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Cerebral Embolism Following Transcatheter Aortic Valve Implantation

Comparison of Transfemoral and Transapical Approaches

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Objectives The objective of this study was to compare the incidence of cerebral embolism (CE) as evaluated by diffusion-weighted magnetic resonance imaging (DW-MRI) following transapical (TA) transcatheter aortic valve implantation (TAVI) versus transfemoral (TF) TAVI.

Background The TA-TAVI approach avoids both the manipulation of large catheters in the aortic arch/ascending aorta and the retrograde crossing of the aortic valve, and this avoidance might lead to a lower rate of CE.

Methods This was a prospective multicenter study including 60 patients who underwent cerebral DW-MRI the day before and within the 6 days following TAVI (TF approach: 29 patients; TA approach: 31 patients). Neurologic and cognitive function assessments were performed at DW-MRI time points.

Results The TAVI procedure was performed with the Edwards valve and was successful in all cases but one (98%). A total of 41 patients (68%) had 251 new cerebral ischemic lesions at the DW-MRI performed 4 ± 1 days after the procedure, 19 patients in the TF group (66%) and 22 patients in the TA group (71%; $p = 0.78$). Most patients (76%) with new ischemic lesions had multiple lesions (median number of lesions per patient: 3, range 1 to 31). There were no differences in lesion number and size between the TF and TA groups. No baseline or procedural factors were found to be predictors of new ischemic lesions. The occurrence of CE was not associated with a measurable impairment in cognitive function, but 2 patients (3.3%) had a clinically apparent stroke within the 24 h following the procedure (1 patient in each group).

Conclusions TAVI is associated with a high rate of silent cerebral ischemic lesions as evaluated by DW-MRI, with no differences between the TF and TA approaches. These results provide important novel insight into the mechanisms of CE associated with TAVI and support the need for further research to both reduce the incidence of CE during these procedures and better determine their clinical relevance. (J Am Coll Cardiol 2011;57:18–28) © 2011 by the American College of Cardiology Foundation

Transcatheter aortic valve implantation (TAVI) has become an alternative treatment for those patients with symptomatic severe aortic stenosis considered at very high or prohibitive surgical risk (1). Transfemoral (TF) TAVI is the most commonly used approach, and it involves advancing a large catheter (18- to 24-F) containing the valve through the aortic arch and retrogradely crossing a severely diseased native aortic valve, both well-known potential risk factors for cerebral embolism (2–5). The risk of cerebral embolism during TF-TAVI might be even higher if we take into consideration that the population undergoing TAVI nowadays consists of very old patients with a high prevalence of atherosclerotic disease (6,7). Kahlert et al. (8) and Ghanem et al. (9) have recently shown that TF-TAVI was associated with >70% incidence of new cerebral lesions following the procedure as evaluated by diffusion-weighted magnetic res-

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onance imaging (DW-MRI). Transapical (TA) TAVI has become an alternative to the TF approach in patients with nonappropriate (i.e., too small, diseased, and/or severely calcified) iliofemoral arteries (1). The TA approach consists of directly puncturing the ventricular apex through a small left lateral thoracotomy and then advancing the new valve through a catheter inserted through the ventricular apex and located at the mid portion of the left ventricular cavity. It has been hypothesized that by avoiding both the manipulation of large catheters in the ascending aorta/aortic arch and the retrograde crossing of the native aortic valve, TA-TAVI might be associated with a lower rate of cerebral embolism. Also, comparing the incidence of cerebral ischemia of TA and TF approaches might provide important new insights regarding the mechanisms of cerebral embolism associated with TAVI procedures. However, no data exist on the incidence of cerebral embolism associated with TA-TAVI as evaluated by DW-MRI. The objectives of this prospective multicenter study were to: 1) compare TA-TAVI versus TF-TAVI with respect to the incidence of cerebral embolism as evaluated by DW-MRI; and 2) determine the predictive factors associated with cerebral embolism during the TAVI procedures.

Abbreviations and Acronyms

CT = computed tomography
DW = diffusion weighted
MMSE = Mini Mental State Examination
MRI = magnetic resonance imaging
NIHSS = National Institutes of Health Stroke Scale
TA = transapical
TAVI = transcatheter aortic valve implantation
TEE = transesophageal echocardiography
TF = transfemoral

Methods

Patients. Patients who underwent TAVI under the Canadian compassionate clinical use program at the Quebec Heart & Lung Institute, Quebec City, Quebec, Canada (January 2008 to February 2010) and St. Paul's Hospital, Vancouver, British Columbia, Canada (August 2008 to December 2009) were screened for inclusion in the study. Patients with the diagnosis of symptomatic severe aortic stenosis considered nonoperable or very high surgical risk candidates were evaluated by a multidisciplinary team composed of interventional cardiologists and cardiac surgeons to determine TAVI eligibility. Depending on the size, disease, and degree of calcification of iliofemoral arteries as evaluated by aorto-iliofemoral angiography and/or computed tomography (CT), the patients were selected for the TF or TA approach (10). Patients were excluded if they had any contraindication to undergo an MRI study or if they were unable to have an MRI performed within 24 h prior to TAVI. The protocol was approved by the local ethics committee of each center, and all patients provided written informed consent to participate in the study.

Transesophageal echocardiography (TEE) and CT. All patients underwent TEE before and/or during the TAVI procedure, and the presence of aortic plaques ≥4 mm in the ascending aorta/aortic arch was recorded. In patients who underwent thoracic CT without contrast injection before the procedure, the CT images of the aortic valve were analyzed offline in the cardiac CT core lab of the Quebec Heart & Lung Institute by experienced technicians blinded to clinical data and supervised by a cardiologist (E.L.). Briefly, a prospective echocardiogram (ECG)-gated scan protocol was performed during a single breath hold at end-diastole (70% to 80% RR interval) to cover the entire cardiac silhouette in the axial plane (64 × 0.6 mm collimation, reconstruction increment 1.5 mm, rotation time 0.33 s) by noncontrast multidetector CT (Somatom Definition, Siemens AG, Erlangen, Germany). Three-dimensional multiplanar reconstruction was performed to examine the aortic valve in-plane (2-mm slice thickness, 2 to 5 slices per valve for full coverage) and precisely measure leaflet calcifications defined as pixels >130 Hounsfield units (TeraRecon, San Mateo, California). Aortic valve leaflet calcium volumes (mm^3) were determined using the modified Simpson technique (11,12).

TAVI procedures. The TAVI procedures have been extensively detailed in previous studies (10). All procedures were performed with the Edwards valve (Edwards SAPIEN or SAPIEN XT, Edwards Lifesciences Inc., Irvine, California), which consists of a trileaflet pericardial bovine valve mounted in a stainless steel (Edwards SAPIEN) or cobalt-chromium (SAPIEN XT) stent that is deployed by a balloon expandable mechanism. The valve was available in 23- and 26-mm sizes. Both TF and TA procedures were performed under general anesthesia, with similar anesthesia-ventilation techniques throughout the entire study period, without cardiopulmonary bypass. Balloon aortic valvuloplasty was systematically performed before valve implantation. In the TF approach, the native aortic valve was crossed with a standard straight soft-tip guidewire that was subsequently exchanged for a stiff guidewire. The balloon-mounted valve was advanced through a 22-F (23-mm valve) or 24-F (26-mm valve) sheath with the Retroflex delivery catheter (Edwards Lifesciences). After the native aortic valve was crossed, the new valve was positioned using fluoroscopic, angiographic, and TEE guidance and subsequently expanded under rapid pacing (180 to 220 beats/min). The number of rapid pacing runs per procedure was recorded. The TA approach consisted of a direct puncturing of the ventricular apex through a small left lateral thoracotomy and then advancing a 26-F sheath through the ventricular apex up to the mid ventricular cavity. The aortic valve was crossed with a soft J tip guidewire that was subsequently exchanged for a stiff J tip guidewire, which was advanced to the descending aorta. Following valvuloplasty, the Edwards valve was advanced antegradely through the 26-F catheter up to the native aortic valve, and then valve positioning and deployment followed similar steps as the retrograde TF approach. In all TA cases, catheter retrieval and ventricular

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apical repair was performed under rapid pacing (13). Anticoagulation during the procedure was obtained with intravenous heparin, and the dose was adjusted to obtain an activated clotting time >250 s. Patients received aspirin and clopidogrel after the procedure. Procedural success was defined as the implantation of a functioning valve within the aortic annulus, without intraprocedural mortality.

Cerebral DW-MRI procedures. Cerebral DW-MRI exams were performed within the 24 h before TAVI and within 6 days following the procedure. The DW-MRI was performed with a 1.5-T MR unit and a circular polarized head coil (Philips Achieva, Best, the Netherlands; General Electric, Fairfield, Connecticut). The imaging protocol included isotropic DW (3 orthogonal directions and subsequent averaging) and direction-dependent DW (section-selection direction) single-shot echo-planar sequences (repetition time [ms]/echo time [ms] 6,000/100; matrix 128 × 128, interpolated to 256 × 256; section thickness 5 mm; and b values 0, 500, and 1,000 s/mm^2). Isotropic DW overcame signal changes in DW caused by anisotropic diffusion characteristics in white matter fibrous structures. Moreover, apparent diffusion coefficient maps were calculated to exclude false-positive reading results in the DW sequences caused by a T2 shine-through effect. T2-weighted turbo spin-echo MRI (2,500/85; matrix 260 × 512; flip angle 180°; and section thickness 5 mm) and T1-weighted spin-echo MRI (440/12; matrix 169 × 256; flip angle 70°; and section thickness 5 mm) were also performed. All DW-MRI exams were analyzed offline by a neuroradiologist blinded to the clinical data. The presence, number, size, and location (right vs. left hemisphere; anterior or posterior vascular territory) of all new focal diffusion abnormalities were recorded.

Neurologic and cognitive function assessment. The neurologic assessment was obtained with the National Institutes of Health Stroke Scale (NIHSS) questionnaire, and the global cognitive function was assessed with the Mini Mental State Examination (MMSE). Patients were asked to complete the 2 questionnaires at the same time points as the cerebral MRI exams. The NIHSS is a 15-item scale test assessing level of consciousness, gaze, vision, facial palsy, extremity weakness, limb ataxia, sensory loss, language, and dysarthria (14). The MMSE is a 30-point test for evaluation of cognitive impairment briefly sampling orientation, registration, attention, calculation, recall, and language (15).

Statistical analyses. Results are expressed as mean ± SD for continuous variables and percentage for categoric parameters. When a variable was not normally distributed, the result was expressed as median (range or interquartile range). Comparisons between 2 groups were performed using the Student t test or Wilcoxon test for continuous variables and the chi-square test for categoric data. Comparisons between >2 groups were made using analysis of variance (ANOVA) for normally distributed continuous data, Kruskal-Wallis for non–normally distributed continuous data, and chi-square test for categoric data. Differences were considered statistically significant at $p < 0.05$. The data were analyzed with SAS statistical software, version 9.1.3 (SAS Institute Inc., Cary, North Carolina).

Results

A total of 81 patients underwent a cerebral DW-MRI exam within the 24 h before TAVI. Of these, 60 patients had a second MRI exam at 4 ± 1 days following the procedure and constituted the study population. The reasons for not performing the post-procedural MRI in 21 patients were the following: patient death (n = 5), patient refusal (n = 6), temporary or permanent post-procedural pacemaker implantation (n = 6), hemodynamic or respiratory instability (n = 3), and abortion of the procedure owing to large aortic annulus as measured by TEE (n = 1). None of the patients who did not undergo a second MRI had a clinically apparent stroke. The clinical, ECG, and CT data of the study population are shown in Table 1. Pre-procedural CT images of the native aortic valve were available in 38 of the 60 patients. On the basis of iliofemoral anatomy, 29 patients (48%) were selected for the TF approach and 31 (52%) for the TA approach. The TA candidates more frequently had a history of coronary artery disease, had a smaller aortic annulus size, exhibited a lower amount of calcium in the native aortic valve as evaluated by CT, and received more frequently the 23-mm Edwards valve. The procedure was successful in all but one patient (98.4%), in whom the impossibility of stabilizing the balloon during balloon valvuloplasty owing to severe septal hypertrophy protruding in the left ventricular outflow tract prevented valve implantation.

Cerebral MRI data. Pre-procedural MRI showed the absence of acute ischemic lesions in all patients and the presence of old ischemic lesions in 32 patients (53%), most of them (84%) <1 cm. Post-procedural DW-MRI data for the entire study population and for the TF and TA groups are presented in Table 2. The post-procedural MRI exam was performed 4 ± 1 days following the TAVI procedure. A total of 251 new ischemic lesions were detected in 41 patients (68%), with a median number of 3 lesions per patient (range 1 to 36) (Figs. 1 and 2). Most patients (76%) with new lesions had multiple lesions that were distributed in the 2 cerebral hemispheres (73%) and cerebral vascular territories (anterior and posterior; 66%). Most lesions (91%) were <1 cm in size, and no patient had a lesion >5 cm. There were no differences between the TF and TA groups regarding the percent of patients with new ischemic lesions (TF 66%, TA 71%; p = 0.78), the median number of lesions per patient (TF 3, 25th to 75th interquartile range: 1 to 7; TA 4, 25th to 75th interquartile range: 2 to 9; p = 0.38), or lesion size (<1 cm 92% and 91% in TF and TA groups, respectively; p = 1.0).

The clinical, echocardiographic, CT, and procedural characteristics of the patients with new ischemic lesions compared with those without new lesions following TAVI are

Table 1 Clinical and Procedural Characteristics of the Study Population

Variables	All Patients (n = 60)	Transfemoral (n = 29)	Transapical (n = 31)	p Value
Clinical characteristics				
Age (yrs)	83 ± 7	84 ± 7	81 ± 7	0.17
Male sex	30 (50)	16 (55)	14 (45)	0.61
Diabetes	15 (25)	9 (31)	6 (19)	0.38
Dyslipidemia	44 (73)	17 (59)	27 (87)	0.02
Hypertension	45 (75)	19 (66)	26 (84)	0.14
Current smokers	1 (2)	0	1 (3)	1.00
Chronic atrial fibrillation/flutter	14 (23)	7 (24)	7 (23)	1.00
Coronary artery disease	44 (73)	17 (59)	27 (87)	0.02
Prior stroke	9 (15)	4 (14)	5 (16)	1.00
Peripheral vascular disease	19 (32)	5 (17)	14 (45)	0.03
Carotid stenosis >50%	6 (10)	2 (7)	4 (13)	0.67
COPD	14 (23)	6 (21)	8 (26)	0.77
eGFR <60 ml/min	53 (88)	25 (86)	28 (90)	0.70
STS-PROM score (%)	7.7 ± 4.6	8.1 ± 5.5	7.3 ± 3.6	0.55
Logistic EuroSCORE	18.9 ± 12.8	17.6 ± 11.3	20.1 ± 14.1	0.46
Echocardiographic variables				
Mean aortic gradient (mm Hg)	43 ± 17	42 ± 15	44 ± 19	0.76
Aortic valve area (cm^2)	0.63 ± 0.18	0.67 ± 0.18	0.61 ± 0.17	0.22
LVEF (%)	55 ± 13	52 ± 16	57 ± 11	0.15
LVEF <40%	10 (17)	7 (24)	3 (10)	0.17
Aortic annulus diameter (TEE, mm)	22 ± 2	23 ± 2	21 ± 2	<0.0001
Aortic plaques ≥4 mm (TEE)	17 (28)	8 (28)	9 (29)	0.57
Computed tomography				
Aortic valve leaflet calcium volume (mm^3)	2,020 (1,350–4,140)	2,870 (1,890–5,300)	1,650 (1,300–2,570)	0.04
Procedural variables				
Valve diameter (mm)				
23	28 (47)	10 (34)	18 (58)	0.12
26	30 (50)	17 (59)	13 (42)	
Catheter size (F)				
22	10 (17)	10 (34)	—	
24	17 (28)	17 (59)	—	
26	31 (52)	—	31 (100)	
Ratio aortic annulus/valve diameter	0.84 ± 0.17	0.84 ± 0.25	0.85 ± 0.04	0.91
Rapid pacing runs	5 ± 2	4 ± 2	6 ± 2	<0.0001
Procedure duration (min)	83 (70–140)	120 (96–180)	72 (65–81)	0.07
Successful procedure	59 (98)	28 (97)	31 (100)	0.48
Procedural complications				
Valve embolization	0	0	0	—
Valve malposition	1 (2)	0	1 (3)	1.00
Need for second valve	2 (3)	0	2 (6)	0.49
Severe hypotension needing hemodynamic support	2 (3)	0	2 (6)	0.49
Major access site complications	5 (8)	3 (10)	2 (6)	1.00
Life-threatening arrhythmias	2 (3)	1 (3)	1 (3)	1.00

Values are expressed as mean ± SD, n (%), or median (interquartile range) for skewed variables.

COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; STS-PROM = Society of Thoracic Surgeons Predicted Risk Of Mortality; TEE = transesophageal echocardiography.

presented in Table 3. Patients with new lesions tended to more frequently be male, have a history of coronary artery disease, and to exhibit a higher transvalvular aortic gradient at baseline. There were no differences between patients with and without new lesions regarding the prevalence of aortic plaques ≥4 mm as evaluated by TEE (24% vs. 37%; p = 0.36), and the volume of calcium in the native aortic valve (2,340 mm^3, range 1,300 to 4,140 mm^3 vs. 1,830 mm^3, range 1,460 to 3,430 mm^3; p = 0.88). Finally, there were no differences in the procedural characteristics of the patients with new lesions compared with those without new lesions. The clinical, ECG, CT, and procedural characteristics of the study population grouped according to the presence of none, one, or multiple new lesions in the post-procedural DW-MRI exam are shown in Table 4. There were no differences

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Table 2 DW-MRI Findings Following TAVI

Variables	All Patients (n = 60)	Transfemoral (n = 29)	Transapical (n = 31)	p Value
Patients with new lesions	41 (68)	19 (66)	22 (71)	0.78
Total number of lesions	251	83	168	
Lesions per patient	3 (2–8)	3 (1–7)	4 (2–9)	0.38
Patients with single lesion	10 (24)	5 (26)	5 (23)	1.00
Patients with multiple lesions	31 (76)	14 (74)	17 (77)	
Lesion location, patients				
Right hemisphere	7 (17)	4 (21)	3 (14)	0.68
Left hemisphere	4 (10)	1 (5)	3 (14)	
Bilateral lesions	30 (73)	14 (74)	16 (73)	
Anterior circulation territory	9 (22)	5 (26)	4 (18)	0.58
Posterior circulation territory	5 (12)	3 (16)	2 (9)	
Anterior and posterior circulation territories	27 (66)	11 (58)	16 (73)	
Lesion size, cm				
<1	229 (91)	76 (92)	153 (91)	1.00
1–5	22 (9)	7 (8)	15 (9)	1.00
>5	0	0	0	—
Time of post-procedural DW-MRI, days	4 (2–6)	4 (2–6)	5 (3–6)	0.37

Values are expressed as n (%) or median (interquartile range) for skewed variables.
DW-MRI = diffusion-weighted magnetic resonance imaging; TAVI = transcatheter aortic valve implantation.

between patients with none, one, or multiple new lesions following TAVI, except for a higher rate of single lesions in patients with peripheral vascular disease.

Neurologic and cognitive function assessment. Post-procedural neurologic evaluation with the NIHSS score showed no differences compared with baseline examinations (median 0, range 0 to 8 for both time periods; p = 1.0). Patients with new cerebral ischemic lesions exhibited similar median post-procedural NIHSS values as those with no new lesions (0, range 0 to 8 vs. 0, range 0 to 3, respectively; p = 1.0). However, clinically apparent neurologic complications occurred in 2 patients who presented with a stroke within 24 h following the TAVI procedure. One patient who underwent TF-TAVI presented immediately after the procedure with diplopia that persisted up to hospital discharge, and another patient who underwent TA-TAVI presented with a right-sided stroke. The DW-MRI exams showed multiple new cerebral ischemic lesions disseminated in the 2 cerebral hemispheres and vascular territories in both patients (7 and 11 new lesions in the TF and TA patients, respectively).

The post-procedural cognitive assessment with the MMSE test exhibited similar values to the one performed at baseline (median 28, range 16 to 30 vs. 28, range 17 to 30; p = 0.14). Also, there were no differences in the post-procedural MMSE score of the patients with new MRI lesions compared with those without new lesions (28, range 16 to 30 vs. 28, range 18 to 30; p = 0.90).

Discussion

TAVI was associated with a high rate (68%) of new cerebral lesions as evaluated by DW-MRI. The new cerebral lesions were multiple and distributed in the 2 cerebral hemispheres and vascular territories in most patients, strongly suggesting an embolic origin. Although the use of large catheters in the aortic arch/ascending aorta and the retrograde crossing of the native aortic valve were avoided, the TA approach was not associated with a reduction of post-procedural new cerebral lesions compared with the TF approach. No independent predictors of new lesions were identified among the clinical, echocardiographic, CT, and procedural variables, and this included the presence of aortic plaques ≥4 mm and the amount of calcium in the native aortic valve. Finally, the vast majority of new cerebral lesions were small and not associated with any measurable impairment in neurologic or cognitive function. However, 2 patients (3.3%, 1 patient in each group) presented with a clinically apparent stroke within 24 h following the procedure.

Incidence of cerebral embolism: the TF and TA approaches. Omran et al. (5) showed that patients with severe valvular aortic stenosis who underwent retrograde catheterization of the aortic valve had a high risk of cerebral embolism, with an incidence as high as 22% as evaluated by DW-MRI in those patients who underwent retrograde crossing of the aortic valve. Kahlert et al. (8) found an incidence of new ischemic lesions following TF-TAVI as high as 84% at a median time of 3 days following the procedure in 32 patients. A balloon expandable valve (Edwards) was used in most patients in that study. Ghanem et al. (9) evaluated the incidence of cerebral embolism by DW-MRI in 22 patients who underwent TF-TAVI with a self-expandable valve (CoreValve revalving system, Medtronic, Minneapolis, Minnesota). The incidence of new cerebral lesions was as high as 73%, with 10% of the patients also exhibiting clinically apparent neurologic impairment. Consistent with these results, we

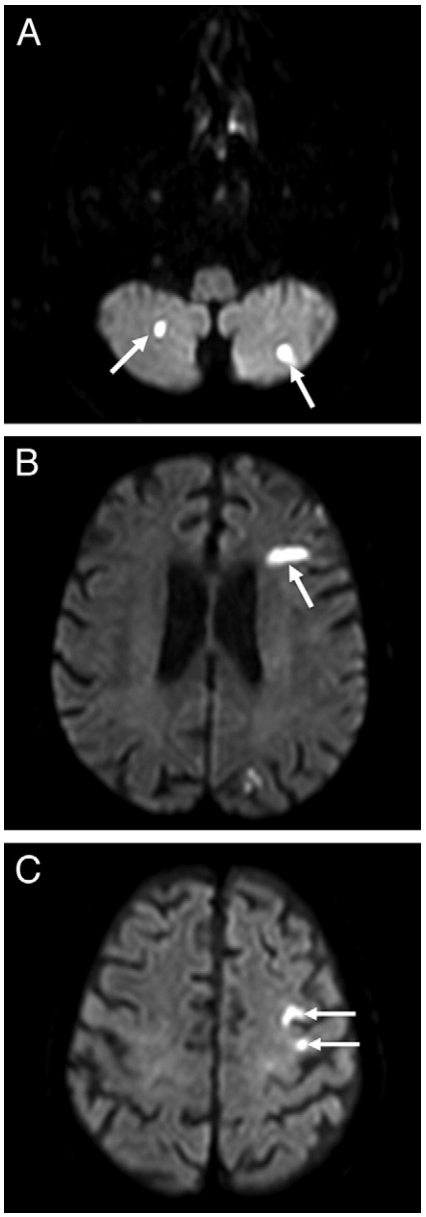

Figure 1 **DW-MRI Images Following TA-TAVI**

Diffusion-weighted magnetic resonance imaging (DW-MRI) images following transapical transcatheter aortic valve implantation (TA-TAVI) in an 83-year-old patient showing multiple acute ischemic lesions in the left and right cerebellum **(A, white arrows)** and left frontal territory **(B and C, white arrows)**.

found an incidence of 66% of new ischemic lesions following TF-TAVI with the Edwards valve. In all of these studies, including ours, the new lesions were multiple and disseminated in the 2 cerebral hemispheres and vascular territories, a pattern that strongly suggests an embolic origin.

It has been suggested that TAVI by the TA approach might be associated with a lower rate of cerebral embolic events by avoiding the use of large catheters across the aorta and the retrograde crossing of the native aortic valve. In this regard, Himbert et al. (16) and Bleiziffer et al. (17) reported a lower incidence of clinically apparent stroke in patients undergoing TA-TAVI compared with those who had TF-TAVI, but these findings have not been confirmed by other larger studies including the 2 (TF and TA) approaches (18–20). The present study is the first to determine the incidence of cerebral ischemic defects as evaluated by DW-MRI following TA-TAVI and has shown that the rate of new ischemic lesions in the TA approach (71%) is similar to the rate in the TF approach (66%). Also similar to the TF approach, new ischemic lesions following TA-TAVI were usually multiple (median number per patient 4, ranging from 1 to 31) and dispersed in the 2 cerebral hemispheres and vascular territories. The similarity in lesion rate and location between the 2 TAVI approaches suggests that the mechanisms responsible for cerebral embolism are not solely related to catheter manipulation in the aorta or retrograde passage through the aortic valve.

Mechanisms of cerebral embolism associated with TAVI. The use of diagnostic catheters in the ascending aorta during left heart catheterization or coronary interventions has been associated with a very high rate of cerebral microemboli as determined by multifrequency transcranial Doppler (4,21–25). Most (>90%) cerebral microemboli occurring during left heart catheterization are gaseous and are usually detected during contrast injection or catheter flushing; only a minority of these microemboli are solid, most likely secondary to mechanical fragmentation of atherosclerotic plaques or clots from the tip of the catheter (2–4). However, despite the very high incidence of microembolic signals during these procedures, the incidence of DW-MRI lesions has ranged between 10% and 35% (4,26–28), much lower than the rate observed in TAVI. The TAVI procedure involves the use of both small diagnostic catheters for contrast injection throughout the procedure and the use of very large semirigid catheters containing the crimped stent valve. The advancement of a large catheter across the aortic arch and ascending aorta in TF-TAVI might have been associated with a significant number of solid microemboli (2–4). However, the lack of association between the occurrence of new ischemic lesions and the atherosclerotic risk factors and aortic atheroma burden in our study, and the similar rate of embolic events in the TF and TA groups, suggest that this is probably not the main mechanism of cerebral ischemic lesions during TAVI procedures. On the other hand, the use of very large catheters in both the TF and TA approaches favors a significant increase in the frequency and severity of air embolism. Various studies have shown that gaseous embolism during intra-arterial cardiac or cerebral procedures may be associated with brain damage and neuropsychologic deficits (29–32). Air embolism could be of special importance in TA-TAVI, in which a 26-F catheter is inserted and kept in the left ventricular cavity throughout the entire procedure, with many exchanges through the catheter in-

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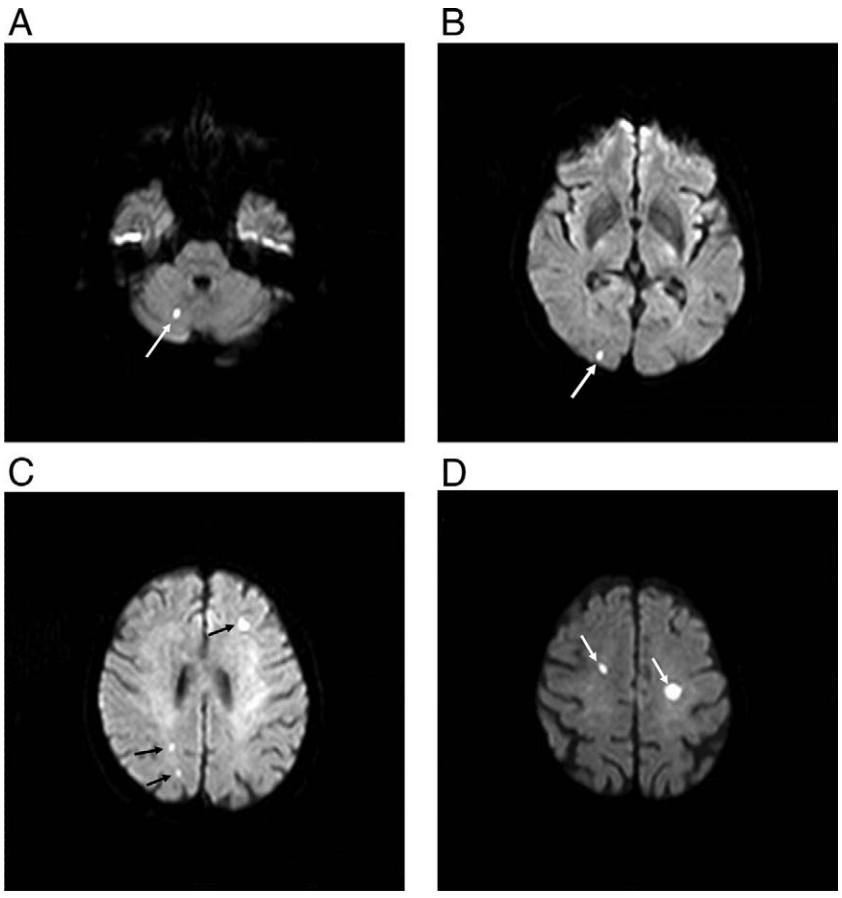

Figure 2 **DW-MRI Images Following TF-TAVI**

Diffusion-weighted magnetic resonance imaging (DW-MRI) images following transfemoral transcatheter aortic valve implantation (TF-TAVI) in an 86-year-old patient showing multiple acute ischemic lesions in the right cerebellum **(A, white arrow)**, right occipital territory **(B, white arrow)**, left frontal and right parietal territories **(C, black arrows)**, and left and right frontal superior territories **(D, white arrows)**.

cluding diagnostic catheters, wires, balloons, and the valve prosthesis. In fact, the TEE images usually show several showers of bubbles during the procedure, especially during the advancement of the valvuloplasty balloon and transcatheter valve. A careful flushing of the catheters before insertion, checking for the presence of air bubbles within the catheter before balloon/valve insertion, and ensuring adequate patient ventilation with oxygen concentration at 100% during insertion and retrieval of the balloon/valve through the catheter might help to reduce the incidence of cerebral embolism during these procedures. Finally, catheter retrieval in the TA approach leads to a short direct communication between the left ventricular cavity and the external air space, which might also play a role in the occurrence of cerebral air embolism in these cases.

It has been shown that crossing a stenosed aortic valve during retrograde cardiac catheterization was associated with up to 22% of silent cerebral embolisms (4), most likely related to the dislodgement of calcific valve particles of the stenosed valve (33). The TF-TAVI involves crossing the aortic valve with a large catheter and the stent containing the valve and could contribute to the occurrence of acute cerebral lesions. However, the absence of differences in the rate of cerebral embolism between TF and TA approaches suggests that this might not be the main mechanism of cerebral embolism in TF cases. On the other hand, TAVI involves at least 2 episodes of maximum stretching of the aortic valve leaflets (i.e., balloon valvuloplasty and valve implantation). It seems plausible that creating such major mechanical stress on a diseased aortic valve would be associated with the dislodgement of a significant amount of valve particles that could lead to cerebral embolism. Again, the fact that the TF and TA approaches had nearly identical cerebral embolism rates suggests that this might be one of the main mechanisms of cerebral embolism during TAVI procedures. However, we did not find any correlation between the severity of valve leaflet calcification and the occurrence of new cerebral ischemic lesions following TAVI. This lack of association might be due in part to the fact that the quantification of total calcium volume by CT

Table 3 Baseline and Procedural Characteristics of the Study Population According to the Presence or Absence of New Cerebral Ischemic Lesions Following TAVI

Variables	New Cerebral Ischemic Lesions		p Value
	Yes (n = 41)	No (n = 19)	
Clinical characteristics			
Age (yrs)	83 ± 8	82 ± 6	0.79
Male sex	24 (59)	6 (32)	0.09
Diabetes	11 (27)	4 (21)	0.75
Dyslipidemia	31 (76)	13 (68)	0.55
Hypertension	32 (78)	13 (68)	0.52
Current smokers	1 (2)	0	1.00
Chronic atrial fibrillation/flutter	10 (24)	4 (21)	1.00
Coronary artery disease	33 (80)	11 (58)	0.11
Prior stroke	7 (17)	2 (11)	0.71
Peripheral vascular disease	14 (34)	5 (26)	0.77
Carotid stenosis >50%	3 (7)	3 (16)	0.37
COPD	9 (22)	5 (26)	0.74
eGFR <60 ml/min	35 (85)	18 (95)	0.41
STS-PROM score (%)	8.1 ± 5.2	6.9 ± 2.9	0.27
Logistic EuroSCORE	19.5 ± 14.2	17.6 ± 9.5	0.59
Echocardiographic variables			
Mean aortic gradient (mm Hg)	44.8 ± 19.3	38.6 ± 11.2	0.12
Aortic valve area (cm^2)	0.63 ± 0.19	0.65 ± 0.12	0.55
LVEF (%)	54.5 ± 12.1	56.3 ± 15.9	0.65
LVEF <40%	8 (20)	2 (11)	0.48
Aortic annulus diameter (TEE, mm)	22 ± 2	21 ± 2	0.66
Aortic plaques ≥4 mm	10 (24)	7 (37)	0.36
Computed tomography			
Aortic valve leaflet calcium volume (mm^3)	2,340 (1,300–4,140)	1,830 (1,460–3,430)	0.88
Procedural variables			
Valve diameter (mm)			
23	18 (44)	10 (53)	0.78
26	21 (51)	9 (47)	
Ratio aortic annulus/valve diameter	0.83 ± 0.21	0.87 ± 0.04	0.23
Rapid pacing runs	5 ± 2	5 ± 2	0.29
Procedure duration	82 (70–124)	96 (65–180)	0.27
Successful procedure	40 (98)	19 (100)	1.00
Procedural complications			
Valve embolization	0	0	—
Valve malposition	1 (2)	0	1.00
Need for second valve	2 (5)	0	1.00
Severe hypotension needing hemodynamic support	1 (2)	1 (5)	0.54
Major access site complications	2 (5)	3 (16)	0.31
Life-threatening arrhythmias	2 (5)	0	1.00

Values are expressed as mean ± SD, n (%), or median (interquartile range) for skewed variables.
Abbreviations as in Tables 1 and 2.

does not necessarily capture the information about the distribution, location (i.e., calcium nodules located intrinsically within the valve leaflet or extrinsically at the surface of the leaflet), and propensity of valvular calcification to embolize. Also, the fact that the CT data were not available in all patients (68%) may have limited the ability to detect an association between CT calcification scoring and cerebral embolism.

It is well known that the occurrence of episodes of severe hypotension can be associated with cerebral damage, especially in those patients with significant carotid disease (34). The TAVI with the Edwards valve involves at least 2 short episodes of extreme hypotension owing to the use of rapid pacing runs during balloon valvuloplasty and valve implantation. However, no correlation was found between the number of rapid pacing runs and the presence and number of new ischemic lesions in our study, and those patients with carotid stenosis ≥50% did not exhibit a higher rate of new lesions. This strongly suggests that the occurrence of cerebral lesions was not related to the rapid pacing strategy. The number of patients with complications needing hemodynamic support was low (n = 2), precluding any comprehen-

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Table 4 Baseline and Procedural Characteristics of the Study Population According to the Presence of None, Single, or Multiple New Cerebral Ischemic Lesions Following TAVI

Variables	No Lesions (n = 19)	Single Lesions (n = 10)	Multiple Lesions (n = 31)	p Value
Baseline characteristics				
Age (yrs)	82 ± 6	84 ± 7	82 ± 8	0.86
Male sex	6 (32)	6 (60)	18 (58)	0.17
Diabetes	4 (21)	2 (20)	9 (29)	0.78
Dyslipidemia	13 (68)	8 (80)	23 (74)	0.86
Hypertension	13 (68)	7 (70)	25 (81)	0.66
Current smokers	0	0	1 (3)	0.87
Chronic atrial fibrillation/flutter	4 (21)	1 (10)	9 (29)	0.55
Coronary artery disease	11 (58)	8 (80)	25 (81)	0.21
Prior stroke	2 (11)	2 (20)	5 (16)	0.80
Peripheral vascular disease	5 (26)	7 (70)	7 (23)	0.03
Carotid stenosis >50%	3 (16)	2 (20)	1 (3)	0.13
COPD	5 (26)	3 (30)	6 (19)	0.71
eGFR <60 ml/min	18 (95)	8 (80)	27 (87)	0.42
STS-PROM score (%)	6.9 ± 2.9	9.7 ± 7.7	7.5 ± 4.1	0.28
Logistic EuroSCORE	17.6 ± 9.5	18.6 ± 10.9	19.8 ± 15.2	0.84
Echocardiographic variables				
Mean aortic gradient (mm Hg)	39 ± 11	49 ± 14	44 ± 21	0.31
Aortic valve area (cm^2)	0.65 ± 0.12	0.56 ± 0.21	0.65 ± 0.19	0.31
LVEF (%)	56 ± 16	54 ± 15	55 ± 11	0.89
LVEF <40%	2 (11)	2 (20)	6 (19)	0.72
Aortic annulus diameter (TEE, mm)	21 ± 2	21 ± 2	22 ± 2	0.45
Aortic plaques ≥4 mm	7 (37)	4 (40)	6 (19)	0.28
Computed tomography				
Aortic valve leaflet calcium volume (mm^3)	1,830 (1,460–3,430)	3,030 (1,060–4,320)	2,320 (1,450–2,830)	0.90
Procedural variables				
Valve diameter (mm)				
23	10 (53)	5 (50)	13 (42)	0.77
26	9 (47)	4 (40)	17 (55)	
Ratio aortic annulus/valve diameter	0.87 ± 0.04	0.77 ± 0.29	0.85 ± 0.17	0.30
Rapid pacing runs	5 ± 2	6 ± 3	5 ± 2	0.54
Procedure duration	96 (65–180)	82 (70–100)	82 (70–150)	0.25
Successful procedure	19 (100)	9 (90)	31 (100)	0.17
Procedural complications				
Valve embolization	0	0	0	—
Valve malposition	0	0	1 (3)	1.00
Need for a second valve	0	0	2 (6)	0.67
Severe hypotension needing hemodynamic support	1 (5)	1 (10)	0	0.23
Major access site complications	3 (16)	0	2 (6)	0.45
Life-threatening arrhythmias	0	0	2 (6)	0.67

Values are expressed as mean ± SD, n (%), or median (interquartile range) for skewed variables.
Abbreviations as in Tables 1 and 2.

sive analysis of the role of this factor in the occurrence of cerebral lesions.

Silent cerebral infarction and neurocognitive function. It has been shown that silent cerebral infarction is frequently associated with subtle deficits in physical and cognitive function that commonly go unnoticed, as well as with an increased risk of subsequent stroke and dementia (35). However, previous studies regarding the clinical relevance of cerebral microemboli and silent cerebral ischemic lesions during cardiac procedures have reported mixed results. Although some studies have shown no correlation between silent infarction and neurologic and cognitive functions (36–38), others have reported significant impairment in neurocognitive functions in cases of cerebral embolism following a cardiac procedure (4,21,39). This might be due in part to the method used for analysis of neurocognitive function. We used the MMSE, a quick screening tool of global cognitive function, to evaluate cognitive function pre- and post-TAVI, and we did not find any association between the occurrence of new ischemic lesions and neurocognitive function. We cannot exclude the possibility that a more extensive neurocognitive evaluation might have been

able to detect subtle changes in neurocognitive function. Interestingly, Gerriets et al. (40) recently reported a moderate but significant correlation between silent infarction and early cognitive function decrease following coronary artery bypass grafting, but this correlation disappeared at a 3-month follow-up. Consistent with our results, Kahlert et al. (8) did not find any measurable impairment in neurocognitive function following TF-TAVI as evaluated by the MMSE, despite a high incidence (84%) of silent ischemic events. The reported incidence of clinically apparent stroke following TAVI has been between 2% and 4% in most series, also consistent with the results of the present study (16–20,41). Kahlert et al. (8) suggested that the incidence of cerebral embolism associated with TF-TAVI was higher than that following surgical aortic valve replacement. However, no surgical studies to date have included such an extremely high risk group of patients as those treated by TAVI, and only the results of prospective studies such as the PARTNER (Placement of Aortic Transcatheter Valve) trial will provide definite data comparing the rate of cerebrovascular events following TAVI and surgical procedures.

Study limitations. The comparison between the TF and TA groups was not performed in a randomized way. However, this was partially compensated for by the fact that very few differences in baseline characteristics were observed between the 2 groups, and none of the variables exhibiting differences was found to be a predictor of cerebral embolism. Also, the way patients were selected for TF or TA approach reflects the clinical practice of the vast majority of clinical TAVI programs. We did not use transcranial Doppler, and this precluded determining the type (solid vs. gaseous) and timing of the cerebral microemboli during the TAVI procedure. Although this is the largest study evaluating the occurrence of cerebral embolism by DW-MRI following TAVI, the relatively small sample size might have limited our ability to detect independent predictors of cerebral embolism. Also, this was an exploratory study with a sample size determined on an empiric basis, and the results regarding the absence of differences in cerebral embolism between TF and TA groups should be confirmed in a larger and adequately powered sample size trial.

Conclusions

This first multicenter study evaluating the incidence of cerebral embolism by DW-MRI after TA- and TF-TAVI procedures showed that new cerebral ischemic lesions occurred in about two-thirds of the patients, regardless of the approach. The lack of differences between TA and TF approaches suggests that the mechanical stress of the aortic valve during balloon valvuloplasty/valve implantation and the occurrence of gaseous embolism might be the main mechanisms linking the TF- and TA-TAVI procedures to cerebral embolism. However, no predictive factors of cerebral embolism were found, reflecting the complexity of evaluating the mechanisms, which are probably multifactorial, of cerebral embolism in these procedures. These results support the need of further research to both improve the profile and reduce the size of TAVI catheters and evaluate the efficacy of using protection systems for cerebral circulation during TAVI.

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