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ORIGINAL INVESTIGATIONS

Brain Injury After Transcatheter Replacement of Bicuspid Versus Tricuspid Aortic Valves

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ABSTRACT

BACKGROUND An increasing number of bicuspid aortic valve (BAV) patients are undergoing transcatheter aortic valve replacement (TAVR), but the risk of brain injury in diffusion-weighted magnetic resonance imaging (DW-MRI) is currently unknown.

OBJECTIVES This study sought to evaluate the risk of brain injury in BAV patients following TAVR.

METHODS A total of 204 consecutive severe aortic stenosis patients who underwent TAVR were enrolled. A total of 83 (40.7%) patients were BAV patients, and the other 121 patients were tricuspid aortic valve (TAV) patients. All patients received DW-MRI at baseline, and after TAVR.

RESULTS Median ages (76 years [interquartile range (IQR): 71 to 81 years] vs. 79 years [IQR: 74 to 83 years]; $p = 0.004$) and Society of Thoracic Surgeons scores (4.87 [IQR: 3.72 to 8.54] vs. 6.38 [IQR: 3.96 to 9.50]; $p = 0.044$) of the BAV and TAV patients were significantly different, while the overt stroke rates (2.4% vs. 1.7%; $p = 0.704$) were comparable between the 2 groups. BAV patients were associated with higher number of new lesions (4.0 [IQR: 1.0 to 8.0] vs. 2.0 [IQR: 1.0 to 5.0]; $p = 0.008$), total lesion volume (290 mm^3 [IQR: 70 to 930 mm^3] vs. 140 mm^3 [IQR: 35 to 480 mm^3]; $p = 0.008$), and the volume per lesion (70.0 mm^3 [IQR: 45.0 to 115.0 mm^3] vs. 57.5 mm^3 [IQR: 24.5 to 93.0 mm^3]; $p = 0.037$) in DW-MRI. Moreover, the proportion of patients with lesions larger than 1 cm^3 (28.6% vs. 10.9%; $p = 0.005$) was higher in BAV patients than in TAV patients.

CONCLUSIONS BAV patients may encounter more severe brain injuries not only due to greater number of lesions, but also due to larger lesion size in the early phase after TAVR. (Transcatheter Aortic Valve Replacement Single Center Registry in Chinese Population [TORCH]; NCT02803294) (J Am Coll Cardiol 2020;76:2579-90) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACA = anterior cerebral artery
AS = aortic stenosis
BA = basilar artery
BAV = bicuspid aortic valve
DW-MRI = diffusion-weighted magnetic resonance imaging
IQR = interquartile range
MCA = middle cerebral artery
PCA = posterior cerebral artery
STS = Society of Thoracic Surgeons
TAV = tricuspid aortic valve
TAVR = transcatheter aortic valve replacement
VA = vertebral artery

Transcatheter aortic valve replacement (TAVR) is an established therapy in symptomatic severe aortic stenosis (AS) patients at prohibitive, high, and moderate risk for surgical aortic valve replacement (1–6). The U.S. Food and Drug Administration has expanded the indication to include severe AS patients who are at low risk for death or major complications associated with open-heart surgery for several transcatheter heart valves (7,8). Although many randomized clinical trials for TAVR show excellent outcomes, bicuspid aortic valve (BAV) stenosis was excluded from these clinical trials due to its unique morphological features (1–9). Only a few small series and registry studies demonstrated the safety and efficacy of TAVR in BAV patients (10–14). Recently, several studies have demonstrated a high incidence of new cerebral ischemic lesions on post-TAVR diffusion-weighted magnetic resonance imaging (DW-MRI) (15–17). However, there is no study that has assessed the number, volume, and distribution of the new cerebral ischemic lesions on post-TAVR DW-MRI in the BAV patients. Therefore, in the present study, we aim to compare brain injury after TAVR between BAV and TAV stenosis by post-TAVR DW-MRI.

METHODS

STUDY DESIGN AND PATIENT POPULATION. The TORCH (Transcatheter Aortic Valve Replacement Single Center Registry in Chinese Population) registry (NCT02803294) is a single-center prospective cohort study in Chinese population. The registry was initiated in June 2016, and BAV patients were also included in this registry. We collected data from the TORCH registry. The study was approved by the medical ethics committee of the Second Affiliated Hospital of Zhejiang University and carried out according to the principles of the Declaration of Helsinki. All patients provided written informed consent for TAVR and the use of anonymous clinical, procedural, and follow-up data for research.

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For this study, we consecutively collected all severe AS patients >18 years of age treated with transfemoral TAVR determined by an interdisciplinary heart team from December 1, 2016, to December 31, 2019 in the TORCH registry. Exclusion criteria were: 1) implantation of incompatible metallic prosthesis or foreign body contraindicated to the DW-MRI examination, including pacemaker implantation; 2) history of a stroke or transient ischemic attack within the prior 6 months; 3) absence of DW-MRI examination for other reasons (i.e., in-hospital death, conversion to surgical aortic valve replacement, and unplanned cardiopulmonary bypass before the DW-MRI examination), intolerance due to clinical situation, and refusal of the DW-MRI examination or overscheduling; and 4) poor quality of imaging or out of the window period cannot be analyzed. All patients completed a 30-day follow-up.

Patients underwent a standard screening algorithm including echocardiography and multislice computed tomography. Aortic annulus size was measured by multislice computed tomography in 3mensio software (3mensio Medical Imaging BV, Bilthoven, the Netherlands). The threshold for detecting aortic root calcification was set at 650 Hounsfield units; then, calcium volume score was measured within the region from the left ventricular outflow tract to the leaflet tips. Calcification of the aortic arch was visually quantified as grade 0 (no calcification), grade I (calcification involving less than or equal to one-third of the vessel length and circumference), grade II (calcification involving greater than one-third to two-thirds of the vessel length and circumference), and grade III (calcification involving greater than two-thirds of the vessel length and circumference) (18). The transvalvular mean gradient, effective orifice valve area, and maximum transvalvular velocity were measured by transthoracic echocardiography (19). Carotid artery stenosis more than 70% was assessed according to the 2003 Society of Radiologists in Ultrasound consensus criteria (20).

TAVR procedures were performed in our hybrid operating room as previously reported (21,22). Unfractionated heparin was used in all procedures (50 to 70 U/kg) to maintain an activated clotting time >250 s. General anesthesia or local anesthesia with sedation was used during the procedure based on the evaluation from the anesthetist. Balloon valvuloplasty and post-dilatation were employed according to operator discretion. A large proportion of patients were implanted with self-expanding valves, such as the CoreValve (Medtronic, Minneapolis, Minnesota), VenusA-Valve (Venus Medtech, Hangzhou, China), VitaFlow (Microport, Shanghai, China), and Taurus One-Valve (Peijia Medical, Suzhou, China). The rest of the patients were implanted with the mechanically expandable Lotus valve (Boston Scientific, Marlborough, Massachusetts) or balloon-expandable Edwards SAPIEN XT or SAPIEN 3 valves (Edwards Lifesciences, Irvine, California). Almost all patients were treated with dual antiplatelet therapy (aspirin

100 mg and clopidogrel 75 mg) with no indication of anticoagulation after TAVR; when anticoagulation treatment was indicated, patients received warfarin or new oral anticoagulants.

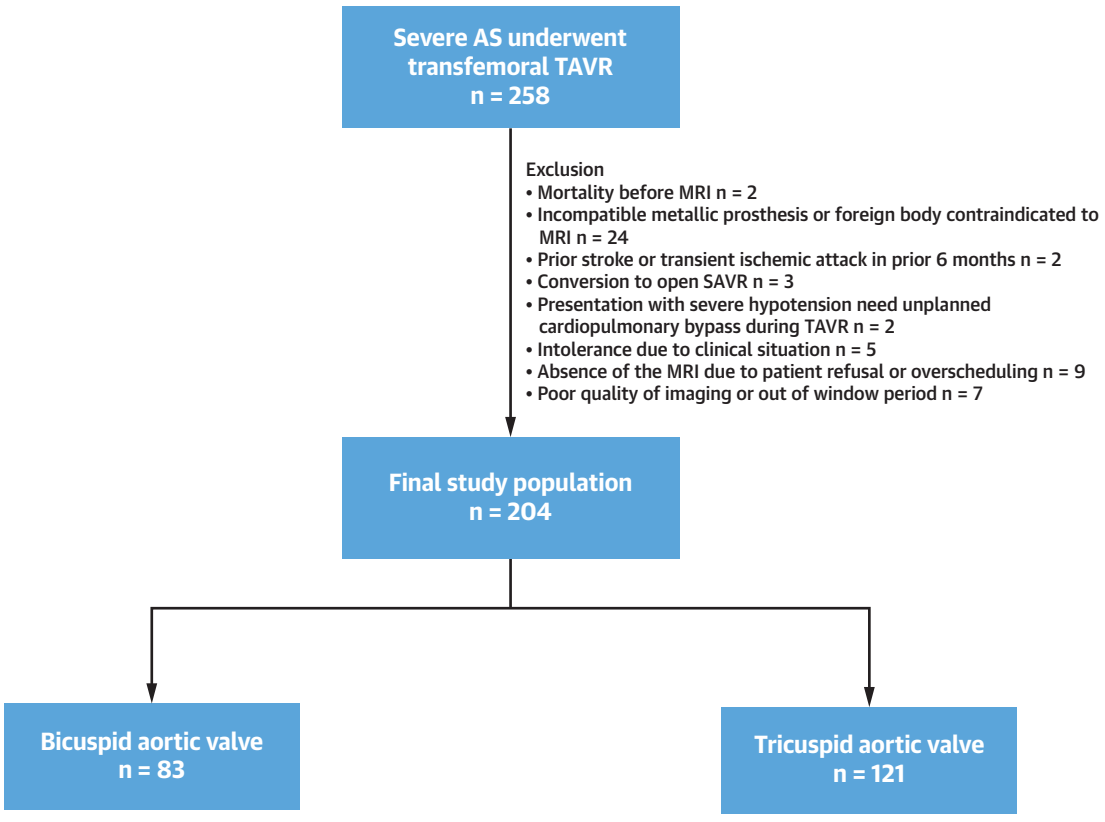
BICUSPID AORTIC VALVE. BAV morphology was classified as BAV or TAV according to the number of cusps and presence of raphes by Sievers and Schmidtke (23). Type 0 was assigned to the congenitally malformed valves with 2 symmetric cusps or leaflets, 2 commissures, and 1 parallel zone of apposition between leaflets. Type 1 was assigned to valve morphologies with 1 raphe, and type 2 when 2 raphes were present. Two authors (Y.X.H. and Q.F.Z.) reviewed and subsequently confirmed the diagnosis and classification of bicuspid AS in multislice computed tomography imaging before TAVR.

BRAIN MRI. All patients received brain DW-MRI before and within 5.7 ± 2.8 days post-TAVR procedure in the hospital using a 1.5-T or 3-T whole-body MRI system (GE Signa, GE Healthcare, Milwaukee, Wisconsin). The imaging protocol comprised transversal T2-weighted turbo spin echo (1.5-T: repetition time/echo time = 4,800/100 ms; 3-T: repetition time/echo time = 3,300/80 ms) and transversal fluid-attenuated inversion recovery (1.5-T: repetition time/echo time = 6,000/120 ms; 3-T: repetition time/echo time = 1,200/140 ms). DWI was performed with a spin-echo echo-planar pulse sequence (1.5-T: repetition time/echo time = 2,921/78 ms, matrix = 128 × 256; section thickness = 5 mm; intersection gap = 1 mm; total acquisition time = 21.4 s; 3-T: repetition time/echo time = 3,866/47 ms, matrix = 128 × 256, section thickness = 5 mm, intersection gap = 1 mm, total acquisition time = 46.3 s) with diffusion sensitization b-values of 0 and 1,000 s/mm^2. Apparent diffusion coefficient maps were calculated to identify findings with restricted diffusion. A new lesion was defined as a focal hyperintense area detected by the fluid-attenuated inversion recovery sequence, corresponding to a restricted diffusion signal in the diffusion-weighted imaging sequence, and confirmed by apparent diffusion coefficient mapping to rule out a shine-through artifact. The brain MRI for new ischemic lesions was analyzed by the 2 independent authors with the software and confirmed by the neurological physician by MRIcron software (NeuroImaging Tools and Resources Collaboratory, Columbia, South Carolina). Vascular territories were classified according to previous studies (24,25): anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA) for each side. Furthermore, vascular border zones (watershed zones) were defined as the area between ACA and MCA (ACA/MCA), MCA and PCA (MCA/PCA), vertebral artery (VA), and basilar artery (BA).

DATA COLLECTION. Data collection included baseline characteristics, procedural data, and pre-discharge outcomes. Baseline characteristics consisted of baseline clinical, laboratory, echocardiographic, and computed tomographic data, while pre-discharge outcomes were obtained from the local hospital database and assessed for quality. The incidence of new ischemic lesions, the number of lesions, total lesion volume, and total lesion volume or number of lesions before discharge in DW-MRI were compared between the 2 groups. Clinical outcomes were mortality, stroke (including disabling stroke and nondisabling stroke), and other clinical events before discharge according to the Valve Academic Research Consortium-2 criteria (26). The modified Rankin Scale score was recorded on admission, at 30 days, and at 1 year after TAVR. A face-to-face assessment occurred on admission, at 30 days, and at 1-year follow-up if patients came back to hospital for follow-up, whereas a telephone interview was used for patients who were not convenient to face-to-face assessment. Multiple pre-dilatation was defined as balloon pre-dilatation more than 1 time during the TAVR procedure. All data were stored in the database of TORCH registry and can be traced to the source.

STATISTICAL ANALYSIS. Continuous variables of normal and abnormal distribution were presented as mean ± SD and median (interquartile range [IQR]), respectively. Their distributions between 2 groups was compared by Student's *t*-test and the Mann-Whitney *U* test, respectively. Categorical data were presented as count (percentage) and compared with the chi-square test. The associations of variables at baseline and peri-procedural characteristics with number of lesions in DW-MRI among all patients and patients with self-expanding valve was analyzed using univariate Poisson regression models. The variables with $p < 0.05$ in the univariate Poisson regression models were included in to the multiple Poisson regression model, which explored the association of valve types (BAV and TAV) with number of lesions among all patients and patients with self-expanding valve, respectively. A value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS software version 20.0 (IBM, Armonk, New York) and the figures were created in GraphPad Prism version 6.0 (GraphPad Software, San Diego, California).

FIGURE 1 Patient Selection Flow



Selection of patient for the current analysis. AS = aortic stenosis; MRI = magnetic resonance imaging; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

RESULTS

A total of 204 patients were included in this study, with 83 BAV and 121 TAV patients. The BAV group consisted of 56 type 0 patients and 27 type 1 patients. TAV patients were older than BAV patients (79 years [IQR: 74 to 83 years] vs. 76 years [IQR: 71 to 81 years]; $p = 0.004$) and had higher Society of Thoracic Surgeons (STS) scores (6.38 [IQR: 3.96 to 9.50] vs. 4.87 [IQR: 3.72 to 8.54]; $p = 0.044$). TAV patients had a higher proportion of prior history of stroke (8.3% vs. 1.2%; $p = 0.030$). Patient selection flow is shown in **Figure 1**. All baseline demographics is summarized in **Table 1**.

The aortic valve area (0.50 cm^2 [IQR: 0.39 to 0.68 cm^2] vs. 0.65 cm^2 [IQR: 0.52 to 0.78 cm^2]; $p < 0.001$) and prevalence of moderate or severe aortic regurgitation (13.3% vs. 47.1%; $p < 0.001$) were lower in BAV patients. Carotid stenosis was compared between the 2 groups ($p = 0.499$). Sinotubular junctions were larger (31.01 ± 3.99 mm vs. 28.47 ± 5.29 mm; $p = 0.005$) in the BAV group compared with the TAV group. Larger ascending aorta diameters were observed in BAV patients not only at 40 mm from the annulus (38.42 ± 3.21 mm vs. 36.64 ± 3.84 mm; $p = 0.009$) but also at the maximum ascending aorta plane (42.66 ± 4.22 mm vs. 38.80 ± 4.66 mm; $p < 0.001$). BAV patients had higher left main coronary artery height (16.7 mm [IQR: 14.7 to 19.1 mm] vs. 14.0 mm [IQR: 12.5 to 16.7 mm]; $p < 0.001$) and more severe calcification (calcification score, 949.3 mm^3 [IQR: 568.9 to 1,377.9 mm^3] vs. 723.7 mm^3 [IQR: 423.5 to 1,218.2 mm^3]; $p = 0.011$). The proportion of calcium grade more than mild in aortic arch was lower in BAV patients when compared with TAV patients (12.0% vs. 34.7%; $p < 0.001$). There were no differences between the 2 groups in local anesthetic consideration and predilatation times during the TAVR procedure. The prevalence of post-dilatation was higher in the BAV group than that of the TAV group (63.9% vs. 48.8%; $p = 0.045$). Procedure duration (60 min [IQR: 43 to 85 min] vs. 53 min [IQR: 40 to 72 min]; $p = 0.153$) tended to be longer in BAV patients compared with

TABLE 1 Baseline Characteristics of BAV and TAV Patients

	BAV				
	Type 0 (n = 56)	Type 1 (n = 27)	Total (n = 83)	TAV (n = 121)	p Value
Age, yrs	75 (71–80)	78 (73–82)	76 (71–81)	79 (74–83)	0.004*
Male	33 (58.9)	16 (59.3)	49 (59.0)	75 (62.0)	0.770
BMI, kg/m^2	22.28 ± 2.91	21.96 ± 2.58	22.17 ± 2.79	23.02 ± 3.56	0.058
NYHA functional class III/IV	51 (91.1)	24 (88.9)	75 (90.4)	104 (86.0)	0.391
STS score	4.98 (3.58–8.36)	4.67 (4.00–8.80)	4.87 (3.72–8.54)	6.38 (3.96–9.50)	0.044*
Smoker	11 (19.6)	4 (14.8)	15 (18.1)	21 (17.4)	1.000
Diabetes mellitus	14 (25.0)	10 (37.0)	24 (28.9)	29 (24.0)	0.516
Hypertension	30 (53.6)	13 (48.1)	43 (51.8)	71 (58.7)	0.389
Atrial fibrillation	6 (10.7)	5 (18.5)	11 (13.3)	22 (18.2)	0.440
COPD	13 (23.2)	6 (22.2)	19 (22.9)	30 (24.8)	0.868
Prior PCI	3 (5.4)	5 (18.5)	8 (9.6)	14 (11.6)	0.819
Prior CABG	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	1.000
Prior MI	0 (0.0)	1 (3.7)	1 (1.2)	1 (0.8)	1.000
Prior stroke	0 (0.0)	1 (3.7)	1 (1.2)	10 (8.3)	0.030
Syncope	6 (10.7)	3 (11.1)	9 (10.8)	10 (8.3)	0.626
Medication on admission					0.592
Anticoagulation	5 (8.9)	3 (11.1)	8 (9.6)	14 (11.6)	
Antiplatelet	28 (50.0)	11 (40.7)	39 (47.0)	63 (52.1)	
No antithrombosis	23 (41.1)	13 (48.1)	36 (43.4)	44 (36.4)	
Pre-TTE data					
Mean gradient, mm Hg	51.0 (42.0–75.8)	53.0 (43.0–69.0)	52.0 (42.0–71.0)	53.0 (43.0–61.0)	0.307*
AVA, cm^2	0.47 (0.39–0.63)	0.54 (0.43–0.73)	0.50 (0.39–0.68)	0.65 (0.52–0.78)	<0.001*
Maximum velocity, m/s	5.01 ± 0.93	4.87 ± 0.70	4.96 ± 0.86	4.75 ± 0.72	0.065
AR moderate/severe	6 (10.7)	5 (18.5)	11 (13.3)	57 (47.1)	<0.001
EF, %	58.0 (43.8–63.8)	58.5 (52.0–63.7)	58.5 (47.9–63.7)	58.0 (46.4–65.4)	0.547*
Carotid stenosis (II+)	0 (0.0)	3 (11.1)	3 (3.6)	4 (3.3)	1.000
Pre-CT data					
Area, mm^2	450.5 (389.7–545.8)	427.3 (401.5–497.6)	444.7 (401.5–530.2)	433.8 (387.5–521.0)	0.709*
Perimeter, mm	77.0 (71.9–84.5)	75.7 (72.9–80.4)	76.4 (72.9–83.9)	75.0 (70.9–82.1)	0.561*
STJ diameter, mm	31.80 ± 3.68	28.74 ± 4.11	31.01 ± 3.99	28.47 ± 5.29	0.005
STJ height, mm	25.0 (20.7–27.8)	20.9 (18.8–25.6)	24.3 (19.9–26.8)	21.9 (19.7–25.6)	0.141*
Ascending aorta diameter at 4 cm, mm	38.89 ± 3.37	37.09 ± 2.31	38.42 ± 3.21	36.64 ± 3.84	0.009
Maximum ascending aorta diameter, mm	43.86 ± 3.99	39.22 ± 2.77	42.66 ± 4.22	38.80 ± 4.66	<0.001
RCA height, mm	16.7 (15.0–20.7)	16.3 (13.3–17.8)	16.7 (14.0–18.9)	16.3 (14.1–19.4)	0.694*
LM height, mm	17.0 (14.8–19.9)	14.9 (14.3–16.8)	16.7 (14.7–19.1)	14.0 (12.5–16.7)	<0.001*
Aortic root angle	52.8 ± 9.8	52.7 ± 8.4	52.8 ± 9.4	51.1 ± 8.8	0.338
Calcium score, mm^3	949.1 (504.7–1531.6)	966.4 (676.3–1115.0)	949.3 (568.9–1377.9)	723.7 (423.5–1218.2)	0.011*
Aortic arch calcium (II+)	7 (12.5)	3 (11.1)	10 (12.0)	42 (34.7)	<0.001

Values are median (interquartile range), n (%), or mean ± SD. *Mann-Whitney *U* test.

AS = aortic stenosis; AVA = aortic valve area; AR = aortic regurgitation; BAV = bicuspid aortic valve; BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; CT = computed tomography; EF = ejection fraction; GI = gastrointestinal; LM = left main artery; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PPI = permanent pacemaker implantation; PVD = peripheral vascular disease; RCA = right coronary artery; STJ = sinotubular junction; STS = Society of Thoracic Surgeons; TAV = tricuspid aortic valve; TTE = transthoracic echocardiography.

TAV patients without significance. Moreover, a higher proportion of BAV patients adopted self-expandable devices, while more balloon-expandable and mechanically expandable valves were implanted in TAV patients (BAV vs. TAV: self-expanding valve, 96.4% vs. 75.2%; balloon-expandable valve, 3.6% vs. 22.3%; mechanically expandable valve, 0.0% vs. 2.5%; $p < 0.001$). Echocardiographic and computed tomographic baseline are listed in Table 1. Procedural data are listed in Table 2.

There were 2 BAV patients who experienced a nondisabling stroke while 2 patients in the TAV group had a disabling stroke during their hospital stays. No significant difference was found in other periprocedural complications. One death occurred in the TAV group in hospital. The modified Rankin Scale score was assessed at baseline and at 30-day and 1-year follow-up. There were no significant differences between BAV and TAV patients at baseline ($p = 0.096$) and at 1 year ($p = 0.482$) in the modified

TABLE 2 Procedural Data and DW-MRI Findings Following TAVR

	BAV				
	Type 0 (n = 56)	Type 1 (n = 27)	Total (n = 83)	TAV (n = 121)	p Value
Procedural data					
Local anesthetic	47 (83.9)	24 (88.9)	71 (85.5)	106 (87.6)	0.679
Pre-dilatation					0.121
None	0 (0.0)	0 (0.0)	0 (0.0)	6 (5.0)	
Once	48 (85.7)	14 (51.9)	62 (74.7)	89 (73.9)	
Multiple	8 (14.3)	13 (48.1)	21 (25.3)	26 (21.5)	
Post-dilatation	38 (67.9)	15 (55.6)	53 (63.9)	59 (48.8)	0.045
Duration of procedure, min	60 (49–88)	51 (41–66)	60 (43–85)	53 (40–72)	0.153*
Contrast, ml	125 (112–150)	120 (100–158)	120 (103–150)	110 (100–145)	0.083*
Valve type					<0.001
Self-expanding	56 (100.0)	24 (88.9)	80 (96.4)	91 (75.2)	
Balloon-expandable	0 (0.0)	3 (11.1)	3 (3.6)	27 (22.3)	
Mechanically expandable	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.5)	
Patients with new lesions	48 (85.7)	22 (81.5)	70 (84.3)	92 (76.0)	0.163
Lesion location					0.203
Left hemisphere	4 (8.3)	4 (18.2)	8 (11.4)	20 (21.7)	
Right hemisphere	9 (18.8)	3 (13.6)	12 (17.1)	17 (18.5)	
Bilateral	35 (72.9)	15 (68.2)	50 (71.4)	55 (59.8)	
Lesion size					0.005
≤1 cm^3	35 (72.9)	15 (68.2)	50 (71.4)	82 (89.1)	
>1 cm^3	13 (27.1)	7 (31.8)	20 (28.6)	10 (10.9)	
Total number of lesions	333	139	472	423	
Number of lesions	4.0 (1.0–8.0)	3.0 (1.0–8.0)	4.0 (1.0–8.0)	2.0 (1.0–5.0)	0.008*
Lesion location (≥1)					
ACA	22 (39.3)	10 (37.0)	32 (38.6)	35 (28.9)	0.173
ACA/MCA	26 (46.4)	10 (37.0)	36 (43.4)	33 (27.3)	0.024
MCA lesions	32 (57.1)	13 (48.1)	45 (54.2)	52 (43.0)	0.119
MCA/PCA	4 (7.1)	2 (7.4)	6 (7.2)	8 (6.6)	1.000
PCA	22 (39.3)	11 (40.7)	33 (39.8)	38 (31.4)	0.234
VA/BA	34 (60.7)	10 (37.0)	44 (53.0)	44 (36.4)	0.022
Total lesion volume, mm^3	335 (70–898)	250 (70–1,070)	290 (70–930)	140 (35–480)	0.008*
Volume/number, mm^3	68.0 (41.1–114.3)	80.0 (55.0–125.0)	70.0 (45.0–115.0)	57.5 (24.5–93.0)	0.037*
Time of post-procedural DW-MRI, days	5 (4–7)	5 (5–7)	5 (4–7)	5 (4–7)	0.750*

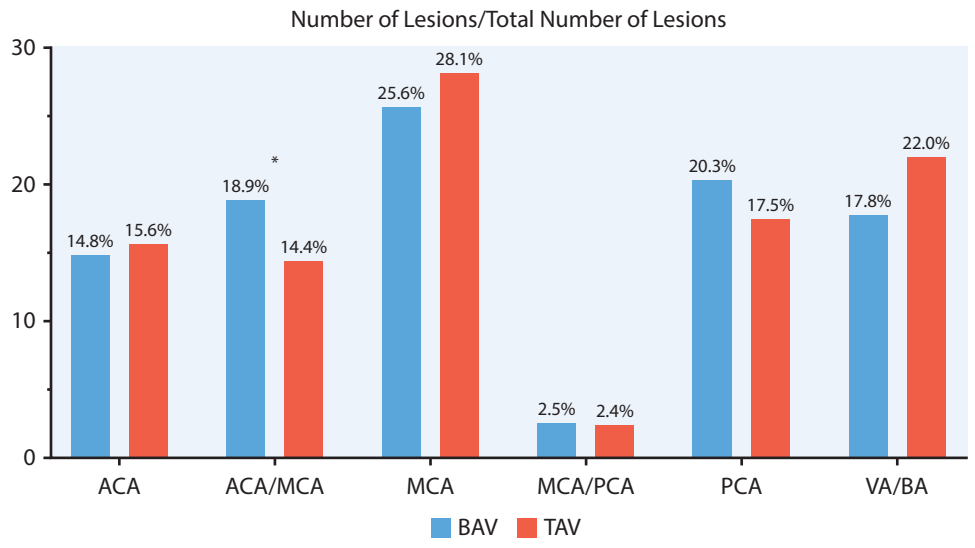
Values are n (%), median (interquartile range), or n. *Mann-Whitney *U* test.

ACA = anterior cerebral artery; BA = basilar artery; DW-MRI = diffusion-weighted magnetic resonance imaging; MCA = middle cerebral artery; PCA = posterior cerebral artery; TAVR = transcatheter aortic valve replacement; VA = vertebral artery; other abbreviations as in Table 1.

Rankin Scale score. Peri-procedural and follow-up clinical outcomes are listed in Supplemental Table 1.

DW-MRI DATA. DW-MRI was performed several days after TAVR in both the BAV and TAV groups. There was no difference between the 2 groups in the number of days after TAVR that the DW-MRI was performed. The incidence of new ischemic cerebral lesions in BAV patients after TAVR was not different from those in TAV patients (84.3% vs. 76.0%; p = 0.163). However, the number of lesions was higher in the BAV group (4.0 [IQR: 1.0 to 8.0] vs. 2.0 [IQR: 1.0 to 5.0]; p = 0.008) and the proportion of patients with lesion size >1 cm^3 was higher in BAV patients (28.6% vs. 10.9%; p = 0.005) (**Table 2**). Moreover, the proportions of patients with new cerebral lesions were higher in BAV patients in the ACA/MCA zone (43.4% vs. 27.3%; p = 0.024) and in the VA/BA zone (53.0% vs. 36.4%; p = 0.022) (**Table 2**). The total volume of new lesions (290 mm^3 [IQR: 70 to 930 mm^3] vs. 140 mm^3 [IQR: 35 to 480 mm^3]; p = 0.008) and volume per lesion (70.0 mm^3 [IQR: 45.0 to 115.0 mm^3] vs. 57.5 mm^3 [IQR: 24.5 to 93.0 mm^3]; p = 0.037) were significantly bigger in the BAV group when compared with the TAV group (**Central Illustration**). The cerebral ischemic lesions in the patients with a self-expanding valve were similar to results in all patients (Supplemental Table 2). The distribution of the number of lesions in ACA, ACA/MCA, MCA, MCA/PCA, PCA, and VA/BA zones were comparable in BAV and TAV patients without statistical significance (**Figure 2**, Supplemental Table 3). BAV (p < 0.001), self-expanding prosthetic valve

FIGURE 2 **The Location Distribution of the New Cerebral Ischemic Lesions in BAV and TAV Patients After TAVR**



The distribution depicted as the ratio of new ischemic lesion number to total lesion number in each vascular territory and vascular border zones (watershed zones). ACA = anterior cerebral artery; ACA/MCA = vascular border zones (watershed zones) between anterior cerebral artery and middle cerebral artery; BA = basilar artery; BAV = bicuspid aortic valve; MCA = middle cerebral artery; MCA/PCA = vascular border zones (watershed zones) between middle cerebral artery and posterior cerebral artery; PCA = posterior cerebral artery; TAV = tricuspid aortic valve; TAVR = transcatheter aortic valve replacement; VA = vertebral artery; VA/BA = vascular border zones (watershed zones) between vertebral artery and basilar artery.

($p = 0.002$), age ($p < 0.001$), sex ($p = 0.015$), left ventricular ejection fraction ($p < 0.001$), carotid stenosis ($p = 0.018$), aortic arch calcium ($p = 0.018$), post-dilatation ($p < 0.001$), and procedure duration ($p < 0.001$) were independent predictors of new ischemic lesion occurrence in the multivariable Poisson regression model in all patients (**Table 3**). Meanwhile, BAV ($p < 0.001$), age ($p < 0.001$), left ventricular ejection fraction ($p < 0.001$), post-dilatation ($p = 0.029$), and procedure duration ($p < 0.001$) were still independent associated with number of lesions in self-expanding valve patients using the multivariate Poisson regression modeling (Supplemental Table 4).

DISCUSSION

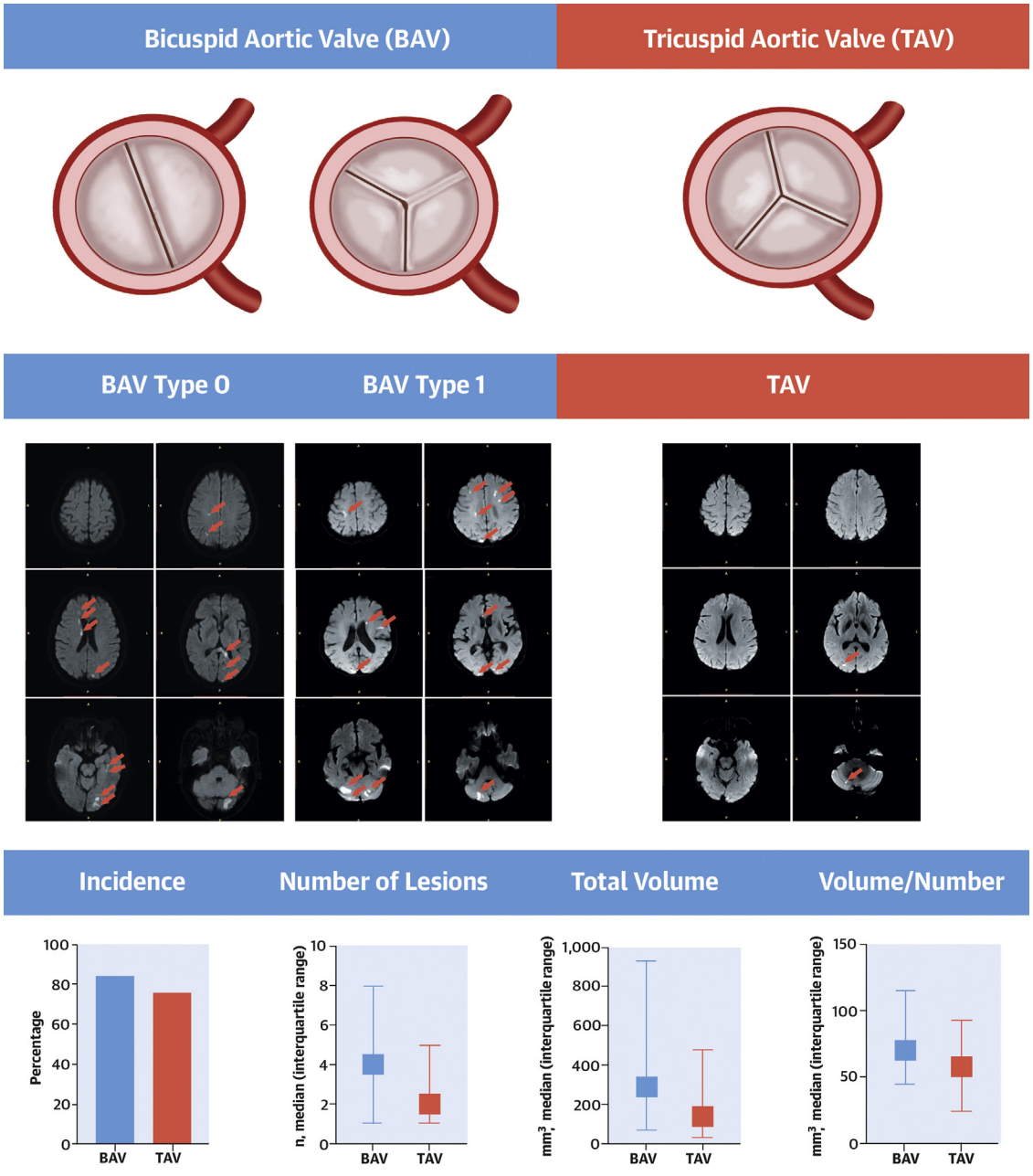
The main findings of the present study are that BAV patients may experience a higher number of cerebral ischemic lesions. Moreover, the BAV patients are also associated with larger size of new lesions after TAVR, accompanied with frequent deployment of self-expandable devices, longer procedure duration, and more frequent post-dilatation.

The BAV is often heavily calcified and accompanied with raphe (fusion between adjacent cups) and concomitant aortopathy (dilatation of the ascending aorta), which may require additional surgical treatment of the aorta. As TAVR in BAV patients presents both anatomical and clinical challenges, BAV patients were usually excluded from many major randomized TAVR clinical trials (1-6). Until now, only a few studies have reported the safety and efficacy of TAVR in BAV patients (11-14). This study found that the overt stroke rate was 2.4% in BAV patients and 1.7% in TAV patients. Consistent with the present findings, Makkar et al. (10) also reported that younger and intermediate-to-low risk bicuspid AS patients undergoing TAVR had higher prevalence of stroke when compared with tricuspid AS patients, which was similar to our results.

In our study, the prevalence of type 0 reached 67% (n = 56 of 83) in BAV patients, which was similar to the previously study in Chinese population (9). However, BAV patients with raphe type (type 1) were found of higher prevalence in European and Western countries with a higher proportion of severe stenosis, mortality, and need for aortic valve surgery (27). In our study, no significant difference in the number, total volume, and volume per lesion of cerebral ischemic lesions was found after TAVR between type 0 and type 1 BAV groups.

PROCEDURAL MECHANISM OF CEREBRAL ISCHEMIC LESIONS. In the present study, TAVR in BAV patients was not only feasible, but also led to a longer

CENTRAL ILLUSTRATION **Brain Injury Detected by Diffusion-Weighted Magnetic Resonance Imaging Between Bicuspid Aortic Valve and Tricuspid Aortic Valve Patients After Transcatheter Aortic Valve Replacement**



Fan, J. et al. J Am Coll Cardiol. 2020;76(22):2579-90.

(Top) Schematic presentations of various bicuspid aortic valve (BAV) and tricuspid aortic valve (TAV) morphology. BAV included no raphe type (type 0) and raphe type (type 1). **(Middle)** Image obtained in 74-year-old type 0 BAV patient, 80-year-old type 1 BAV patient, and 74-year-old TAV patient showed ischemic lesions in different levels of diffusion-weighted magnetic resonance imaging **(red arrows)**. **(Bottom)** Incidence of ischemic lesions, number of ischemic lesions, total volume of ischemic lesions, and volume of per ischemic lesion in diffusion-weighted magnetic resonance imaging. Values are presented median (interquartile range).

TABLE 3 The Adjusted Association of the Relevant Variables With Number of Lesions in DW-MRI, Using Poisson Regression Model

	Univariate Poisson Regression		Multivariate Poisson Regression	
	β (SE)	p Value	β (SE)	p Value
Native valve type				
TAV	Ref	–	Ref	–
BAV	0.487 (0.067)	<0.001	0.497 (0.096)	<0.001
Prosthetic valve type				
Balloon and mechanically expandable valve	Ref	–	Ref	–
Self-expanding valve	0.082 (0.088)	0.354	-0.355 (0.113)	0.002
Age	0.022 (0.005)	<0.001	0.044 (0.007)	<0.001
Sex				
Female	Ref	–	Ref	–
Male	-0.193 (0.067)	0.004	-0.236 (0.097)	0.015
BMI	-0.027 (0.010)	0.010	-0.015 (0.012)	0.223
Hypertension				
No	Ref	–	Ref	–
Yes	-0.091 (0.067)	0.175	-0.045 (0.082)	0.581
Atrial fibrillation				
No	Ref	–	Ref	–
Yes	-0.341 (0.103)	0.001	-0.047 (0.166)	0.776
Prior stroke				
No	Ref	–	Ref	–
Yes	-0.197 (0.162)	0.222	0.082 (0.190)	0.667
Medication				
No antithrombosis	Ref	–	Ref	–
Antiplatelet	0.140 (0.072)	0.052	-0.009 (0.089)	0.924
Anticoagulation	0.015 (0.119)	0.900	-0.052 (0.208)	0.802
Mean gradient	0.004 (0.001)	<0.001	0.000 (0.001)	0.792
AR				
None to mild	Ref	–	Ref	–
Moderate to severe	-0.416 (0.077)	<0.001	-0.080 (0.109)	0.461
EF	0.011 (0.003)	<0.001	0.014 (0.003)	<0.001
Carotid stenosis				
<70%	Ref	–	Ref	–
≥70%	-1.252 (0.335)	<0.001	-0.910 (0.384)	0.018
Calcium score	0.111 (0.042)	0.009	-0.077 (0.059)	0.193
Aortic arch calcium				
None to mild	Ref	–	Ref	–
Moderate to severe	-0.378 (0.085)	<0.001	-0.910 (0.384)	0.018
Multiple pre-dilatation				
No	Ref	–	Ref	–
Yes	0.061 (0.078)	0.437	-0.023 (0.094)	0.803
Post-dilatation				
No	Ref	–	Ref	–
Yes	0.308 (0.069)		0.309 (0.087)	<0.001
Duration of procedure, min	0.010 (0.001)	<0.001	0.011 (0.001)	<0.001
Contrast, ml	0.004 (0.001)	<0.001	0.000 (0.001)	0.814

All variables in the table were included in the multiple Poisson regression model.
SE = standard error; other abbreviations as in Tables 1 and 2.

procedure duration, which may be related to higher post-dilation frequency in the BAV group. A previous study identified balloon valvuloplasty and actual valve positioning and deployment as the primary cause of cerebral embolization during TAVR procedure by transcranial doppler (28). Histopathological analysis of debris captured by a dual filter-based embolic protection device (Montage Dual Filter System, Claret Medical, Santa Rosa, California) in 81 TAVR patients revealed that these tissues originated from the native aortic valve leaflets, aortic wall, or left ventricular myocardium and were more frequent with the use of balloon-expandable systems and more oversizing (29). It is possible that essential

manipulations like crossing a calcified aortic valve and subsequent instrumentation within the aortic root including valve positioning and placement are equally responsible for dislodgment of material from the aortic valve and aorta (29). Therefore, it is reasonable that the procedural complexity in BAV patients with longer procedure duration and higher post-dilation frequency may add to the risk of cerebral injury by increasing the number of new ischemic lesions after TAVR in DW-MRI.

PREDICTIVE FACTORS OF CEREBRAL ISCHEMIC LESIONS. In the current study, we systemically analyzed the new ischemic lesions, and found that BAV patients had a higher proportion of larger lesions and a greater number of lesions, especially in the ACA/MCA and VA/BA zones. Patients with BAV are usually younger with larger lesion size as examined by DW-MRI. In contrast, older patients (TAV population) usually have a higher likelihood of cerebral atrophy, which may result in smaller size lesions. Though TAV patients had more prior stroke, this did not appear to have an effect on new cerebral ischemic lesions in DW-MRI and on neurological outcomes in the TAVR patients.

The previous studies showed that age, STS score, duration of procedure, fluoroscopy time, and prosthetic valve type were related to the ischemic lesions in DW-MRI (30). In our multivariate Poisson regression analysis, we identified that BAV, prosthetic valve type, age, left ventricular ejection fraction, post-dilatation, and procedure duration were independent factors influencing the number of new lesions. Procedural complexity due to complex BAV anatomy may necessitate post-dilatation in BAV patients. The higher proportion of post-dilatation with rapid pacing may increase the duration of procedure and the risk of hypoperfusion. Hemodynamic abnormalities were most frequently documented to increase the risk of infarct in the vascular border zones (watershed zones), especially the anterior watershed border zone between ACA and MCA (31,32). Moreover, heavy calcification could also increase the risk of small debris originating from the calcified native aortic valve, causing heavier damage in the younger BAV patients.

CEREBRAL ISCHEMIC LESIONS AND PROTECTION DEVICES IN TAVR. New cerebral ischemic lesions were found in 74% to 100% of patients after TAVR in DW-MRI (15–17). Though some studies showed that new ischemic lesions are not linked to apparent neurological symptoms, there is evidence that perioperative ischemia may increase the risk of cognitive function and long-term dementia (33,34).

In the randomized CLEAN-TAVI (CLaret Embolic Protection ANd TAVI) study, the number of DW-MRI cerebral ischemic lesions decreased after use of the cerebral protection devices in patients undergoing TAVR and significantly improved short-term neurological outcome (35). Moreover, the DEFLCT III (A randomized evaluation of the TriGuard™ HDH embolic deflection device during transcatheter aortic valve implantation) trial also demonstrated that TriGUARD Embolic Deflection Device (Keystone Heart, Tampa, Florida) during TAVR procedure could reduce ischemic brain volume, and subjects experienced fewer neurologic deficits (36). However, there is no commercial cerebral protective devices approved by the China Food and Drug Administration, which could avoid new cerebral ischemic lesions during TAVR procedure. In our study, the neurological function assessments using the modified Rankin Scale score were comparable between BAV and TAV patients even without the cerebral protective device.

CLINICAL IMPLICATIONS. The present study is the first to provide insights into the risk of brain injury in DW-MRI for the TAVR procedure in BAV patients. Further studies are necessary to show whether TAVR is suitable for BAV patients when considering brain injury complications. Cerebral embolic protection devices may be recommended for TAVR, especially in BAV patients, to avoid cerebral ischemic lesions that potentially deteriorate neurological and cognitive function.

STUDY LIMITATIONS. One limitation of the present study is that this is a single-center, nonrandomized study. There may be some bias by excluding possibly clinically worse-off patients unable to tolerate MRI; therefore, findings need to be confirmed by a larger randomized clinical trial. Even though the prevalence of patients with prior atrial fibrillation or new onset atrial fibrillation were similar between the 2 groups, cardiac thrombus associated with atrial fibrillation should not be excluded as a potential contributor to microthrombosis. Moreover, new generation devices could be used for TAVR in the clinical trial to see whether this result could be replicated. Inherent to the nature of this study in age and STS score, the results cannot extrapolate to younger, lower-risk patients, although the trends are likely to be similar and the need for protection devices is also recommended. The present study still requires long-term follow-up to complete the mortality, stroke, neurological, and cognitive function assessment.

CONCLUSIONS

A significantly higher frequency of larger new cerebral ischemic lesions after TAVR are found in BAV patients in the early phase after TAVR, which needs to be further confirmed by future studies.

AUTHOR DISCLOSURES

Dr. Leon has served as a nonpaid member of the scientific Advisory Board of Edwards Lifesciences; and has been a consultant to Abbott Vascular and Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Patients with stenotic BAVs undergoing TAVR may experience more severe brain injuries both in terms of the number of lesions and larger lesion size than those with TAV disease.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to compare the safety and efficacy of cerebral embolism protection devices in patients with BAV and TAV undergoing TAVR.

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KEY WORDS bicuspid aortic valve, brain injury, cerebral ischemic lesions, transcatheter aortic valve replacement

APPENDIX For expanded Methods and References sections and supplemental tables, please see the online version of this paper.