Cerebral Infarction after Transcatheter Aortic Valve Implantation in Japan: Retrospective Analysis at a Single High-Volume Center

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Background: Perioperative cerebral infarction is one of the concerning complications after transcatheter aortic valve implantation in patients with aortic stenosis. Several studies have reported on this complication; however, those included only Caucasians and analyzed a small number of cases. Here, we report on the characteristics and risk factors of symptomatic cerebral infarction after transcatheter aortic valve implantation in a single, high-volume center in Japan. *Methods:* We included 308 consecutive patients who underwent transcatheter aortic valve implantation in our facility between 2013 and 2016. We retrospectively analyzed the occurrence, characteristics, and prognoses of symptomatic cerebral infarction within 7 days after the procedure and statistically compared the risk factors between patients with or without cerebral infarction. *Results:* Five patients (1.6%) suffered from symptomatic cerebral infarction, which was usually recognized just after the procedure, with mild symptoms. Long-term prognoses tended to be good unless other factors influenced disability. Comorbidities, such as carotid artery stenosis and peripheral artery disease, were significantly higher in patients with cerebral infarction ($P = .036$ and .002, respectively); in addition, coronary artery disease and longer anesthesia duration (indicating challenging catheter procedures) tended to be associated with cerebral infarction ($P = .080$ and .069, respectively). *Conclusions:* Symptomatic cerebral infarction occurred in 1.6% of patients after transcatheter aortic valve implantation in a single, high-volume center in Japan; the infarctions were of mild severity tending toward good long-term prognoses. We speculate arterial embolism from atherosclerotic large arteries, especially from the aortic arch, during catheter procedures might be the mechanistic basis of cerebral infarction.

Key Words: Aortic stenosis—transcatheter aortic valve implantation—cerebral infarction—peripheral artery disease

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Introduction

Transcatheter aortic valve implantation (TAVI) is an alternative treatment for patients with severe aortic stenosis (AS) who are not suited for surgical aortic valve replacement (AVR). AS prevalence increases with age, and aged patients facing high risk in surgical procedures usually do not select AVR as a treatment option; a previous report indicated that 33% of elderly patients (≥75 years old) with severe symptomatic AS refused surgery.[1] This has led to widespread use of TAVI worldwide, with better clinical outcomes than medical treatment[2-4], and almost identical outcomes to AVR.[5,6]

Perioperative cerebral infarction is one of the concerning complications after TAVI. Previous studies have reported the incidence of symptomatic and magnetic resonance imaging (MRI)-defined asymptomatic cerebral infarction in the acute phase (usually within 7 days) after TAVI were 3.3%-8.8% and 60.7%-94%, respectively[5,7–11]; these are slightly higher than those after AVR, which were reported to be 1.8%-2.5% and 43%, respectively.[5,12] There seem to be multifactorial mechanisms underlying post-TAVI cerebral infarction, but procedure-related embolic stroke is thought to be the main cause; an analysis of embolic protection devices used in TAVI procedures revealed that 99% of the filters contained embolic debris, including thrombus, calcification, valve tissue, arterial wall, and foreign material.[13]

Several studies have reported the frequency, risk factors, and topographic distribution of perioperative cerebral infarction after TAVI.[5,7-11,13] These studies considered both types of cerebral infarction (symptomatic and asymptomatic), and found that age, arch and descending aorta atheroma, and catheterization duration were risk factors for post-TAVI cerebral infarction.[11] However, risk factors for symptomatic cerebral infarction alone remain unknown. While 1 report indicated that asymptomatic cerebral infarction after TAVI was associated with cognitive impairment in long-term follow-up,[9] another study reported that post-TAVI asymptomatic cerebral infarction had no negative effect on patient quality of life.[5] In the present study, we focused only on symptomatic cerebral infarction after TAVI because we thought low quality of life, induced by symptomatic cerebral infarction, has a greater impact on elderly patients.

Previous studies involved primarily Caucasian patients and fewer than 100 cases per report. In our facility, TAVI has been performed ever since it was introduced in Japan; approximately 100 TAVI procedures are performed annually. Here, we report patient characteristics and risk factors for post-TAVI symptomatic cerebral infarction in a high-volume center in Japan, and discuss our findings within the context of published literature.

Materials and Methods

Study Design and Data Collection

The study protocol, which complied with the declaration of Helsinki, was approved by the local human research ethics committee, Keio University School of Medicine (#20130270). Between October 2013 and October 2016, 308 consecutive patients underwent TAVI at Keio University Hospital in Tokyo, Japan. A multidisciplinary heart team, including cardiologists and cardiovascular surgeons, assessed the adaptation of TAVI. All 308 patients enrolled in the present single-center retrospective study after providing written informed consent.

Medical information, including age, sex, body mass index, New York Heart Association classification, vascular risk factors (hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease, smoking, carotid artery stenosis (≥50% stenosis), peripheral artery disease (PAD), coronary artery disease (CAD), atrial fibrillation, history of past cerebral infarction/hemorrhage, and laboratory data were obtained from medical records. Aortic valve pressure gradient and ejection fraction were assessed via transthoracic echocardiography before TAVI. Calcification of the aortic valve and the coronary artery was evaluated using the Agatston score,[14] which was based on the extent of calcification of the aortic valve or the coronary artery detected using an unenhanced computed tomography (CT) scan. The score was calculated using the following formula: the area (mm^2) of the calcification speck, showing more than 130 Hounsfield units (HUs), multiplied by the weighted density score given to the highest attenuation value in the region of interest, categorized as 130-199 HU = 1, 200-299 HU = 2, 300-399 HU = 3, >400 HU = 4. Aortic arch plaques (≥4 mm) were evaluated using enhanced chest CT scan, which was a routine imaging test before TAVI if renal function was normal and was performed in most cases (303/308 cases). Evaluation using transesophageal cardiac echosonography was not conducted because it was performed only in 121 cases. The targets for evaluation were identified using HUs defined as: vessel wall, 30-80 HU; media contrast, 120-150 HU; and calcification, 250-300 HU. Finally, investigators measured the height of the plaques in enhanced CT images modified with appropriate brightness. We assessed the global level of fitness and frailty using a clinical frailty scale, which ranged from 1 (very fit) to 9 (terminally ill).[15]

We retrospectively analyzed the occurrence of symptomatic cerebral infarction within 7 days after TAVI. At first, symptoms were usually recognized by attending physicians or nurses and then all these cases were finally diagnosed by a neurologist via examination and imaging tests, usually MRI or CT in case of contraindication for MRI. Infarct volume (μL) was calculated by multiplying the maximum length (cm), maximum transverse diameter (cm), and maximum height (cm) measured using diffusion

weighted imaging on the MR scans and finally dividing by 2. Neurological symptom severity was assessed using the National Institutes of Health Stroke Scale (NIHSS). Routine head imaging tests after TAVI were not performed in the present study. Patients suffering from cerebral infarction received standard stroke treatment. The modified Rankin Scale (mRS) score was used to assess long-term prognosis via face-to-face or telephone interviews 6 months postcerebral infarction.

TAVI Procedure

TAVI was performed using one of the following devices; SAPIEN-XT, SAPIEN S3 (Edwards LifeSciences, Irvine, CA, USA), CoreValve, CoreValve Evolut R (Medtronic, Minneapolis, MN, USA), without cerebral protection devices under general anesthesia (175 cases; 57%), or local anesthesia (133 cases; 43%). During the study, several operators performed TAVI under the supervision of 1 fixed attending doctor.

Statistical Analysis

Continuous variables are presented as mean ± SD, ordinal variables as median and range, and categorical data as frequencies and percentage. In univariate analysis to identify the factors for post-TAVI cerebral infarction, the Mann−Whitney test was used for continuous variables and the Fisher's exact test for ordinal variables and categorical data. Only factors associated with a P value less than 0.10 in univariate analysis were evaluated in multiple logistic regression analysis, in which P values less than 0.05 were considered statistically significant. Statistical analysis was performed using GraphPad Prism software version 6 (GraphPad Software Inc., La Jolla, CA, USA) for the Mann−Whitney test and the Fisher's exact test, and the SPSS software version 24 (SPSS Inc., Chicago, Ill, USA) for multiple logistic regression analysis.

Results

Characteristics of Patients with Cerebral Infarction After TAVI

Among 308 patients (107 male patients) with a mean age of 84.0 years, 5 patients (1.6%) suffered symptomatic cerebral infarction within 7 days after TAVI. TAVI was performed under single or double antiplatelet therapy with/without anticoagulation therapy in most cases. The characteristics of the 5 patients with cerebral infarction are described below and are summarized in Table 1. Briefly, symptomatic cerebral infarction was usually recognized just after all TAVI procedures were completed, which indicated that cerebral infarction occurred during TAVI. The symptoms were not severe at onset in most cases (median NIHSS was 2 with a range of 1-5). The long-term prognosis tended to be good, unless factors other than cerebral infarction influenced disability (e.g.,

Table 1. *Clinical characteristics of 5 patients with symptomatic cerebral infarction after TAVI*

Pt. No.	Age/Sex	Onset time after TAVI	Infarct site	Symptoms at onset	NIHSS at onset	Catheter approach	Anesthesia	Periprocedural antithrombotic therapy	Therapy	mRS score at 6 mos	Preoperative frailty scale
1	81/M	Just after TAVI	Lt. MCA cortex	Rt. arm palsy	1	TF	General	Aspirin Clopidogrel	Edaravone	0	2
2	86/F	Just after TAVI	Lt. corona radiata	Cons. disturbance Rt. hemiplegia	5	TF	General	Aspirin	Edaravone	4*	4
3	85/F	Just after TAVI	Rt. Thalamus Rt. Midbrain, Rt. Pons Both Cerebellum	Lt. arm palsy	2	TF	General	Aspirin Apixaban	Glycerol	1	4
4	92/F	Just and 6 d after TAVI	Lt. basal ganglia and corona radiata (detected by CT)	Rt. arm numbness Rt. hemiplegia	2	TA	General	Aspirin Clopidogrel	None	5†	6
5	88/F	Just after TAVI	Rt. MCA (watershed area) Lt. MCA cortex	Cons. disturbance Lt. hemiplegia	3	TF	Local	Aspirin Ticlopidine	Edaravone Argatroban	2	3

Abbreviations: Cons. disturbance, conscious disturbance; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TA, trans apical; TAVI, transcatheter aortic valve implantation; TF, transfemoral.
*General condition worsened due to appetite loss.
†Due to cervical spinal injury.

cases 2 and 4). The preoperative frailty scale score in cases with poor long-term prognoses (cases 2 and 4) was relatively higher than in those with good prognoses.

Case 1

An 81-year-old male patient (with a preoperative frailty scale score of 2, indicating "Well") became aware of right arm palsy just after TAVI (NIHSS = 1). Head MRI revealed multiple acute small infarctions, indicating embolic stroke within the left middle cerebral artery (MCA) area, and a lesion on his left precentral knob was thought have caused the right arm palsy. He was treated with edaravone (free radial scavenger) and dual platelet therapy was continued. His arm paralysis improved within 5 days, and the mRS score at 6 months was 0, indicating absence of sequelae.

Case 2

An 86-year-old female patient (with a preoperative frailty scale score of 4, indicating "Vulnerable") experienced a disturbance in consciousness just after TAVI; however, the disturbance in consciousness improved without treatment, and only right hemiplegia remained (NIHSS = 5). Head MRI revealed acute cerebral infarction on the left corona radiate, which was perfused by perforating arteries from the MCA. Her medical history and imaging tests indicated reperfusion of the embolus stagnated in the M1 part of the left MCA. She was treated with edaravone. Her long-term prognosis was poor with an mRS score of 4 at 6 months, mainly due to loss of appetite for unknown reasons, limiting rehabilitation.

Case 3

An 85-year-old female patient (with a preoperative frailty scale score of 4) became aware of left arm palsy (NIHSS = 2). A head MRI showed multiple, acute cerebral infarctions in the posterior circulation area, including the right thalamus, right midbrain, pons, and cerebellum. Although the possibility of cardiac embolism owing to pre-existing atrial fibrillation could not be excluded, we speculated that her stroke was related to the TAVI procedure because it happened just after TAVI and she was under anticoagulant therapy with good adherence. She was treated with Glycerol (hyperosmolar agent), and the palsy resolved almost completely at discharge. Her mRS score 6 months post-TAVI was 1.

Case 4

A 92-year-old female patient (with a preoperative frailty scale score of 6, indicating "Moderately Frail") became aware of numbness in her arm just after TAVI, but she did not complain about it. Six days after TAVI, she fell down from her bed, and we noticed symptoms of right hemiplegia (NIHSS = 2). Due to the presence of a pacemaker, we performed head CT scanning, which indicated multiple, small, low-density areas in the left basal ganglia and corona radiata. Although it was challenging to verify the detailed mechanism of this infarction without MRI, 2 possible mechanisms were suspected in this case: (1) embolic stroke, and (2) hemodynamic infarction related to post-TAVI hypotension (systolic blood pressure was approximately100 mm Hg). She was treated with rehabilitation alone because 6 days had passed before we noticed her symptoms. Her paralysis did not improve during hospitalization, and she suffered spinal cord injury incidentally after discharge, leading to poor prognosis with a mRS score of 5 six months after TAVI.

Case 5

An 88-year-old female patient (with a preoperative frailty scale of 3, indicating "Managing Well") experienced a disturbance in consciousness and left hemiplegia just after TAVI (NIHSS = 3). A head MRI showed acute cerebral infarction in the right MCA watershed area and the left cortex. Multiple lesions in several vascular territories indicated embolic stroke. She was treated with edaravone and argatroban (intravenous Xa inhibitor). Improvement in paralysis was poor at discharge; however, gradually improved afterwards. Her mRS score was 2 six months after TAVI.

Infarct Distribution

We assessed the distribution pattern and total volume of infarcts (Table 2), and representative MRI images are shown in Figure 1. Regarding hemispheric distribution in the cerebrum, 1 case with lesions in the posterior

Table 2. *Distribution of infarct lesions*

	No. of cases	No. of lesions	Total volume of lesions (μl)
Hemispheric distribution			
Right hemisphere	1*	11	7,625
Left hemisphere	4*	9	4,003
Anterior—Posterior distribution			
Anterior circulation	4	20	11,678
Posterior circulation	1	9	2,580
Location in brain parenchyma			
Cerebrum			
Cortical branch	2†	16	7,998
Perforating branch	3†	5	4,005
Brain stem	1	2	365
Cerebellum	1	6	1,840

*One case had lesions on the both hemispheres.
†Two cases had lesions in the both areas of cortical and perforating branch.

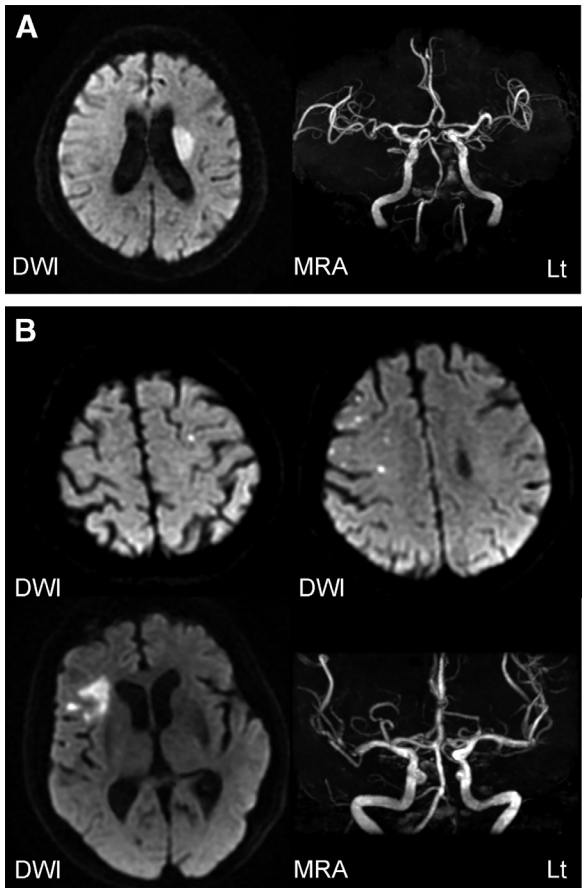

Figure 1. *Representative brain images of patients with post-TAVI cerebral infarction. Case 2 (A): Diffusion weighted images (DWI) of MR scans showed acute infarction in the left corona radiata, while MR angiography (MRA) showed no stenosis/occlusion in the left middle cerebral artery (MCA), indicating reperfusion of embolus stagnated in the M1 part of the left MCA. Case 5 (B): DWI showed multiple acute infarctions in the right middle cerebral artery area, and a tiny lesion in the left cortex. MRA revealed no stenosis/occlusion in intracranial arteries. Abbreviations: Lt,left; TAVI, transcatheter aortic valve implantation.*

circulation area (Case 3) was not included. Three patients had lesions in the left hemisphere, and 1 had lesions in both hemispheres; there were 11 lesions (a total volume of 7625 μl) in the right hemisphere versus 9 lesions (a total volume of 4003 μl) in the left hemisphere. Regarding the comparison between anterior and posterior circulation, the infarcts were predominant in the anterior, rather than in the posterior, circulation; there were 20 lesions (a total volume of 11678 μl) in the anterior circulation in 4 cases and 9 lesions (a total volume of 2580 μl) in the posterior circulation in 1 case. Finally, regarding the location in the brain parenchyma, the number of cases with perforating branch lesions and those with cortical branch lesions in the cerebrum was approximately the same. However, cortical branch area was more dominant than the perforating branch area in terms of number and total volume of lesions, with 16 lesions (a total volume of 7998 μl) and 5 lesions (a total volume of 4005 μl), respectively. These results indicated that the mechanism underlying the stroke could be embolism because cortical infarction is typically thought to be embolic stroke. There was no massive infarction in any of the cases.

Patient Characteristics and Risk Factors for Cerebral Infarction after TAVI

We compared characteristics and vascular risk factors between patients with or without cerebral infarction. In univariate analysis (Table 3), comorbidities, such as carotid artery stenosis and PAD, were significantly associated with cerebral infarction (P = .036 and .002, respectively) and a higher aortic valve calcium score, in the Agatston score, was a negative predictor of cerebral infarction (P = .027). CAD and longer anesthesia duration might be related to the occurrence of cerebral infarction; however, the difference was not significant (P = .080 and .069, respectively). The prevalence of an aortic arch plaque (≥4 mm) and diabetes mellitus were not significantly different between patients with/without cerebral infarction (P = .16 and P = .11, respectively). Other risk factors, such as history of old stroke, cardiac function (indicated via the New York Heart Association classification and ejection fraction), severity of AS (assessed using aortic valve mean pressure gradient), pre/post dilatation during the TAVI procedure, and the type of anesthesia (general versus. local) were not associated with cerebral infarction. In multiple logistic regression, including only the factors associated with a P value less than 0.10 in univariate analysis, PAD remained significantly associated with cerebral infarction (Table 4).

The Approach in the TAVI Procedure

Among the 308 patients, 4 different catheter approaches were used; trans femoral (TF), trans apical (TA), trans iliac, and direct aortic. The most popular approach was TF, accounting for almost 90% of all cases, followed by TA (almost 10%); the other approaches were rare (Table 5). The incidence of cerebral infarction in the TF group and the TA group was 1.5% (4/272 cases) and 3.4% (1/29 cases), respectively. The difference between the 2 groups was not significantly different, as shown by results of Fisher's exact test (P = .400).

Antithrombotic Therapy During TAVI

Among the 5 patients with cerebral infarction, at least 1 antithrombotic drug (single antiplatelet, 1 case; dual antiplatelet, 3 cases; single antiplatelet + anticoagulant, 1 case) was used in the periprocedural period. Likewise, in most (94.1%) of the 303 patients without cerebral infarction, at least 1 antithrombotic drug (single antiplatelet, 134 cases; dual antiplatelet, 81 cases; anticoagulant, 21 cases; single antiplatelet + anticoagulant, 46 cases; dual antiplatelet + anticoagulant, 3 cases) was used. Meanwhile, the 18 patients without

Table 3. *Risk factors for cerebral infarction after TAVI*

	Univariate analysis		
	Cerebral infarction (-) (n = 303)	Cerebral infarction (+) (n = 5)	*P* value
Age (y, mean ± SD)	84.0 ± 5.4	86.4 ± 4.0	.37
Sex (male)	106 (35.0%)	1 (20%)	.66
Body mass index (% ± SD)	22.1 ± 3.5	22.6 ± 1.0	.59
NYHA classification (median: range)	3 (1-4)	3 (2-3)	.36
Smoking (%)	105 (34.7%)	2 (40%)	1.00
Dyslipidemia (%)	149 (49.2%)	3 (60%)	.68
Diabetes mellitus (%)	77 (25.4%)	3 (60%)	.11
Hypertension (%)	239 (78.9%)	5 (100%)	.59
Chronic kidney disease (%)	189 (62.4%)	3 (60%)	1.00
History of old cerebral infarction (%)	20 (6.6%)	0 (0%)	1.00
History of old intracranial hemorrhage (%)	2 (0.7%)	0 (0%)	1.00
Carotid artery stenosis (50% over) (%)	18 (5.9%)	1 (20%)	.036
Peripheral artery disease (%)	43 (14.2%)	4 (80%)	.002
Coronary artery disease (%)	118 (38.9%)	4 (80%)	.08
Atrial fibrillation (%)	74 (24.4%)	1 (20%)	1.00
Creatinine (Cre) (mg/dl ± SD)	1.06 ± 0.66	1.15 ± 0.37	.33
low-density lipoprotein cholesterol (LDL) (mg/dl ± SD)	98.6 ± 26.9	88.4 ± 35.1	.56
high-density lipoprotein cholesterol (HDL) (mg/dl ± SD)	52.5 ± 14.8	46.8 ± 7.0	.38
triglyceride (TG) (mg/dl ± SD)	107.1 ± 59.1	131.6 ± 42.6	.14
HbA1c (% ± SD)	5.9 ± 0.8	6.7 ± 1.0	.18
BNP (mg/dl ± SD)	400.8 ± 493.4	299 ± 126.0	.62
Aortic valve mean pressure gradient (mm Hg ± SD)	45.4 ± 19.0	42.6 ± 15.1	.63
Ejection fraction (% ± SD)	65.6 ± 39.7	63.1 ± 4.6	.70
Aortic valve Ca score (score ± SD)	2885.8 ± 1865.4	1473.4 ± 301.3	.027
Coronary artery Ca score (score ± SD)	1119.6 ± 1228.8	2053.7 ± 2524.5	.32
Aortic arch plaque (≥4 mm); evaluated in 303 cases	87/298 (29.2%)	3/5 (60%)	.16
TAVI Predilation (+)	135 (44.6%)	3 (60%)	.34
TAVI Postdilation (+)	52 (17.2%)	1 (20%)	1.00
General anesthesia (vs Local anesthesia)	171 (56.4%)	4 (80%)	.39
Anesthesia time (min ± SD)	135.6 ± 56.9	187.2 ± 74.1	.069

Abbreviations: TAVI, transcatheter aortic valve implantation; NYHA, New York Heart Association; BNP, brain natriuretic peptide; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglyceride; Cre, Creatinine.

antithrombotic therapy in the periprocedural period were among the cases without cerebral infarction (Table 6).

Discussion

Several studies have addressed cerebral infarction after TAVI.[5,7–11,13] However, these studies addressed both symptomatic and symptomatic cerebral infarction with no detailed assessment of symptoms, their severity, or prognoses. In the present study, we report the details of symptomatic cerebral infarction after TAVI assessed by neurologists using data from a high-volume center in Japan.

Table 4. *Adjusted odds ratio of risk factors for cerebral infarction after TAVI*

	Odds ratio	95% CI	*P* value
Carotid artery stenosis	1.026	.448-2.352	.951
Peripheral artery disease	23.62	1.216-156.8	.034
Coronary artery disease	3.310	.307 -35.65	.324
Aortic valve Ca score	.999	.997-1.000	.077
Anesthesia time	1.007	.995 -1.020	.224

Abbreviations: CI, cerebral infarction; TAVI, transcatheter aortic valve implantation.

The severity of cerebral infarction at onset assessed using NIHSS was 2 (median) on a scale of 1-5, which is usually considered mild. Long-term prognoses, which were assessed using mRS score at 6 months after TAVI, were generally good, except for 2 cases with high frailty scores. We infer that poor outcomes were mainly correlated with severe frailty existing before TAVI, not due to stroke sequelae.

A previous study reported more lesions in the right hemisphere than in the left.[7] The present study showed the same trend in analysis, based on the number and volume of lesions. However, this right-side dominance was influenced by only 1 case (Case 5), and most other cases had infarcted lesions in the left hemisphere, which was inconsistent with the above previous study. Although the discrepancy between our study and the previous study might

Table 5. *Comparison of catheter insertion sites*

	No. of cases without CI (% of each approach/ total cases without CI)	No. of cases with CI (% of each approach/ total cases with CI)	Incidence rate of CI per each approach
Trans femoral	268 (88.4%)	4 (80.0%)	1.5% (4/272)
Trans apical	28 (9.2%)	1 (20%)	3.4% (1/29)
Trans iliac	2 (.7%)	0 (0%)	0% (0/2)
Direct aortic	5 (1.7%)	0 (0%)	0% (0/5)
Total	303	5	1.7% (5/303)

Abbreviations: CI, cerebral infarction; TAVI, transcatheter aortic valve implantation.

Table 6. *Comparison of antithrombotic therapy in the periprocedural period*

	No. of cases without CI (% of each medication/ total cases without CI)	No. of cases with CI (% of each medication/ total cases with CI)	Incidence rate of CI per each medication
None	18 (5.9%)	0 (0%)	0% (0/18)
Antiplatelet	134 (44.2%)	1 (20%)	.7% (1/135)
Dual antiplatelet	81 (26.7%)	3 (60%)	3.6% (3/84)
Anticoagulant	21 (6.9%)	0 (0%)	0% (0/21)
Antiplatelet + anticoagulant	46 (15.2%)	1 (20%)	2.1% (1/47)
Dual antiplatelet + anticoagulant	3 (.99%)	0 (0%)	0% (0/3)
Total	303	5	1.7% (5/303)

Abbreviation: CI, cerebral infarction.

be due to the difference in the study target (only symptomatic stroke or both symptomatic and asymptomatic stroke) or difference in procedure (with/without protection device use), we speculate that this left-side dominance in the analysis of the number of cases could be explained based on catheter procedures. In the TF approach, the curved catheter frequently touches the vascular wall at the top of the arch, where the left common carotid artery branches, resulting in artery-to-artery embolism in the left hemisphere. We also recognized the predominant presence of infarcted lesions in the anterior circulation compared with the posterior circulation. This might have been influenced by cerebral blood flow distribution; a previous study reported that carotid (anterior)/vertebral (posterior) cerebral blood flow distribution was 72%/28%.[16]

Univariate analysis showed that comorbidities, such as carotid artery stenosis and PAD, were significantly associated with cerebral infarction; in addition, CAD and longer anesthesia duration might also be associated with cerebral infarction. Multiple logistic regression analysis revealed that only PAD had significant association with the occurrence of cerebral infarction; however, PAD, CAD, and carotid artery stenosis were mutually confounding factors, and all of them could occur based on large vessel atherosclerosis; a previous study found that CAD and PAD were risk factors for aortic arch atherosclerosis.[17] Long anesthesia duration usually indicates challenging catheter procedures, which might result in artery-to-artery embolism from the aortic arch, as reported previously.[11] Taken together, our results allow us to speculate arterial embolism from atherosclerotic large arteries, especially from the aortic arch, during catheter procedures might be the mechanism underlying post-TAVI cerebral infarction; a similar mechanism has been suggested in past studies involving both symptomatic and asymptomatic infarction.[5,11] Even though the low incidence of cerebral infarction in our study might not have enough statistical power to detect the significant difference in the prevalence of aortic arch plaque (≥4 mm) between the cases with/without cerebral infarction (P= .16), our results indicate that physicians must be aware that patients with PAD, carotid stenosis, and CAD might have atherosclerotic changes and are at a high risk of cerebral infarction after TAVI. Moreover, despite diabetes mellitus not showing a significant difference or a trend for difference in the present study (P= .11), it might be better to pay close attention to the cases with diabetes mellitus if we consider that diabetes mellitus is generally 1 of the risk factors for cerebral infarction.[18,19]

AS severity, assessed using the mean pressure gradient, was not significantly different between patients with or without cerebral infarction. Conversely, calcification of the aortic valve, evaluated using the Agatston score, was significantly lower in the patients with cerebral infarction. Based on these results, we speculated that aortic valves in

patients with cerebral infarction may not stiffen due to calcification, and other factors, such as atherosclerosis, could have caused the stiffness. Pathology investigations of samples obtained through post-TAVI cerebral thrombectomy suggested that the ruptured valve itself is an embolic source.[20] Therefore, we hypothesized that the atheroma-rich valve is easily ruptured during valve implantation or dilation, resulting in cerebral infarction.

Of the 4 different catheter approaches used for TAVI in our facility, the TF approach was the most common, followed by the TA approach. The difference in cerebral infarction incidence between these 2 approaches was not different statistically, similar to that reported in a previous study.[8]

Considering antithrombotic therapy in the periprocedural period of TAVI, there appeared to be no association between the number and type of antithrombotics and occurrence of cerebral infarction, although the cerebral infarction incidence rate was too small to determine such an association.

We have summarized the literature reporting cerebral infarction in the acute phase (within 7 days) after TAVI (Table 7); all studies, including the present study, found a very high average patient age (approximately 80 years old) and a predominant number of females. The incidence of symptomatic cerebral infarction in the present study was 1.6%, which was similar to, but a bit lower than, that in previous reports (3.3%-8.8%),[5,7-11] and was almost the same as the incidence after AVR in Japan (1.8%), reported in the Japan Cardiovascular Surgery Database.[12] Previous studies primarily, comprising Caucasians, have reported that unprotected TAVI could cause higher occurrence of cerebral infarction[10] and that an embolic protection device was effective in preventing embolic stroke.[21] Such protection devices are currently not available in Japan. However, the present study revealed a favorable incidence rate without using an embolic protection device. Although the reason for this result is unclear, the difference in periprocedural antithrombotic therapy (anticoagulants were used in some cases in the present study, mainly for atrial fibrillation) or the frequent use of local anesthesia might be possible explanations.

Our study has some limitations. First, there were too few cerebral infarction patients to perform appropriate statistical analysis. Second, our study focused only on symptomatic cerebral infarction alone and did not measure cognitive function. Therefore, the influence of asymptomatic cerebral infarction on cognitive function was unclear. Moreover, our study included only cases where attending physicians or nurses recognized patients' symptoms and where routine examination by neurologists was not performed. Therefore, we cannot exclude the possibility that we missed cases with minor or spontaneously improved symptoms. Third, our results are not necessarily representative of all of Japan, because the study was done only in our facility, an advanced TAVI center with well-trained personnel.

Table 7. *Summary of literature reporting asymptomatic/symptomatic cerebral infarction in the acute phase (within 7 days) after TAVI*

Authors (published year)	Country	No. of cases	Age (mean)	Sex (male, %)	Anesthesia	Protection device	Incidence of asymptomatic CI (assessment period after TAVI)	Incidence of symptomatic CI (assessment period after TAVI)	Antithrombotic drugs
Rodes-Cabau J et al.[8] (2011)	Canada	60	83	50	General	N/R	68% (6 d)	3.3% (1 d)	Aspirin + Clopidogrel
Fairbairn TA et al.[11] (2012)	United kingdom	31	81	35	General	N/R	79% (2 d)	6% (2 d)	Aspirin + Clopidogrel
Uddin et al.[5] (2015)	United kingdom	70	80.5	44	General	N/R	77% (7 d)	N/R	Aspirin + Clopidogrel
Lansky AJ et al.[10] (2016)	United states	34	83.2	65.9	Local (34.1%)General (65.9%)	No use	94% (4 ± 2 d)	8.8% (2 d)	Aspirin + Clopidogrel
Ghanem A et al.[9] (2017)	Germany	28	80	50	General	N/R	60.7% (3 d)	N/R	N/R
Fanning JP et al.[7] (2018)	Australia	31	82.3	41.5	General	Use	61% (3 ± 1 d)	N/R	N/R
Our study	Japan	308	84.0	34.7	Local (43%) General (57%)	No use	N/R	1.6% (7 d)	Antiplatelet therapy with/without anticoagulation therapy

Abbreviations: CI, cerebral infarction; N/R, not reported; TAVI, transcatheter aortic valve implantation.

Conclusion

The incidence of symptomatic cerebral infarction after TAVI without embolic protection device use in a high-volume center in Japan was 1.6%, which is similar to, but a bit lower than, previous studies. Stroke severity was mild, and long-term prognoses tended to be good unless the patients were frail before TAVI. Comorbidities, such as carotid artery stenosis and PAD, were significantly associated with cerebral infarction; in addition, CAD and longer anesthesia duration (indicating challenging catheter procedures which potentially cause artery-to-artery embolism from the aortic arch) might have been associated with cerebral infarction. Based on these results, we speculated that embolism from atherosclerotic large arteries, especially from the aortic arch, during catheter procedures might be the mechanism underlying post-TAVI cerebral infarction. Understanding the risk factors, severity, and prognoses of post-TAVI symptomatic cerebral infarction is important in patient selection and decision-making.

Declaration of Competing Interest

Kentaro Hayashida and Hideyuki Shimizu are clinical proctors for Edwards Lifesciences.

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