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Implantation: A Prospective Pilot Study With Diffusion-Weighted Magnetic
Resonance Imaging**

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Risk and Fate of Cerebral Embolism After Transfemoral Aortic Valve Implantation

A Prospective Pilot Study With Diffusion-Weighted Magnetic Resonance Imaging

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Objectives	The aim of this study was prospective investigation of silent and clinically apparent cerebral embolic events and neurological impairment after transfemoral aortic valve implantation (TAVI).
Background	TAVI is a novel therapeutic approach for multimorbid patients with severe aortic stenosis. We investigated peri-interventional cerebral embolism with diffusion-weighted magnetic resonance imaging (DW-MRI) and its relationship to clinical and serologic parameters of brain injury.
Methods	Cerebral DW-MRI was performed before, directly, and 3 months after TAVI with the current third-generation self-expanding CoreValve (Medtronic, Minneapolis, Minnesota) prosthesis. At the timepoints of the serial MRI studies, focal neurological impairment was assessed according to the National Institutes of Health Stroke Scale (NIHSS), and serum concentration of neuron-specific enolase (NSE), a marker of the volume of brain tissue involved in an ischemic event, were determined.
Results	Thirty patients were enrolled; 22 completed the imaging protocol. Three patients (10%) had new neurological findings after TAVI, of whom only 1 (3.6%) had a permanent neurological impairment. Of the 22 TAVI patients with complete imaging data, 16 (72.7%) had 75 new cerebral lesions after TAVI presumed to be embolic. The NIHSS and NSE were not correlated with DW-MRI lesions.
Conclusions	The incidence of clinically silent peri-interventional cerebral embolic lesions after TAVI is high. However, in this cohort of 30 patients, the incidence of persistent neurological impairment was low. (Incidence and Severity of Silent and Apparent Cerebral Embolism After Conventional and Minimal-invasive Transfemoral Aortic Valve Replacement; NCT00883285) (J Am Coll Cardiol 2010;55:1427-32) © 2010 by the American College of Cardiology Foundation

Transfemoral aortic valve implantation (TAVI) is a novel therapeutic option for multimorbid, elderly patients with symptomatic aortic stenosis (1). Transfemoral aortic valve implantation involves mechanical stress to the aorta and the aortic valve caused by catheter manipulation, balloon dilation, retrograde valve positioning, and frame expansion. The incidence of clinically apparent cerebral ischemia related to TAVI ranges from 0.6% to 10% (1–3). Hence, there has been concern regarding the peri-interventional risk of cerebral embolism.

Cerebral diffusion-weighted magnetic resonance imaging (DW-MRI) enables detection and localization of acute ischemic lesions with high sensitivity and specificity. Previously, DW-MRI has been employed to evaluate the risk of cerebral embolism associated with cardiovascular procedures (4). Furthermore, embolic lesions detected by DW-MRI have been associated with clinical impairment and serologic biomarkers of brain damage (5). More specifically, neuron-specific enolase (NSE) concentration has been found to correlate closely with the volume of ischemic stroke (6). However, its relationship to TAVI-related cerebral embolism has not been elucidated yet.

Thus, the aim of this pilot study was to investigate the incidence of clinically silent and apparent cerebral embolism in patients undergoing TAVI and to correlate DW-MRI findings with clinical and serologic markers of brain damage.

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Abbreviations and Acronyms

DW-MRI = diffusion-weighted magnetic resonance imaging

E1 = before transfemoral aortic valve implantation

E2 = within 3 days of transfemoral aortic valve implantation

E3 = 3 months after transfemoral aortic valve implantation

NIHSS = National Institutes of Health Stroke Scale

NSE = neuron-specific enolase

TAVI = transfemoral aortic valve implantation

Methods

Between November 2008 and June 2009, all patients scheduled for TAVI at our institution were screened for inclusion into this prospective study. Indication for TAVI was in concordance with the recent consensus statement (7). Detailed inclusion and exclusion criteria are depicted in the Online Methods section. The study was approved by the local medical ethics committee, and all patients signed informed, written consent. Cerebral DW-MRI was performed in patients before (E1), within 3 days (E2), and 3 months after (E3) TAVI (Fig. 1). At these

timepoints, focal neurological impairment was assessed by a certified cardiologist following a standardized protocol according to the National Institutes of Health Stroke Scale (NIHSS), and serum NSE was determined (Liaison NSE, Diasorin, Italy).

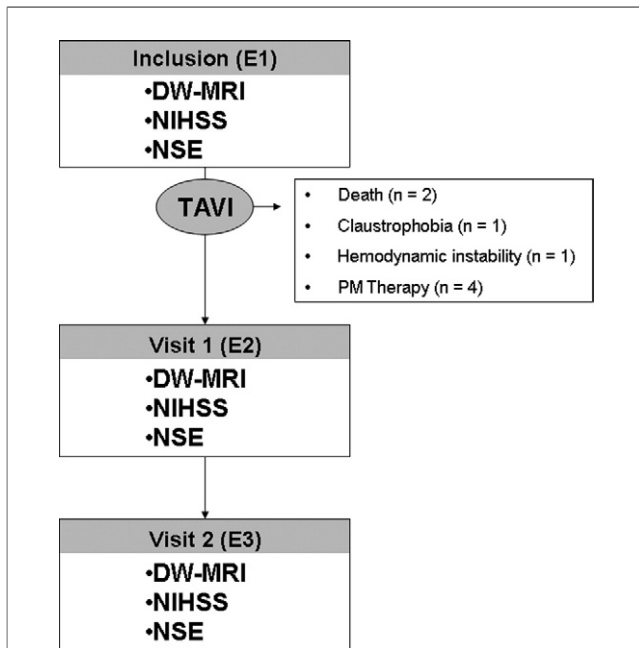


Figure 1 Study Protocol

Thirty patients were eligible for the study protocol. Eight patients could not be investigated with magnetic resonance imaging (MRI) serially due to death, hemodynamic instability, new-onset of claustrophobia, and necessity of post-interventional permanent pacemaker (PM) therapy. DW-MRI = diffusion-weighted magnetic resonance imaging; E1 = before transfemoral aortic valve implantation; E2 = within 3 days of transfemoral aortic valve implantation; E3 = 3 months after transfemoral aortic valve implantation; NIHSS = National Institutes of Health Stroke Scale; NSE = neuron-specific enolase; TAVI = transfemoral aortic valve implantation.

Table 1 Patient Characteristics

Clinical data	
Age, yrs	79.3 ± 4.8
Male	8 (36.4)
Body mass index, kg/m ²	26 ± 6.2
Log. EuroScore, %	19.4 ± 13.5
STS score–mortality, %	6.2 ± 4.2
STS score–permanent stroke, %	2.8 ± 1.3
Peak-to-peak-gradient, mm Hg	50.3 ± 22
Ejection fraction, %	53 ± 16.6
NT-pro-BNP level, pg/ml	3,323 (948–10,220)
NYHA functional class	3 ± 0.5
Comorbidities	
Hypertension	21 (95)
Diabetes	5 (23)
Smoking	8 (36)
Dyslipidemia	20 (91)
Creatinine, mg/dl	1.5 ± 1.2
Hemodialysis	2 (9)
CHADS ₂ score	3.1 ± 1.1
Prior stroke	6 (27)
Prior TIA	3 (14)
PVD	15 (68)
Aortic atheroma ≥4 mm	11 (50)

Values are mean ± SD, n (%), or median (interquartile range).

NT-pro-BNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association functional class; PVD = peripheral vascular disease; STS = Society of Thoracic Surgeons; TAVI = transfemoral aortic valve implantation; TIA = transient ischemic attack.

MRI. Quantitative cranial DW-MRI was performed with a 1.5-T whole body system (Intera, Philips Medical Systems, Best, the Netherlands). Scans were read by 2 experienced radiologists blinded to the timing of the imaging and the neurological status of the patient. In case of discrepancy, a consensus reading was held. Detailed protocols and method of data analysis are presented in the Online Methods section.

TAVI. The third-generation (18-F) CoreValve revalving system (Medtronic, Inc., Minneapolis, Minnesota) consists of a tri-leaflet bioprosthetic porcine pericardial tissue valve mounted and sutured in a self-expanding nitinol frame. Details of TAVI are described in the Online data and have been published previously (1).

Statistical analyses. Continuous variables are presented as mean ± SD. Ordinal data were analyzed by means of Cochran-Armitage test for trend. Categorical variables were compared by chi-square statistics or Fisher exact test. The paired, 2-sided Student *t* test and the Mann-Whitney-Wilcoxon test were used for comparison. Association between frequency of embolic events and continuous variables was examined by Spearman’s correlation.

Results

Thirty patients were enrolled. Clinical and serological investigations could be obtained in 28 patients (93%); 22 patients (73%) completed the entire study protocol (Table 1). The E2 and E3 were performed 2.2 ± 0.4 days and 91 ± 5 days after TAVI, respectively. Two

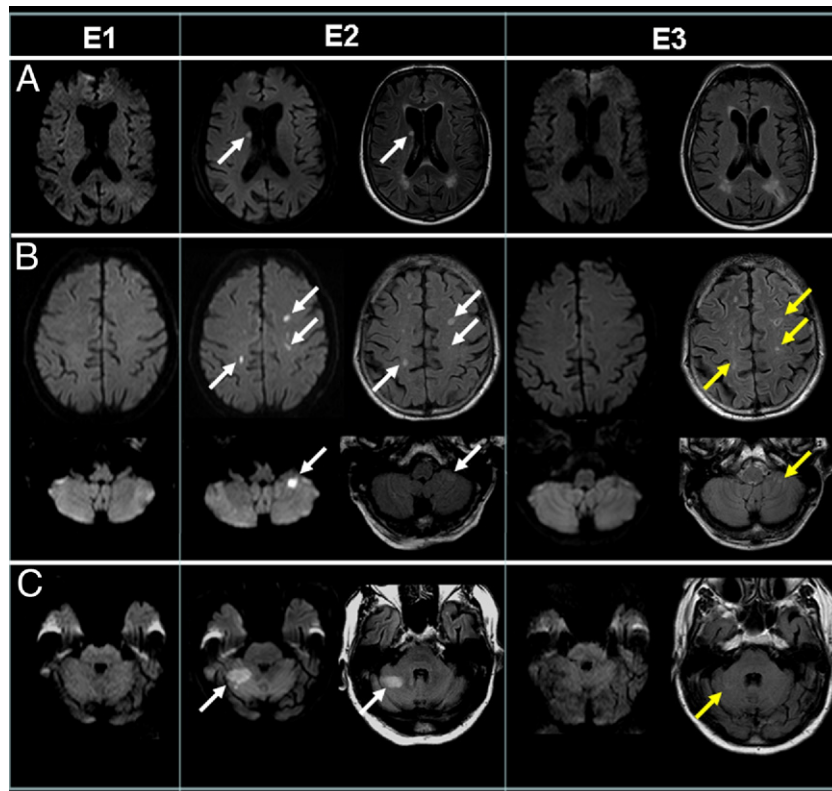


Figure 2 TAVI-Related Cerebral Embolism

(A) Images obtained in an 83-year-old man show 1 ischemic lesion (arrow). The patient had no clinically apparent focal neurological deficits after TAVI (NIHSS: 0). (B) A DW-MRI in a 73-year-old man demonstrates multiple, bilateral embolism of the cerebrum and cerebellum (arrows). Selected emboli demonstrate signal intensity in the fluid-attenuated inversion recovery sequence as sign of neuronal repair (yellow arrows). The patient had no clinically apparent focal neurological deficits after TAVI (NIHSS: 0). (C) Images obtained in an 84-year-old man show 1 ischemic lesion in the right cerebellum (arrow). The patient demonstrated transient ataxia (NIHSS: 4). Abbreviations as in Figure 1.

patients were lost to all E2 and E3 investigations, due to death within 2 days after TAVI due to coronary stent thrombosis (autopsy) and acute heart failure, respectively. The post-interventional necessity of permanent pacemaker implantation (n = 4), new onset of claustrophobia (n = 1), and hemodynamic instability impeding transport to DW-MRI (n = 1) reflect the reasons for the other 6 missing DW-MRI studies.

MRI. All patients showed brain atrophy and hyperintense white matter lesions at E1. Eleven patients revealed lacunar defects, and 5 showed old territorial infarcts. No patient revealed acute ischemic lesions in the baseline DW-MRI. At E2, a total of 75 new lesions were detected (range: 0 to 19 lesions/patient) in 16 patients (72.7%). Representative MRI

Table 2 DW-MRI Lesion Localization and Size After TAVI

Vascular Territories	DW-MRI Lesion Volume Range (cm ³)
Anterior cerebral artery	0.1-59.2
Middle cerebral artery	0.1-4.5
Posterior cerebral artery	0.1-8.6
Vertebro-basilar arteries	0.1-1.6

DWI = diffusion-weighted magnetic resonance imaging; TAVI = transfemoral aortic valve implantation.

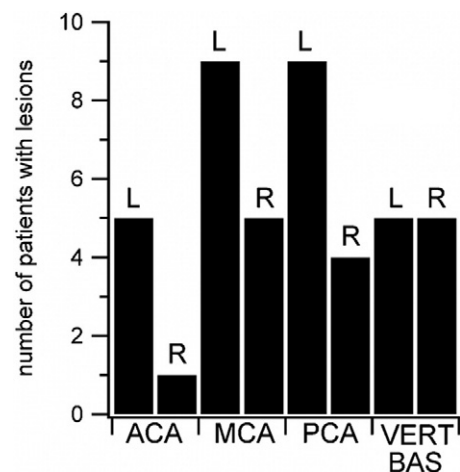


Figure 3 Vascular Distribution of Embolic Lesions

Localization of diffusion-weighted magnetic resonance imaging (DW-MRI) lesions after transfemoral aortic valve implantation (TAVI) depicted as embolic events in each vascular territory on a per-patient basis. ACA = anterior cerebral artery; L = left; MCA = middle cerebral artery; PCA = posterior cerebral artery; R = right; VERT BAS = vertebro-basilar arteries.

examinations are depicted in Figure 2. Thirty-one of 75 lesions (41.3%) were demonstrated in patients with lacunar defects and old infarcts. Of those, 59 and 16 new ischemic lesions were located in supratentorial and infratentorial regions, respectively (Table 2). Interestingly, the majority of the supratentorial lesions (67.8%) were located on the left side (Fig. 3). Three of 16 patients (18.7%) with a TAVI-related cerebral embolism at E2 developed a focal signal increase in the region corresponding to the original index lesion, showing infarcted brain tissue at E3.

To evaluate the association of calculated risks of mortality and permanent stroke, regression analyses of risk scores and frequency of DW-MRI lesions were performed. Post-interventional embolism demonstrated no significant association with calculated mortality with EuroScore ($r = -0.33$, $p = 0.13$), Society of Thoracic Surgeons score ($r = -0.24$, $p = 0.27$), and Society of Thoracic Surgeons score permanent stroke ($r = 0.21$, $p = 0.35$).

Neurological and biochemical evaluation. Patient #1 reported onset of unspecific dizziness 48 h after TAVI (Table 3).

Neurological examination revealed transient cerebellar ataxia (NIHSS: 4). Patient #15 demonstrated onset of persistent severe focal neurological deficits 36 h after TAVI. Neurological assessment showed left-sided hemiparesis resulting in an NIHSS of 16 points. Patient #16 demonstrated transient dysarthria 48 h after TAVI. Three months after TAVI neurological examination revealed no significant deficits in all but 1 (Patient #15) of the surviving 28 patients (3.6%). The NSE did not increase significantly after TAVI ($19.1 \pm 13.5 \mu\text{g/l}$ [E1], $22.6 \pm 7.3 \mu\text{g/l}$ [E2], $14.5 \pm 4.5 \mu\text{g/l}$ [E3]; $p = \text{NS}$).

Potential sources of embolism. To elucidate potential sources of cerebral embolism, baseline characteristics of patients with and without embolic lesions in DW-MRI were compared (Table 4). We observed a slightly higher prevalence of cerebrovascular and peripheral artery disease and aortic atheroma in patients with embolic lesions in DW-MRI. Interestingly, all patients with frame dilation ($n = 4$) had embolic events. Procedural duration of TAVI was not significantly higher in patients with embolic events. Correlation of duration time and number of embolic events was not significant ($r = 0.12$, $p = 0.59$).

Table 3 Individual Neurological Risk and Outcome in Consecutive TAVI Patients

Patient #	Sex/Age (yrs)	Stroke-Risk (%)*	Procedure Time (min)	DW-MRI Lesion (E2) n/Total Volume (cm ³)	NIHSS			Delta NSE†
					E1	E2	E3	
1	M/84	3.5	47	5/4.7	0	4	0	+ 0.6
2	M/88	4.0	87	Not performed‡	0	0	0	+ 2.0
3	F/81	6.3	71	6/2.0	0	0	0	+ 16.7
4	M/85	2.1	90	Not performed§	0	0	— §	— §
5	F/88	2.5	129	1/0.1	0	0	0	+ 31.0
6	F/79	2.7	70	1/0.1	0	0	0	- 0.1
7	M/76	1.9	90	Not performed	0	0	0	+ 14.6
8	F/69	1.4	60	Not performed¶	0	0	0	- 15.0
9	F/78	6.8	92	Not performed‡	0	0	0	+ 10.7
10	F/83	3.7	96	3/1.0	0	0	0	+ 3.7
11	M/73	1.4	103	19/4.9	0	0	0	- 69.9
12	F/88	4.4	103	Not performed§	0	0	— §	+ 21.7
13	F/75	2.9	51	1/0.1	0	0	0	- 1.8
14	M/85	1.7	127	1/1.3	0	0	0	+ 25.1
15	M/80	5.0	142	6/70.3	0	16	16	+ 9.4
16	F/70	2.5	95	17/7.8	0	1	0	+ 2.3
17	F/71	3.9	72	0/0	0	0	0	+ 13.0
18	F/77	2.4	60	2/0.3	0	0	0	+ 6.4
19	M/74	1.4	115	4/0.4	0	0	0	- 0.3
20	M/82	2.8	90	2/0.3	0	0	0	- 7.4
21	F/85	2.2	67	0/0	0	0	0	+ 1.3
22	F/84	2.0	80	0/0	0	0	0	- 13.7
23	F/82	4.8	81	2/0.4	0	0	0	+ 15.8
24	M/69	1.6	105	Not performed‡	0	0	0	+ 8.7
25	F/79	1.5	195	4/0.6	0	0	0	+ 11.7
26	F/80	2.0	112	0/0	0	0	0	+ 1.8
27	F/80	2.7	162	0/0	0	0	0	+ 12.0
28	M/78	3.1	85	0/0	0	0	0	+ 1.6
29	M/75	1.3	73	1/0.3	0	0	0	+ 2.4
30	F/85	5.2	116	Not performed‡	0	0	0	- 4.1

*STS score—permanent stroke; †neuron-specific enolase (NSE) at E1 ($\mu\text{g/l}$) - NSE at E2 ($\mu\text{g/l}$); ‡pacemaker-therapy; §death; |claustrophobia; ¶hemodynamic Instability.

DW-MRI = diffusion-weighted magnetic resonance imaging; E1 = before transfemoral aortic valve implantation; E2 = within 3 days of transfemoral aortic valve implantation; E3 = 3 months after transfemoral aortic valve implantation; NIHSS = National Institutes of Health Stroke Scale; TAVI = transfemoral aortic valve implantation.

Table 4 Patient Characteristics Related to DW-MRI Results

	DW-MRI Lesions Absent (n = 6)	DW-MRI Lesions Present (n = 16)	p Value
Clinical data			
Age, yrs	79.7 ± 5	79.2 ± 4.9	0.84
Male	1 (17)	7 (44)	0.26
Body mass index, kg/m ²	26.1 ± 8	25.9 ± 5.7	0.95
EuroScore, %	19.0 ± 9.2	19.6 ± 15	0.62
STS score–mortality, %	6.5 ± 2.6	6.1 ± 4.7	0.81
STS score–permanent stroke, %	2.7 ± 0.8	2.9 ± 1.5	0.64
NYHA functional class	3 ± 0.6	3 ± 0.5	1.0
Comorbidities			
Hypertension	5 (83)	16 (100)	0.27
Diabetes	1 (17)	4 (25)	1.0
Smoking	1 (17)	7 (44)	0.35
Dyslipidemia	5 (83)	15 (94)	0.48
Creatinine, mg/dl	2.5 ± 2.1	1.2 ± 0.3	0.019
Hemodialysis	2 (33)	0 (0)	0.065
Prior stroke	1 (17)	5 (31)	0.63
Prior TIA	0 (0)	3 (19)	0.53
Peripheral vascular disease	2 (33)	13 (81)	0.054
Cerebral vascular disease	1 (17)	7 (44)	0.35
Aortic atheroma ≥4 mm	2 (33)	9 (56)	0.63
Atrial fibrillation	2 (33)	7 (44)	1.0
Atrial flutter	1 (17)	1 (6)	0.48
CHADS ₂ score	2.8 ± 0.8	3.2 ± 1.2	0.5
Coronary artery disease			
Coronary artery disease	4 (67)	11 (69)	1.0
Prior myocardial infarction	3 (50)	8 (50)	1.0
Prior PCI	1 (17)	8 (50)	0.35
Prior CABG	0 (0)	0 (0)	—*
Procedural data			
Procedure time, min	96.3 ± 35.8	96.6 ± 38.5	0.99
CoreValve 26/29-mm diameter	3/3	11/5	0.75
Additional frame dilation	0 (0)	4 (25)	0.46
Medication (E1)			
Acetylsalicylic acid	6 (100)	16 (100)	—*
Clopidogrel hydrogen sulphate	6 (100)	16 (100)	—*
Beta-blocker	6 (100)	14 (88)	1.0
Statin	5 (83)	13 (81)	1.0
AT1 antagonist	1 (17)	2 (13)	1.0
ACE inhibitor	2 (33)	7 (44)	1.0
Diuretics	5 (83)	11 (69)	0.63

Values are mean ± SD, n (%), or n. *Statistical analysis not feasible.

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft surgery; DW-MRI = diffusion-weighted magnetic resonance imaging; PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

Discussion

Recent studies reported on clinically apparent stroke rates ranging from 0.6% to 10% after TAVI (2,3). In this study we prospectively assessed the frequency of clinically silent and apparent cerebral embolism with DW-MRI in multimorbid patients undergoing TAVI. Our main finding is that TAVI is associated with a high rate of clinically silent cerebral embolism (72.7%). In contrast, clinical symptoms of neurological deficits persisted in only 3.6% of the investigated patients 3 months after TAVI.

At this time, it remains speculative as to which of the following procedural steps is responsible for embolic events: passage of the aortic valve, balloon dilation, retrograde valve positioning, or frame expansion. All were conducted in sequence for ethical reasons. The passage of a stenotic aortic valve with the catheter resulted in an incidence of cerebrovascular embolic lesions as high as 22% (4). The preponderance of left-sided DW-MRI lesions in this study might be the result of flow characteristics and warrants further investigation. The investigation of patients undergoing antegrade transapical AVI with DW-MRI could help

elucidate the influence of retrograde passage of the aortic arch and valve as potential embolic sources.

Three months after TAVI, neurological deficits persisted in only 3.6%. The presence of transient symptoms in 2 further patients did not correlate with ischemic lesions revealed by DW-MRI. Absence of apparent symptoms on the one hand can be explained with location of embolic events in noneloquent brain areas. On the other hand, NIHSS does not detect nonfocal neurological impairment (e.g., memory dysfunction or neurocognitive decline at 3 months) (8). However, the knowledge about silent TAVI-related cerebral embolism could raise awareness for the careful management of peri-interventional anticoagulation. **Study limitations.** The limited number of patients impedes a multivariate statistical analysis identifying independent risk factors for TAVI-related embolism. The incidence of silent and apparent cerebral embolism might differ with the Edwards-SAPIEN prosthesis (Edwards Lifesciences Inc., Irvine, California). Whether patients with similar peri-interventional risk undergoing operative aortic valve replacement would have comparable neurological outcome remains speculative (5).

Conclusions

The incidence of clinically silent peri-interventional cerebral embolic lesions after TAVI is high, whereas the incidence of persistent neurological impairment in elderly patients with multiple high-risk comorbid conditions was low.

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Key Words: aortic stenosis ■ CoreValve ■ embolism ■ percutaneous ■ stroke ■ valvuloplasty.

▶ APPENDIX

For the supplementary Methods section, please see the online version of this article.

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