacunar type (new multifocal spots)	16.9	2.5	10	3	t-PA, aspirin
5	82/F	S	9 hrs 45 min	Major	Rt hemiparesis	New cortical (territorial)	9.2	2.8	14	3	Aspirin, heparin
6	77/M	C	5 hrs 28 min	Major	Lt hemiparesis, Lt neglect	New cortical (territorial)	10.4	3.3	9	3	Aspirin, clopidogrel
7	93/M	S	8 hrs 11 min	Major	Lt hemiparesis	New cortical (territorial) Lacunar type (old multifocal spots)	12.0	3.9	18	4	Aspirin
8	90/M	C	10 hrs 9 min	Major	Rt leg accentuated lack of strength	Lacunar type (new multifocal spots)	10.3	4.6	14	3	Aspirin
9	82/M	L	1 hr 12 min	Major	Rt hemiparesis, aphasia	New cortical (territorial and watershed) Old lacunar	15.1	3.5	16	4	t-PA, aspirin
10	84/F	C	57 min	Major	Rt hemiparesis	Lacunar type (new multifocal spots)	20.5	3.1	12	3	t-PA, aspirin
11	81/M	S	1 hr 58 min	Minor	Rt hemiparesis, motor aphasia	Lacunar type (new multifocal spots)	15.6	3.0	3	1	t-PA, aspirin
12	78/M	L	4 hrs 12 min	Minor	Apraxia	Lacunar type (rt parietal lobe)	12.4	1.9	4	1	Aspirin, clopidogrel
13	85/F	S	5 hrs 38 min	Minor	Rt hemiparesis, dysarthria	New cortical (territorial) Old lacunar (multiple)	12.6	2.6	5	1	Aspirin, clopidogrel
14	85/F	P	15 hrs 1 min	Minor	Blurry vision	New cortical (territorial)	11.9	2.1	3	1	Aspirin, clopidogrel
15	80/M	C	8 hrs 3 min	Minor	Hemianopia	New cortical (territorial)	11.8	3.3	2	1	Aspirin, clopidogrel
16	79/F	L	3 hrs 57 min	Minor	Diplopia	Lacunar type (new spot)	12.8	1.4	3	1	Aspirin, clopidogrel

*C: CoreValve; S: SAPIEN XT; L: Lotus; P: Portico. CVE: cerebrovascular events; NIHSS: National Institutes of Health Stroke Scale; TAV: total atheroma volume; t-PA: tissue plasminogen activator

Online Table 2. Total atheroma volume in patients with and without late cerebrovascular events.

		No late stroke (n=256)	Late stroke (n=6)	*p*-value
Ascending aorta	Total atheroma volume (cm³)	9.8±4.2	10.9±6.5	0.56
Aortic arch	Total atheroma volume (cm³)	2.1±0.5	2.0±1.6	0.88
Descending aorta	Total atheroma volume (cm³)	28.7±11.2	29.3±14.31	0.72
Abdominal aorta	Total atheroma volume (cm³)	9.0±2.3	10.7±2.9	0.51

Online Table 3. Clinical characteristics associated with atheroma burden in the ascending aorta.
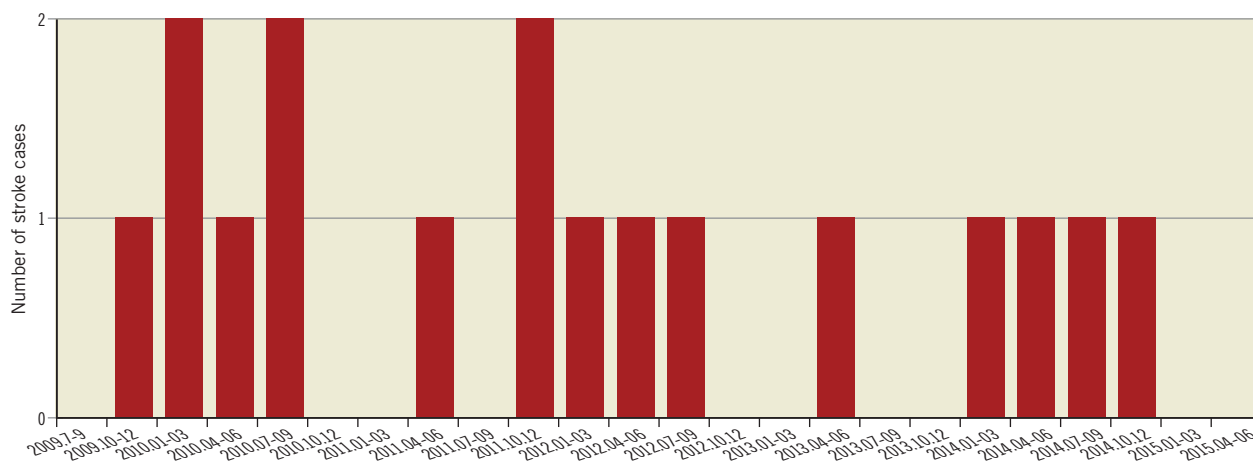
	Below cut-off value (10.3 cm³) of TAV in the ascending aorta (n=216)	Above cut-off value (10.3 cm³) of TAV in the ascending aorta (n=62)	p-value
Age (years)	82.9±5.1	81.4±4.2	0.35
Female, n (%)	103 (47.7)	18 (29.0)	0.04
BMI (kg/m²)	27.2±4.7	27.8±3.4	0.91
Hypertension, n (%)	125 (57.9)	40 (64.5)	0.54
Diabetes, n (%)	88 (40.7)	26 (41.9)	0.89
Dyslipidaemia, n (%)	70 (32.4)	33 (53.2)	0.12
Chronic atrial fibrillation, n (%)	94 (43.5)	20 (32.2)	0.11
Coronary artery disease, n (%)	109 (50.5)	39 (62.9)	0.13
Prior cerebrovascular event, n (%)	17 (7.9)	17 (27.4)	0.04
Peripheral artery disease, n (%)	28 (12.9)	6 (9.7)	0.82
COPD, n (%)	92 (42.6)	20 (32.2)	0.12
eGFR (mL/min/1.73 m²)	51.1±22.5	55.8±16.2	0.42

BMI: body mass index; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate

Online Table 4. Clinical characteristics associated with atheroma burden in the aortic arch.

	Below cut-off value (2.9 cm³) of TAV in the aortic arch (n=227)	Above cut-off value (2.9 cm³) of TAV in the aortic arch (n=51)	p-value
Age (years)	83.7±4.6	82.5±5.2	0.51
Female, n (%)	102 (44.9)	10 (19.6)	0.009
BMI (kg/m²)	26.3±4.2	28.4±3.8	0.34
Hypertension, n (%)	142 (62.5)	39 (76.5)	0.07
Diabetes, n (%)	91 (40.1)	22 (43.1)	0.61
Dyslipidaemia, n (%)	78 (34.4)	36 (70.5)	0.02
Chronic atrial fibrillation, n (%)	86 (37.9)	18 (35.3)	0.65
Coronary artery disease, n (%)	118 (52.0)	36 (70.5)	0.08
Prior cerebrovascular event, n (%)	23 (10.1)	15 (29.4)	0.08
Peripheral artery disease, n (%)	24 (10.6)	5 (9.8)	0.98
COPD, n (%)	89 (39.2)	21 (41.2)	0.59
eGFR (mL/min/1.73 m²)	52.4±22.1	53.4±15.2	0.87

BMI: body mass index; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate

Online Figure 1. *Distribution of acute CVE.*