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Original article

# Self-expandable transcatheter aortic valve replacement is associated with frequent periprocedural stroke detected by diffusion-weighted magnetic resonance imaging

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ABSTRACT

*Background:* Little evidence is available regarding the risk of peri-procedural stroke detected by diffusion-weighted magnetic resonance imaging (DW-MRI) after transcatheter aortic valve replacement (TAVR). Our purpose was to evaluate stroke risk after TAVR using DW-MRI by enrolling consecutive patients who underwent transfemoral TAVR and post-procedural DW-MRI.

*Methods:* We prospectively enrolled 113 consecutive patients who underwent transfemoral TAVR and post-procedural DW-MRI. We used balloon-expandable valves as first-line therapy and selected self-expandable valves only for patients with narrow sinotubular junctions or annuli. We set the primary endpoint as the number of high intensity areas (HIA) detected by DW-MRI regardless of the size of the area. To evaluate the risks of the primary endpoint, we employed a multivariable linear regression model, setting the primary endpoint as an objective variable and patient and clinical backgrounds as explanatory variables.

*Results:* Median patient age was 84 years, and 36.3% were men. Ninety-three patients underwent balloon-expandable TAVR and 20 underwent self-expandable TAVR. Symptomatic stroke occurred in 6 (5.3%) whereas asymptomatic stroke occurred in 59 (52.2%) patients. The incidence of symptomatic and total stroke was higher in patients who underwent self-expandable TAVR than those who underwent balloon-expandable TAVR (30.0% vs. 0.0%, $p < 0.001$ and 90.0% vs. 50.5%, $p = 0.001$, respectively). A multivariable linear regression model demonstrated an increased primary endpoint when self-expandable TAVR was performed ($p < 0.001$). The other covariates had no significant relationship to the primary endpoint. Akaike information criterion-based stepwise statistical model selection revealed that valve type was the only explanatory variable for the best predictive model.

*Conclusions:* Self-expandable valves were associated with increased numbers of HIA on DW-MRI after TAVR in patients with severe aortic stenosis.



## Introduction

Aortic stenosis (AS) is one of the major cardiac valvular diseases. The number of patients with severe AS is increasing with the aging of the population [1–5]. Since severe AS significantly impairs patient's quality of life due to heart failure, syncope, and angina which may lead to sudden cardiac death and poor prognosis, surgical aortic valve

*Abbreviations:* DW-MRI, diffusion-weighted magnetic resonance imaging; HIA, high intensity areas; TAVR, transcatheter aortic valve replacement.

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replacement (SAVR) has been performed for decades as one of the promising treatment options for severe AS even without solutions addressing the problems associated with high-risk surgical patients [1–5]. To meet this clinical need for the management of high-surgical-risk patients with severe AS, transcatheter aortic valve replacement (TAVR) has been introduced and its clinical indications have expanded from high-surgical-risk patients to intermediate-risk patients with satisfactory safety and efficacy [1–5].

Based on this perspective, many recent studies on TAVR are focusing on the way to improve safety and efficacy such as by evaluating the risk of complications of TAVR [6,7]. For example, stroke is one of the major TAVR-related complications [8–10]. Ischemic stroke occasionally accompanies hemorrhagic stroke and can be fatal and impair quality of life significantly if it is disabling; even silent ischemic cerebral infarction is associated with dementia and cognitive decline [11]. The incidence of silent ischemic stroke detected by diffusion-weighted magnetic resonance imaging (DW-MRI) was reported to be 68–84% after TAVR, which may be associated with any of the following: higher aortic arch atheroma grade classified on transesophageal echocardiography (TEE), current smoking, baseline creatinine level, and aortic valve plaque with intermediate enhanced multi-detector computed tomography (MDCT) score (50–130 HU) [10,12–17]. However, concerning the risk factor of ischemic stroke detected by DW-MRI, no evidence has been established, possibly due to the small number of studies or advancements of interventional medical devices [10,12–18]. The purpose of this single-center, prospective study was to evaluate the risk of stroke after TAVR using DW-MRI.

## Methods

### *Study population*

This single-center prospective observational study enrolled 113 consecutive patients with severe AS who underwent transfemoral TAVR and post-procedural DW-MRI at Osaka City University Hospital from January 2016 to July 2018 (Fig. 1). The indication for TAVR at our institution during the study period included patients who were supposedly high-risk for SAVR considering general conditions including patient backgrounds, echocardiographic, and MDCT findings. The decision was made by the heart team comprising an interventional cardiologist, cardiovascular surgeon, anesthesiologist, radiologist, nurse, and physical therapist. Among 190 possible TAVR candidates, we excluded 25 patients without transfemoral TAVR (22 transapical, 1 transsubclavian, and 2 direct aorta approach) and 52 patients without DW-MRI examinations because of contraindications such as non-conditional pacemaker ($n = 16$), inappropriate general conditions including heart failure ($n = 3$), unstable vital signs ($n = 2$), claustrophobia ($n = 1$), or unavailability of MRI due to overscheduling ($n = 30$). Our study protocol complied with the Declaration of Helsinki and was approved by our institutional ethics committee (Approval No. 3518). Written informed consent was obtained from all patients. Several cases were previously reported in an image-content sharing web journal, but this study does not violate duplication policy of the journal [19].

### *Standard procedure of TAVR*

We performed transfemoral TAVR under general anesthesia in a hybrid operating room except for one patient who underwent TAVR under local anesthesia considering the general risks associated with significant emphysema. During the procedure, heparin was administered intravenously to reach an activated clotting time of 250–300 s. First, we inserted a 14–18 Fr sheath into the femoral artery and crossed a straight guidewire into the left ventricle with a 5 Fr Judkins right catheter. Next, we performed balloon aortic valvuloplasty (BAV) if the aortic valve was too narrow for a transcatheter heart valve (THV). After that, we carefully delivered a THV through the femoral sheath and

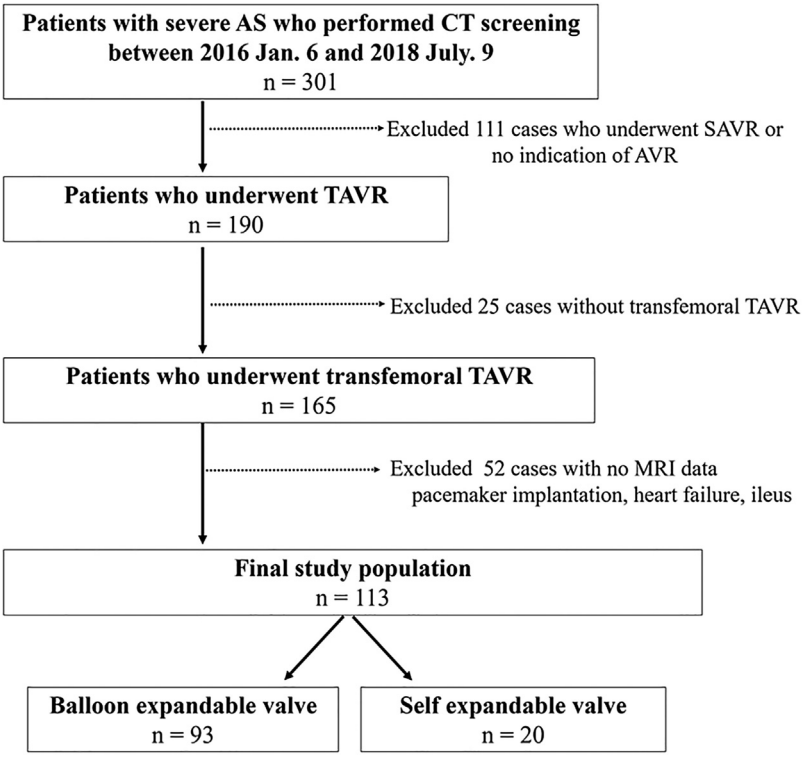


**Fig. 1.** Patient selection flow.
AS, aortic stenosis; AVR, aortic valve replacement; CT, computed tomography; DW-MRI, diffusion-weighted magnetic resonance imaging; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

performed TAVR. THVs were classified as balloon-expandable valves (Edwards Sapien XT or Sapien 3 Transcatheter Heart Valve, Edwards Lifesciences, Irvine, CA, USA) or self-expandable valves (Medtronic classic CoreValve or CoreValve EvolutR, Medtronic, Inc., Minneapolis, MN, USA). We used balloon-expandable valves as first-line therapy and selected self-expandable valves only for patients with narrow sinotubular junctions (STJ) or annuli. We implanted the THVs under fluoroscopic- and TEE-guidance with rapid right ventricular apical pacing (180–200 ppm) in case of balloon expandable valves or control pacing (90–120 ppm) in case of self-expandable valves.

*Data collection*

All data shown in the tables and figures were collected prospectively. Pre-procedural enhanced MDCT data were obtained to evaluate annular area and perimeter, diameter of STJ, calcium volume of the aortic valve, porcelain aorta, and aortic arch plaque. The estimated oversizing rate was calculated by the following formula; [(estimated THV area/annular area measured by MDCT) − 1]) × 100 for balloon-expandable valve and [(THV size × 3.14 − annular perimeter measured by MDCT)/annular perimeter measured by MDCT] × 100 for self-expandable valve following previous reports [20,21]. MDCT data were assessed using the SYNAPSE VINCENT analyzing software (Fujifilm, CO., Ltd, Tokyo, Japan). We defined calcification of the aortic valve complex (from annular basal ring to ST junction) as an area with a CT value ≧600 HU, and aortic arch plaques were considered to be present when atherosclerotic plaques were present from the brachiocephalic to the left subclavian artery.

We performed brain MRI within 4 weeks after TAVR. DW-MRI was obtained using the 1.5 T (Achieva, Philips Healthcare, The Netherlands or Avanto, Siemens Medical Systems, Erlangen, Germany) or 3.0T system (Achieva and Ingenia, Philips Healthcare) and images were obtained in 5-mm slices. Images were interpreted by 2 radiologists. The high intensity areas (HIA) of DW-MRI after TAVR was considered as TAVR-associated cerebral infarction. The rationale was that restricted diffusion of brain ischemic tissue starts to occur at 30 min after the event and continues for a maximum of 4 weeks [22].

*Endpoints and statistical analysis*

Continuous variables are summarized using medians and interquartile ranges (quartiles 1–3) and categorical variables are summarized using means of counts and percentages. We set the primary endpoint as the number of HIA detected by DW-MRI regardless of the area size. Secondary endpoints included procedural complication rates such as symptomatic or asymptomatic stroke, coronary occlusion, and permanent pacemaker implantation. Inpatient mortality, 180-day survival, and cumulative incidence of symptomatic stroke after TAVR were also evaluated as secondary endpoints. To evaluate the risk of DW-MRI stroke after TAVR, we employed univariable and multivariable linear regression models by setting the number of HIA of DW-MRI as an objective variable. Explanatory variables were selected clinically based on previously reported stroke risks after TAVR. The Akaike information criterion (AIC) was used to find the optimal statistically predictive model in a stepwise way. Since linear regression revealed that valve type was associated with primary endpoint, we performed additional exploratory comparisons of each variable between balloon-expandable valve and self-expandable valve groups as an ad-hoc analysis. In addition, the relationship between valve type and the number of HIA on DW-MRI was also confirmed by the propensity score matching analysis to evaluate the robustness of the result, using a multivariable linear regression model with the protocol described in the previous manuscript [23,24]. Shortly, the propensity score was calculated with a logistic regression model by setting the treatment as the response variable and baseline characteristics and procedural information that were significantly different between 2 groups (balloon expandable and self-expandable) as explanatory variables, which included age, estimated glomerular filtration rate, oversizing rate, and BAV before THV deployment. Differences in continuous and categorical variables between groups were compared using the Wilcoxon rank-sum test or the chi-square test, respectively. A 180-day survival and cumulative incidence of symptomatic stroke were estimated using the Kaplan–Meier method with 95% confidence interval (CI). The differences between groups were evaluated using the log-rank test. Statistical analyses were performed using R software packages (version 3.4.1; R Development Core Team). The significance level of statistical hypothesis testing was set at 0.05 and the alternative hypothesis was two-sided.

## Results

Patient characteristics are listed in Table 1. The median age was 84 years old, and 36.3% were men. The Society of Thoracic Surgeons (STS) risk score was 6.9 (interquartile range 5.5–9.4), and mean aortic valve pressure gradient (AVPG) was 49 (38–63) mmHg. A total 93 patients underwent balloon-expandable TAVR and 20 underwent self-expandable TAVR. There were no significant differences in patient characteristics between the groups except for age and estimated glomerular filtration rate.

Table 2 shows the procedural and outcome information. In total, 45.1% patients underwent pre-procedural BAV during TAVR with a valve size of 26 (23–26) mm and oversizing rate of 16.2 (9.2–21.8)%. Consequently, mean and peak AVPG in echocardiography improved to 11 (8–14) mmHg and 20 (16–27) mmHg, respectively. Symptomatic stroke occurred in 6 (5.3%) patients whereas asymptomatic stroke occurred in 59 (52.2%) with 1 (0–3) HIA on DW-MRI among these 65 patients. In the ad-hoc comparison between balloon vs. self-expandable TAVR, patients who underwent self-expandable TAVR received larger sizes of THV leading to higher oversizing ratios, and lower mean and peak AVPG compared to the balloon-expandable TAVR group. The incidence of symptomatic and total stroke including asymptomatic stroke was higher in patients who underwent self-expandable TAVR than those who underwent balloon-expandable TAVR (30.0% vs. 0%, $p < 0.001$ and 90.0% vs. 50.5%, $p = 0.001$, respectively). Likewise, the number of HIA by DW-MRI was larger in patients with self-expandable TAVR than those with balloon-expandable TAVR ($p < 0.001$). We present representative cases in Fig. 2. In addition, 180-day survival and the cumulative incidence of symptomatic stroke are shown in Fig. 3. There was no significant difference in 180-day survival (long-rank $p = 0.579$), whereas the 180-day cumulative incidence of symptomatic stroke was higher in the self-expandable TAVR group (log-rank $p < 0.001$). Two patients with balloon-expandable valves died on days 35 and 55 after TAVR due to respiratory failure and strangulated ileus, respectively. No patient treated with self-expandable valve died during the 180-day follow-up period. Estimated 180-day mortality was 2.3% (95% CI 0.0–5.3) for balloon-expandable valve vs. 0% [95% CI not applicable (N/A) because no one died] for self-expandable valves. In contrast, symptomatic stroke occurred in one patient with a self-expandable valve on the day of TAVR. The estimated cumulative incidence of 180-day symptomatic stroke was 0% (95% CI N/A) for balloon-expandable valve vs. 30% (95% CI 0.525–0.933) for self-expandable valve.

Uni- and multi-variable linear regression models demonstrated that the number of HIA on DW-MRI increased when self-expandable TAVR was performed ($p < 0.001$ in multivariable model), and other covariates had no significant relationship with

**Table 1**
Patient characteristics.

| Parameters | Total ($n$ = 113) | Balloon-expandable ($n$ = 93) | Self-expandable ($n$ = 20) | $p$-Value |
|---|---|---|---|---|
| Patient characteristics | | | | |
| Age (years) | 84 (81–87) | 83 (80–86) | 87 (83–90) | 0.014 |
| Men | 41 (36.3) | 31 (33.3) | 10 (50.0) | 0.160 |
| BSA ($m^2$) | 1.44 (1.32–1.55) | 1.44 (1.33–1.55) | 1.42 (1.31–1.55) | 0.749 |
| Coronary risks and past history | | | | |
| Hypertension | 108 (95.6) | 89 (95.7) | 19 (95.0) | 0.890 |
| Dyslipidemia | 61 (54.0) | 52 (55.9) | 9 (45.0) | 0.374 |
| Diabetes mellitus | 23 (20.4) | 18 (19.4) | 5 (25.0) | 0.570 |
| Current smoking | 7 (6.2) | 7 (7.5) | 0 (0.0) | 0.205 |
| Atrial fibrillation | 25 (22.1) | 19 (20.4) | 6 (30.0) | 0.350 |
| Prior CABG | 3 (2.7) | 3 (3.2) | 0 (0.0) | 0.416 |
| Previous myocardial infarction | 7 (6.2) | 5 (5.4) | 2 (10.0) | 0.437 |
| Previous ischemic stroke | 12 (10.6) | 9 (9.7) | 3 (15.0) | 0.483 |
| NYHA class | 2 (2–3) | 2 (2–3) | 2 (2–2) | 0.318 |
| Clinical frailty scale | 4 (3–4) | 4 (3–4) | 4 (3–4) | 0.507 |
| STS score | 6.9 (5.5–9.4) | 6.6 (5.2–9.4) | 8.0 (6.2–9.7) | 0.192 |
| Logistic Euro score | 15.1 (10.7–22.7) | 16.9 (10.7–22.9) | 12.5 (8.2–17.3) | 0.116 |
| Laboratory data on admission | | | | |
| e-GFR (mL/min/1.73 $m^2$) | 52.4 (41.5–59.2) | 53.4 (43.3–63.2) | 43.5 (36.9–51.9) | 0.006 |
| BNP (pg/mL) | 215 (77–402) | 187 (66–405) | 285 (184–394) | 0.216 |
| Medication on admission | | | | |
| Aspirin | 27 (23.9) | 22 (23.7) | 5 (25.0) | 0.898 |
| Thienopyridine | 18 (15.9) | 14 (15.1) | 4 (20.0) | 0.583 |
| SAPT | 25 (22.1) | 20 (21.5) | 5 (25.0) | 0.733 |
| DAPT | 10 (8.9) | 8 (8.6) | 2 (10.0) | 0.842 |
| Warfarin | 4 (3.5) | 2 (2.2) | 2 (10.0) | 0.085 |
| Edoxavan | 8 (7.1) | 6 (6.5) | 2 (10.0) | 0.575 |
| Apixaban | 8 (7.1) | 7 (7.5) | 1 (5.0) | 0.689 |
| Rivaroxaban | 2 (1.8) | 1 (1.1) | 1 (5.0) | 0.227 |
| TTE data on admission | | | | |
| LVEF (%) | 60 (55–65) | 60 (55–65) | 61 (57–64) | 0.943 |
| Mean AVPG (mmHg) | 49 (38–63) | 49 (39–62) | 43 (29–69) | 0.297 |
| Peak AVPG (mmHg) | 83 (73–106) | 84 (74–104) | 76 (69–116) | 0.484 |
| Aortic valve area ($cm^2$) | 0.54 (0.45–0.68) | 0.55 (0.45–0.68) | 0.50 (0.41–0.67) | 0.388 |
| Pre CT data | | | | |
| Annular area ($mm^2$) | 386 (342–451) | 389 (344–465) | 370 (332–394) | 0.114 |
| Annular perimeter (mm) | 69.8 (65.7–76.6) | 70.0 (65.8–76.8) | 68.4 (65.2–71.6) | 0.323 |
| STJ major axis (mm) | 27.2 (25.2–29.2) | 27.2 (25.2–29.2) | 26.5 (24.7–28.2) | 0.170 |
| Calcium volume of aortic valve ($mm^2$) | 490 (339–736) | 488 (331–737) | 547 (385–704) | 1.000 |
| Porcelain aorta | 19 (16.8) | 15 (16.1) | 4 (20.0) | 0.675 |
| Aortic arch plaque | 35 (31.0) | 29 (31.2) | 6 (30.0) | 0.917 |

Categorical variables are shown as numbers (percentages) and continuous variables are shown as medians (25–75 percentiles).
AVPG, aortic valve pressure gradient; BSA, body surface area; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; CT, computed tomography; DAPT, dual anti-platelet therapy; e-GFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SAPT, single anti-platelet therapy; STJ, sinotubular junction; STS, Society of Thoracic Surgeons; TTE, transthoracic echocardiography.

the primary endpoint (Table 3). The AIC-based statistical model selection revealed that valve type was the only explanatory variable for the best-fit model. This result was also confirmed with the propensity score matching analysis (estimate, 2.359; 95% CI, 0.426–4.292; $p$ = 0.019) after adjustments of propensity score, in which 28 patients were matched ($n$ = 14 in each group).

## Discussion

In this study, we demonstrated that self-expandable valves were associated with an increased number of HIA detected by DW-MRI. To the best of our knowledge, this is the first study describing significant differences in the number of HIA detected by DW-MRI between balloon-expandable and self-expandable TAVR. Thus, we believe that our results give physicians additional information for safely managing TAVR.

### *Short-term stroke risk after TAVR*

TAVR is reported to have more HIA detected by DW-MRI than SAVR [86% (19 of 22) for the Edwards SAPIEN vs. 80% (8 of 10) for the CoreValve and 48% (10 of 21) for AVR], and higher risk of clinical stroke than SAVR, with a neurologic event rate of 5.5% vs. 2.4% at 30 days and 8.3% vs. 4.3% at 1 year from the PARTNER trial of high-risk patients [10,25]. Several previous studies have evaluated the risk factors for clinical stroke and ischemic lesions on DW-MRI during TAVR [10,12–15]. For example, the PARTNER trial demonstrated that smaller aortic valve areas were an independent risk factor for early clinical stroke [26]. Additionally, possible risk of new ischemic lesions on MRI included higher aortic arch atheroma grade as classified on TEE, smoking history, baseline creatinine level, and aortic valve plaque with an intermediate CT score (50–130 HU) [10,12–17]. However, there is conflicting evidence for risk factors of ischemic lesions on MRI, possibly due to the small number of patients, the miscellaneous source of embolic debris, or the advancements in interventional medical devices [10–12,14,18,26,27]. Therefore, the risks associated with TAVR warrant further evaluation to improve prognosis.

In this study, we demonstrated a relatively low incidence (57.5% in total) of HIA by DW-MRI compared to previous reports of a 68–84% incidence of asymptomatic stroke by DW-MRI [10,12–16]. This can also be explained by medical device advancements, patient selection, and operator experience [18]. However, there is still room for improvement. In our study, the number of HIA on DW-MRI had no significant relationship to previously reported, or clinically suspicious, indices such as STS score, aortic atheroma, pre-procedural BAV,

**Table 2**
Procedural and outcome information.

| Parameters | Total ($n$ = 113) | Balloon-expandable ($n$ = 93) | Self-expandable ($n$ = 20) | $p$-Value |
|---|---|---|---|---|
| Procedural data | | | | |
| Valve type | | | | |
| Edwards SAPIEN XT | 23 (20.4) | 23 (24.7) | – | – |
| Edwards SAPIEN 3 | 70 (62.0) | 70 (75.3) | – | – |
| Medtronic CoreValve | 3 (2.7) | – | 3 (15.0) | – |
| Medtronic EvolutR | 17 (15.0) | – | 17 (85.0) | – |
| Valve size (mm) | 26 (23–26) | 23 (23–26) | 26 (26–29) | <0.001 |
| Oversizing rate (%) | 16.2 (9.2–21.8) | 15.5 (7.8–21.5) | 19.7 (15.9–25.2) | 0.025 |
| Pre BAV | 51 (45.1) | 34 (36.6) | 17 (85.0) | <0.001 |
| Fluoro time (min) | 22 (15–29) | 20 (13–29) | 27 (23–31) | 0.012 |
| Procedure time (min) | 63 (50–97) | 60 (45–100) | 70 (60–91) | 0.285 |
| Anesthesia time (min) | 124 (100–158) | 124 (97–160) | 128 (100–147) | 0.937 |
| Post-procedural TTE | | | | |
| LVEF (%) | 62 (57–65) | 62 (57–65) | 61 (58–64) | 0.717 |
| Mean THVPG (mmHg) | 11 (8–14) | 12 (9–15) | 7 (5–9) | <0.001 |
| Peak THVPG (mmHg) | 20 (16–27) | 23 (18–29) | 15 (9–19) | <0.001 |
| Peri-procedural complications | | | | |
| Total stroke | 65 (57.5) | 47 (50.5) | 18 (90.0) | 0.001 |
| Symptomatic | 6 (5.3) | 0 (0.0) | 6 (30.0) | <0.001 |
| Disabling stroke | 1 (0.9) | 0 (0.0) | 1 (5.0) | 0.030 |
| Asymptomatic | 59 (52.2) | 47 (50.5) | 12 (60.0) | 0.442 |
| No. of HIA by DW-MRI | 1 (0–3) | 1 (0–2) | 4 (2–7) | <0.001 |
| Massive high intensity spot | 0 (0–0) | 0 (0–0) | 0 (0–0) | <0.001 |
| Non-massive high intensity spot | 1 (0–3) | 0 (0–2) | 4 (2–7) | <0.001 |
| Days from TAVR to DW-MRI | 4 (3–8) | 4 (3–7) | 7 (3–8) | 0.297 |
| In hospital deaths | 0 (0.0) | 0 (0.0) | 0 (0.0) | – |
| Coronary occlusion | 4 (3.5) | 3 (3.2) | 1 (5.0) | 0.697 |
| Permanent PM implantation | 3 (2.7) | 2 (2.2) | 1 (5.0) | 0.472 |

Categorical variables are shown as numbers (percentages) and continuous variables are shown as medians (25–75 percentiles).
BAV, balloon aortic valvuloplasty; DW-MRI, diffusion-weighted magnetic resonance imaging; HIA, high intensity areas; LVEF, left ventricular ejection fraction; PM, pacemaker; TAVR, transcatheter aortic valve replacement; THVPG, trans-heart valve pressure gradient; TTE, transthoracic echocardiography.

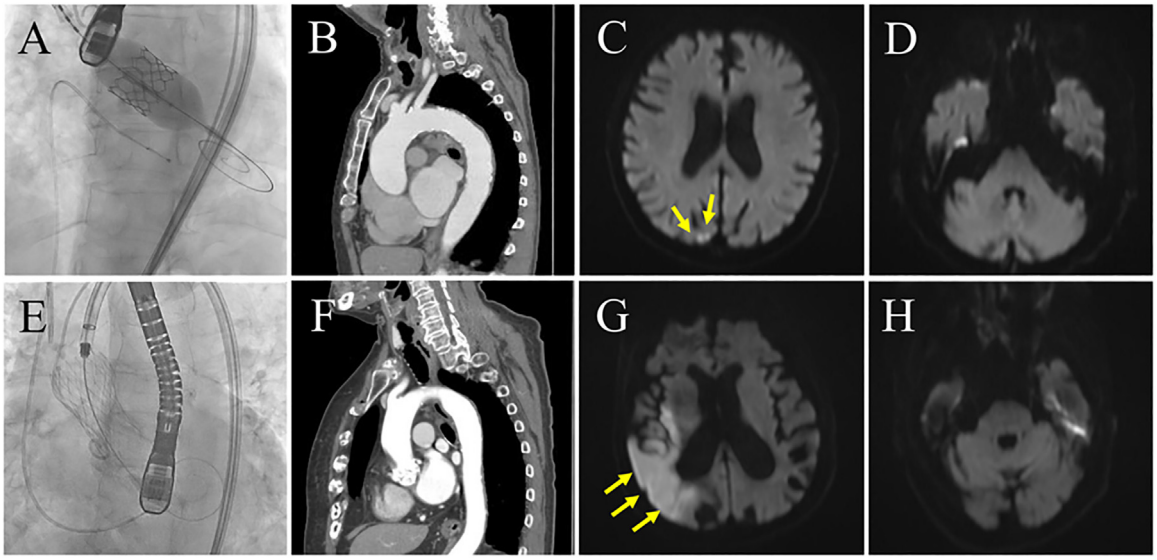


**Fig. 2.** Representative cases. Cases of cerebral infarction after insertion of a 26 mm-sized balloon-expandable Sapien 3 (A–D) and 26-mm sized self-expandable CoreValve (E–H) transfemoral TAVR. (A) and (E) represent cineradiography during TAVR, (B) and (F) reveal pre-procedural enhanced-CT evaluating the aortic arch in the sagittal view, (C) and (G) post-procedural DWI of cerebrum, and (D) and (H) demonstrated post-procedural DWI of cerebellum. Yellow arrows indicate high-intensity area suggesting two spotty infarctions in image (C) and one massive infarction in image (G).
DWI, diffusion-weighted image of magnetic resonance imaging; TAVR, transcatheter aortic valve replacement.

or oversizing rate. In contrast, we first revealed that valve type was associated with the number of HIA detected by DW-MRI even after adjustments for patient and procedural backgrounds, or even in an AIC-based best predictive model, which was an unexpected result.

*Possible mechanism of association between self-expandable valves and frequent HIA*

We speculated that three different aspects of balloon and self-expandable valves contributed to the difference in the number of

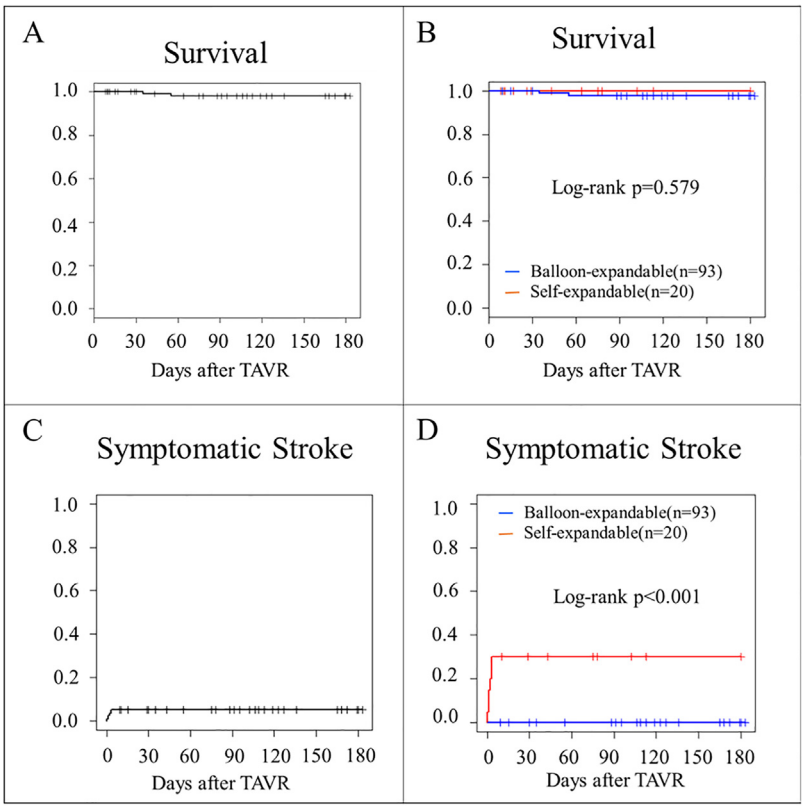


**Fig. 3.** Kaplan–Meier estimates. Survival rate in entire cohort (A) and each sub-group (B), and cumulative incidence of symptomatic stroke in entire cohort (C) and each sub-group (D).
TAVR, transcatheter aortic valve replacement.

**Table 3**
Association of the number of HIA on DW-MRI after TAVR.

| Parameters | Univariate | | Multivariable | | AIC based multivariable | |
|---|---|---|---|---|---|---|
| | Estimate (95% CI) | *p*-Value | Estimate (95% CI) | *p*-Value | Estimate (95% CI) | *p*-Value |
| STS risk score | 0.078 (−0.018 to 0.174) | 0.109 | 0.031 (−0.058 to 0.121) | 0.491 | – | – |
| mean AVPG | −0.011 (−0.036 to 0.014) | 0.392 | −0.002 (−0.027 to 0.024) | 0.900 | – | – |
| Valve type (Self vs Balloon) | 3.413 (2.271–4.555) | <0.001 | 3.231 (1.924–4.537) | <0.001 | 3.413 (2.271–4.555) | <0.001 |
| Oversizing rate | 0.036 (−0.019 to 0.091) | 0.195 | −0.003 (−0.059 to 0.052) | 0.906 | – | – |
| Pre BAV | 1.053 (0.067–2.038) | 0.037 | 0.218 (−0.816 to 1.251) | 0.677 | – | – |
| Calcium volume of aortic valve | −0.001 (−0.002 to 0.001) | 0.233 | −0.001 (−0.002 to 0.001) | 0.458 | – | – |
| Aortic arch plaque | −0.318 (−1.398 to 0.762) | 0.560 | −0.224 (−1.222 to 0.775) | 0.658 | – | – |
| Porcelain aorta | −0.242 (−1.579 to 1.094) | 0.720 | −0.211 (−1.435 to 1.014) | 0.734 | – | – |

AVPG, aortic valve pressure gradient; BAV, balloon aortic valvuloplasty; CI, confidence interval; DW-MRI, diffusion-weighted magnetic resonance imaging; HIA, high intensity areas; OR, odds ratio; STS, Society of Thoracic Surgeons. TAVR, transcatheter aortic valve replacement.

HIA detected by DW-MRI. That is, slow and stepwise implantation of self-expandable valves, their continuously expanding properties, and their larger attachment areas might contribute to this difference. First, Kahlert et al. reported that transcranial Doppler examinations during TAVR showed high-intensity transient signals (HITS) reflective of cerebral embolism, while THV manipulation to native aortic valves, and more HITS were recorded during self-expandable valve release [28]. Because the duration of aortic valve manipulation and deployment with self-expandable valves can be longer than those of balloon-expandable valves, we supposed that patients treated with self-expandable valves would have an increased number of HIA on DW-MRI. Second, self-expandable valves expand continuously for approximately 10 days to best fit the surrounding anatomical structures. Therefore, it is possible that debris from the native valve or surrounding tissues could provoke embolism during the expanding time period for self-expandable valve implantation. This kind of risk occurs only at the timing of implantation with balloon-expandable valves. Third, the larger attachment area of self-expandable valves may have continuous expanding impact not only on the native valve and its surrounding tissue, but also on the aortic root area, which can result in greater debris dissemination from a larger area. These hypotheses can explain our results, but further study is needed to confirm this speculation.

*Clinical outcomes*

In our study, the 180-day survival was not statistically different between balloon and self-expandable valve groups, whereas the 180-day cumulative incidence of symptomatic stroke was higher in the self-expandable valve group. However, we think that clinical event rates should be evaluated based on the results of large clinical studies with significant statistical power. Our results should only be adapted to the assessment related to the number of

HIA by DW-MRI considering the primary purpose of our study and the lack of a large number of study participants. For example, a meta-analysis of 25 multicenter registries and 33 single-center studies concluded that the risk of 30-day stroke after TAVR ranges from 2.4% to 3.8%, and those were similar among valve types [18]. However, we also believe that, in theory, reducing asymptomatic stroke events can lead to reduced symptomatic stroke events as well as a prevention of cognitive decline [11]. Thus, our findings can be applied to future studies and will contribute to improving outcomes after TAVR.

## Limitations

This single center prospective observational study had several limitations that warrant mention. First, the unbalanced number of patients in each study group due to the observational nature of the study should be considered when interpreting our data because some clinical decisions led to selection bias, as mentioned in the Methods section, although we have mitigated this bias using propensity scores in analyzing the outcomes. Second, the short follow-up period of six months made it difficult to adequately assess the clinical impacts including long-term changes in cognitive function. However, we believe that this completely unexpected positive association between valve types and risk of stroke after adjusting for several variables is worth further discussion and should be published in a peer review journal.

## Conclusions

Self-expandable valves were associated with an increased number of HIA detected by DW-MRI after TAVR in patients with severe AS.

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None.

## Conflicts of interest

All authors have no conflict of interest.

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