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Cerebral ischemic injury after transcatheter aortic valve replacement in patients with pure aortic regurgitation

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Considering the surgical risk stratification for patients with severe calcific aortic stenosis (AS), transcatheter aortic valve replacement (TAVR) is a reliable alternative to surgical aortic valve replacement (SAVR) (Fan et al., 2020, 2021; Lee et al., 2021). Despite the favorable clinical benefits of TAVR, stroke remains a dreaded perioperative complication (Auffret et al., 2016; Kapadia et al., 2016; Kleiman et al., 2016; Huded et al., 2019). Ischemic overt stroke, identified in 1.4% to 4.3% of patients in TAVR clinical practice, has been associated with prolonged disability and increased mortality (Auffret et al., 2016; Kapadia et al., 2016; Levi et al., 2022). The prevalence of hyperintensity cerebral ischemic lesions detected by diffusion-weighted magnetic resonance imaging (DW-MRI) was reported to be about 80%, which is associated with impaired neurocognitive function and vascular dementia (Vermeer et al., 2003; Barber et al., 2008; Kahlert et al., 2010).

SAVR is usually recommended for patients with severe pure aortic regurgitation (AR) who require surgery for other indications, with impaired left ventricular systolic function (≤50%) or left ventricular enlargement (Otto et al., 2021). However, a considerable proportion of pure AR patients cannot tolerate SAVR because of the heavy burden of clinical comorbidities. Likewise, prior studies reported that the performance of TAVR in AS patients is superior or non-inferior to that in pure AR patients (Testa et al., 2014; Shi et al., 2021). Pure AR has been considered as a relative contraindication for TAVR due to the increased risk of prosthetic valve dislodgement in the absence of aortic valve calcification (Seiffert et al., 2013; Sawaya et al., 2017). With the further accumulation of operator experience and the advancement of devices over the past few decades, the continuous "off-label" use of TAVR in pure AR patients has become the subject of intense research (Hira et al., 2017; Alharbi et al., 2020). JenaValve (JenaValve Technology, Inc., Irvine, CA, USA) and J-Valve (Suzhou Jiecheng Medical Technology Co., Ltd., Suzhou, China), which feature anchoring by grasping native leaflets, have been commercially approved for the treatment of non-calcified aortic valvular disease. However, the characteristics of cerebral ischemic lesions in pure AR patients remain unclear (Yoon et al., 2017; Stachon et al., 2020). Herein, we aimed to compare the differences in cerebral ischemic lesions between AS and pure AR, as well as explore the detailed characteristics of these lesions in pure AR patients.

A total of 352 patients who underwent TAVR participated in this study. Of these, 287 patients underwent TAVR for AS and 65 for pure AR. The baseline, echocardiographic, and multi-detector computed tomography (MDCT) data of patients are described in Table 1. More than half of the entire study population were male. Pure AR patients were younger (71 (64.5–75.0) years vs. 74.0 (69.0–79.0) years; P=0.002) and had lower Society of Thoracic Surgeons (STS) scores (2.39 (1.48–4.21) vs. 3.89 (2.33–6.39); P<0.001) compared with AS patients. AS patients had a higher prevalence of diabetes mellitus and chronic obstructive pulmonary

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Table 1 Baseline data of AS and pure AR patients

Characteristics	Global (*n*=352)	AS (*n*=287)	Pure AR (*n*=65)	*P* value
Baseline				
Age (years)	73.0 (68.0–78.0)	74.0 (69.0–79.0)	71.0 (64.5–75.0)	0.001
Male	203 (57.7%)	162 (56.4%)	41 (63.1%)	0.329
STS (%)	3.49 (2.11–5.93)	3.89 (2.33–6.39)	2.39 (1.48–4.21)	<0.001
NYHA III/IV	268 (76.1%)	225 (78.4%)	43 (66.2%)	0.037
Smoker	77 (21.9%)	60 (20.9%)	17 (26.2%)	0.355
Hypertension	200 (56.8%)	155 (54.0%)	45 (69.2%)	0.025
Diabetes	68 (19.3%)	65 (22.6%)	3 (4.6%)	0.001
Atrial fibrillation	57 (12.8%)	43 (15.0%)	14 (21.5%)	<0.001
Prior stroke	13 (3.7%)	9 (3.1%)	4 (6.2%)	0.423
COPD	71 (20.2%)	64 (22.3%)	7 (10.8%)	0.036
CKD 4/5	33 (9.4%)	27 (9.4%)	6 (9.2%)	0.965
PVD	25 (7.1%)	19 (6.6%)	6 (9.2%)	0.637
Echocardiography data				
EF (%)	60.0 (47.2–64.6)	60.2 (48.8–64.6)	56.9 (44.5–64.8)	0.186
LVEDD (cm)	4.92 (4.32–5.67)	4.69 (4.23–5.34)	5.95 (5.32–6.64)	<0.001
Max velocity (m/s)	4.56 (4.11–5.21)	4.74 (4.33–5.37)	1.97 (1.75–2.23)	<0.001
Mean gradient (mmHg)	48.0 (38.0–64.0)	52.0 (42.0–67.0)	8.0 (6.0–10.0)	<0.001
AVA (cm²)	0.65 (0.50–0.81)	0.62 (0.47–0.77)	2.03 (1.74–2.43)	<0.001
⩾Moderate MR	98 (27.8%)	73 (25.4%)	25 (38.5%)	0.034
⩾Moderate TR	45 (12.8%)	36 (12.5%)	9 (13.8%)	0.776
MDCT data				
Perimeter (mm)	77.5 (72.3–83.5)	76.5 (72.0–82.7)	82.2 (76.0–88.5)	<0.001
STJ diameter (mm)	31.5±4.7	30.6±4.0	35.5±5.6	<0.001
STJ height (mm)	21.8 (19.2–25.1)	21.3 (19.0–24.1)	25.2 (21.8–29.6)	<0.001
Ascent aortic diameter at 4 cm (mm)	37.7 (34.8–41.0)	37.5 (34.4–40.7)	38.3 (35.6–41.5)	0.081
LM height (mm)	14.3 (12.1–17.0)	14.3 (12.2–16.8)	14.3 (11.7–17.8)	0.877
RCA height (mm)	16.7 (14.7–18.8)	16.6 (14.5–18.6)	17.7 (15.5–21.2)	0.003
Aortic root angle (°)	51.0 (45.0–59.0)	51.0 (46.0–57.0)	56.0 (46.0–61.5)	0.011

Values are expressed as median (IQR), number (percentage), or mean±SD. AS: aortic stenosis; AR: aortic regurgitation; STS: Society of Thoracic Surgeons; NYHA: New York Heart Association; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; PVD: peripheral vascular disease; EF: ejection fraction; LVEDD: left ventricular end-diastolic diameter; AVA: aortic valve area; MR: mitral regurgitation; TR: tricuspid regurgitation; MDCT: multi-detector computed tomography; STJ: sinotubular junction; LM: left main artery; RCA: right coronary artery; SD: standard deviation; IQR: interquartile range; 1 mmHg=133.322 Pa.

disease, but a lower prevalence of hypertension and atrial fibrillation. New York Heart Association (NYHA) functional class III/IV was presented in 78.4% of AS patients and 66.2% of pure AR patients at admission.

In terms of echocardiography, the overall median left ventricle ejection fraction (LVEF) was 60.0%. Pure AR patients showed a more pronounced cardiac dilatation with larger left ventricle diastolic diameters (5.95 (5.32–6.64) cm vs. 4.69 (4.23–5.34) cm; P<0.001). Larger aortic valve area (2.03 (1.74–2.43) cm² vs. 0.62 (0.47–0.77) cm²; P<0.001) and moderate or severe mitral regurgitation (38.5% vs. 25.4%; P=0.034) were more frequently observed in these patients. The dimensions of Valsalva sinuses in pure AR patients were larger, which was manifested not only in the perimeter of annulus area but also in the perimeter of sinotubular junctions ((35.5±5.6) mm vs. (30.6±4.0) mm; P< 0.001). Likewise, aortic root dilatation was more significant in pure AR patients. There were no differences between the two groups in the left main coronary artery ostium height, but the right coronary artery ostium height was significantly higher (17.7 (15.5–21.2) mm vs. 16.6 (14.5–18.6) mm; P=0.003) in pure AR patients.

All patients were implanted with the self-expanding valves. Table 2 shows the periprocedural characteristics. Pre-dilatation (99.0% vs. 0%, P<0.001) and post-dilatation (69.7% vs. 13.8%, P<0.001) were applied more often in the AS group. Pure AR patients had longer

Table 2 Procedural characteristics and in-hospital clinical outcomes

Characteristics	Global (*n*=352)	AS (*n*=287)	Pure AR (*n*=65)	*P* value
Procedural characteristics				
Pre-dilatation	284 (80.7%)	284 (99.0%)	0	<0.001
Post-dilatation	209 (59.4%)	200 (69.7%)	9 (13.8%)	<0.001
Annular rupture	2 (0.6%)	1 (0.3%)	1 (1.5%)	0.336
Coronary obstruction	1 (0.3%)	1 (0.3%)	0	1.000
Aortic dissection	3 (0.9%)	3 (1.0%)	0	0.936
Second valve implantation	31 (8.8%)	25 (8.7%)	6 (9.2%)	0.894
Outcomes before discharge				
Post TAVR hospital stay (d)	5.0 (1.0–7.0)	3.0 (1.0–7.0)	8.0 (6.0–9.0)	<0.001
MACE	12 (3.4%)	10 (3.5%)	2 (3.1%)	1.000
Mortality	1 (0.3%)	1 (0.3%)	0	1.000
Stroke	11 (3.1%)	9 (3.1%)	2 (3.1%)	1.000
Disabling stroke	3 (0.9%)	3 (1.0%)	0	1.000
Non-disabling stroke	8 (2.3%)	6 (2.1%)	2 (3.1%)	0.983
MI	1 (0.3%)	1 (0.3%)	0	1.000
⩾Moderate PVL	18 (5.1%)	17 (5.9%)	1 (1.5%)	0.255
New-onset atrial fibrillation	20 (5.7%)	9 (3.1%)	11 (16.9%)	<0.001
Pacemaker implantation	10 (2.8%)	8 (2.8%)	2 (3.1%)	1.000
Severe PPM	16 (4.6%)	15 (5.3%)	1 (1.6%)	0.362
Medication				<0.001
Anticoagulation	80 (22.8%)	53 (18.5%)	27 (41.5%)	
Antiplatelet	280 (79.5%)	241 (84.0%)	39 (60.0%)	
No antithrombosis	5 (1.4%)	5 (1.7%)	0	

All data are presented as number (percentage) or median (IQR). AS: aortic stenosis; AR: aortic regurgitation; TAVR: transcatheter aortic valve replacement; MACE: major adverse cardiovascular event; MI: myocardial infarction; PVL: perivalvular leakage; PPM: patient-prosthesis mismatch; IQR: interquartile range.

hospital stay than AS patients (P<0.001). The incidence of peri-procedural complications did not differ significantly between the two groups. All patients survived except one who died of myocardial infarction before discharge. Symptomatic stroke occurred in 3.1% of patients before discharge. Three AS patients had disabling stroke, whereas non-disabling stroke occurred in six AS patients and two pure AR patients. The incidence of new-onset atrial fibrillation in the pure AR group was significantly higher than that in AS patients (16.9% vs. 3.1%, P<0.001), which may contribute to the higher proportion of anticoagulation regimens (41.5% vs. 18.5%, P<0.001).

DW-MRI was performed at a median of 3.0 d after TAVR. A total of 1981 new cerebral ischemic lesions were recognized on post-procedural DW-MRI in 298 patients (84.7%), with a median of 3.0 (interquartile range (IQR): 1.0–8.0) lesions per patient (Table 3). Most patients (87.2%), regardless of AS or pure AR, had multiple cerebral ischemic lesions, scattered in the bilateral cerebral hemispheres and cerebrovascular territories (Table 3, Fig. S1). About 86.0% of patients had a total cerebral ischemic lesion volume of <1000 mm^3. There was no significant difference in the rate (85.0% vs. 83.1%; P=0.695) or number (3.0 (1.0–8.0) vs. 3.0 (1.5–7.5); P=0.928) of ischemic lesions between the two groups (Table 3, Fig. S1). The number of lesions counted in any cerebral region was comparable between the two groups (Fig. 1). The median volume of ischemic lesion was 190.0 mm³ in the AS group and 130.0 mm³ in the pure AR group (P=0.585; Table 3, Fig. S1).

Concerning transfemoral (TF)- or transapical (TA)-TAVR, both the number of lesions per patient (3.0 (2.0–7.0) vs. 3.5 (1.0–8.3); P=0.923) and the total lesion volume per patient (120.0 (50.0–650.0) mm^3 vs. 135.0 (35.0–745.0) mm^3, P=0.837) were comparable (Table S1). There were no significant differences in the lesions counts in all cerebral regions except the middle cerebral artery (MCA) and the area between MCA

Table 3 DW-MRI findings for AS and pure AR patients

Characteristics	Global (*n*=352)	AS (*n*=287)	Pure AR (*n*=65)	*P* value
MRI after TAVR (d)	3.0 (1.0–5.0)	2.0 (1.0–4.0)	5.0 (4.0–6.0)	<0.001
Patients with new lesions	298 (84.7%)	244 (85.0%)	54 (83.1%)	0.695
Total new lesions	1981	1618	363	
New lesions per patients	3.0 (1.0–8.0)	3.0 (1.0–8.0)	3.0 (1.5–7.5)	0.928
Patients with a single lesion	38 (12.8%)	33 (13.5%)	5 (9.3%)	0.395
Patients with multiple lesions	260 (87.2%)	211 (86.5%)	49 (90.7%)	
Patients with bi-hemispheric lesions	196 (55.7%)	162 (56.4%)	34 (52.3%)	0.544
Lesion location				
ACA	99 (28.1%)	83 (28.9%)	16 (24.6%)	0.486
ACA/MCA	80 (22.7%)	63 (21.9%)	17 (26.2%)	0.465
MCA	190 (54.0%)	151 (52.6%)	39 (60.0%)	0.281
MCA/PCA	47 (13.4%)	37 (13.4%)	10 (15.4%)	0.594
PCA	171 (48.6%)	140 (48.8%)	31 (47.7%)	0.874
VA/BA	184 (52.3%)	153 (53.3%)	31 (47.7%)	0.413
Lesion volume (mm^3)	55.0 (26.7–88.3)	56.0 (30.0–87.8)	46.7 (15.0–91.3)	0.252
Maximal lesion volume per patient (mm^3)	90.0 (40.0–190.0)	90.0 (40.0–190.0)	70.0 (20.0–185.0)	0.320
Total lesion volume per patient (mm^3)	180.0 (60.0–587.5)	190.0 (60.0–570.0)	130.0 (40.0–715.0)	0.585
Patients with total lesion volume of ⩾1000 mm^3	50 (14.2%)	39 (13.6%)	11 (16.9%)	0.487

All data are presented as median (IQR), number (percentage), or number for skewed variables. DW-MRI: diffusion-weighted magnetic resonance imaging; TAVR: transcatheter aortic valve replacement; AS: aortic stenosis; AR: aortic regurgitation; ACA: anterior cerebral artery; MCA: middle cerebral artery; PCA: posterior cerebral artery; VA: vertebral artery; BA: basilar artery; IQR: interquartile range.

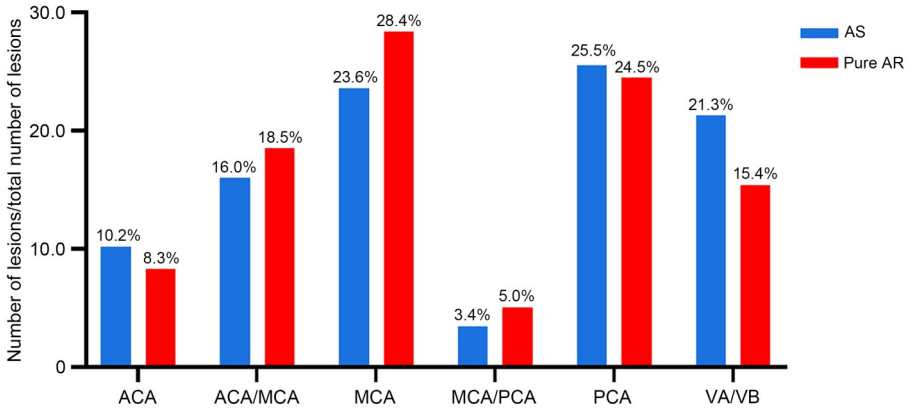

Fig. 1 Distribution of cerebral ischemic lesions in vascular areas in AS and pure AR patients after TAVR. The distribution of cerebral ischemic lesions in vascular areas is depicted as the ratio of number of lesions divided by the total number of lesions. AS: aortic stenosis; AR: aortic regurgitation; TAVR: transcatheter aortic valve replacement; ACA: anterior cerebral artery; MCA: middle cerebral artery; PCA: posterior cerebral artery; VA: vertebral artery; BA: basilar artery.

and posterior cerebral artery (MCA/PCA) regions; there were more numerous lesions in MCA region after TF-TAVR and more lesions in MCA/PCA region after TA-TAVR.

As listed in Table 4, Poisson regression analysis was used to explore baseline risk factors related to the number of ischemic lesions by DW-MRI in the pure AR group. The univariate variables (smoking history, diabetes, cancer, Stage 4 or 5 chronic kidney disease (CKD 4/5), moderate or greater tricuspid regurgitation, and calcification of left ventricular outflow tract (LVOT)) with a $P<0.10$ were subsequently entered into a multivariate Poisson regression model. Finally, the multivariable regression model confirmed that smoking history, CKD 4/5, and the calcification of LVOT were independent risk factors associated with the increased number of cerebral ischemic lesions in pure AR patients.

Table 4 Poisson regression analysis for the prediction of the number of post-procedural lesions in pure AR patients

Characteristics	Univariate Poisson regression		Multivariate Poisson regression	
	B (SE)	*P* value	*B* (SE)	*P* value
Age	0.014	0.315		
Male	−0.246	0.348		
STS	0.009	0.770		
Smoker	−0.687	0.011	−0.672	0.015
Hypertension	−0.088	0.776		
Diabetes	−0.692	0.088	−0.454	0.184
Atrial fibrillation	0.268	0.379		
Cancer	−0.866	<0.001	−0.388	0.108
CKD 4/5	−0.889	0.001	−0.751	0.020
PVD	−0.225	0.454		
Prior stroke	0.839	0.155		
Medication on admission				
Antiplatelet	−0.229	0.422		
Anticoagulation	0.412	0.211		
EF (%)	−0.002	0.873		
≥Moderate MR	0.126	0.633		
≥Moderate TR	0.820	0.015	0.402	0.164
Calcification of annulus	0.426	0.514		
Calcification of leaflets	0.428	0.230		
Calcification of LVOT	0.471	0.001	0.810	<0.001
Calcification of aorta	0.074	0.785		
Calcium score				
650 HU	0.000	0.124		
850 HU	0.000	0.422		
HU+100	0.000	0.940		

Univariate analysis was included in the multivariate Poisson regression analysis model. SE: standard error; AR: aortic regurgitation; STS: the Society of Thoracic Surgeons; CKD: chronic kidney disease; PVD: peripheral vascular disease; EF: ejection fraction; MR: mitral regurgitation; TR: tricuspid regurgitation; LVOT: left ventricular outflow tract; HU: Hounsfield units.

Our data showed a high prevalence (84.7%) of ischemic lesions. To the best of our knowledge, this is the first study to demonstrate that cerebral ischemic lesions are comparable between AS patients and pure AR patients after TAVR; the same was found regarding the comparison between TA- with TF-TAVR in the pure AR subgroup. Moreover, smoking history, CKD 4/5, and calcification of the LVOT were independently associated with the number of ischemic lesions in the pure AR population.

AR is prevalent with an estimated incidence of moderate and severe AR up to 0.5% (Maurer, 2006). However, a considerable number of high-risk patients are not referred to receiving SAVR due to multiple existing commodities (Iung et al., 2003). Considering the technical challenges of prothesis valve anchoring and sealing, pure AR has been regarded as one of the exclusion criteria in most well-designed trials of TAVR. Some studies have reported the early safety and feasibility of TAVR in pure AR (Roy et al., 2013; Yoon et al., 2017). Second-generation "on-label" devices, such as JenaValve and J-Valve, are equipped with anchoring elements specifically designed for non-calcific pure AR (Schäfer et al., 2017; Hensey et al., 2019). In our study, the incidence of major adverse cardiovascular event (MACE) was comparable between AS and pure AR populations, suggesting that pure AR patients could benefit greatly from TAVR. However, pure AR patients tended to have longer hospital stays, which may be due to the higher proportion of the TA approach. The newer-generation JenaValve and J-Valve systems via the TF approach have proved to be associated with favorable outcomes in patients with noncalcified aortic valve disease (Schäfer et al., 2017; Hensey et al., 2019).

Undoubtedly, the etiology of periprocedural stroke is linked to a combination of multiple factors and varies from the timing of stroke. Within the first 2 d after TAVR, as demonstrated by transcranial Doppler ultrasound during the TAVR period (Kahlert et al., 2012), catheter manipulation within the diseased native annulus and aortic arch disrupts both the endothelial covering and the underlying friable calcific material, causing subsequent cardiogenic embolization (Omran et al., 2003; Daneault et al., 2011). Between 2 d to the first month after TAVR, factors strongly predicting early neurological events are likely to be linked to chronic hypotensive episodes (Miller et al., 2012), such as patient comorbidities and clinical antibacterial drug application. Therefore, late stroke (more than 30 d after TAVR) seems to be dominantly related to patients' own characteristics rather than the TAVR procedure (Bosmans et al., 2015). Similarly, cerebral lesions were disseminated in bilateral cerebral hemispheres, suggesting that the essence of the lesions is cardioembolic. Embolized tissues were detached from the native aortic valve leaflets, aortic wall, left ventricular myocardium, and foreign material (van Mieghem et al., 2015; Kapadia et al., 2017).

Differences reported in the incidence of stroke between the AS and the pure AR groups after TAVR are inconclusive. The German nationwide aortic valve replacement clinical practice shows that the incidence of stroke in pure AR patients after TF-TAVR was lower than that in AS patients (1.47% vs. 2.53%) (Stachon et al., 2020). A large-scale study based on the United States Nationwide Readmissions Database presented that the occurrence of stroke after TAVR in the pure AR group was comparable with the pure AS (P=0.745) and AS+AR groups (P=0.621) (Isogai et al., 2021). Previous studies have confirmed that age and the volume of aortic valve calcification are predictors of cerebral embolism after TAVR (Fairbairn et al., 2012; Samim et al., 2015). Balloon dilatation has been found to significantly increase the possibility of detachment of calcified particles (Samim et al., 2015). However, in our study, the incidence of stroke did not appear to differ statistically between the AS and pure AR groups (3.1% vs. 3.1%; P=1.000), despite that AS patients were older, presented with more comorbidities, and had more severe aortic root calcification burden and more balloon pre- and post-dilatation. Consistent with pilot studies, the detection rate of cerebral ischemic foci on DW-MRI was 85.0% in the AS group and 83.1% in the pure AR group (Ghanem et al., 2010; Kahlert et al., 2010). Likewise, no statistical differences were shown in the total number, volume, or distribution of ischemic lesions on DW-MRI between AS and pure AR patients.

Yoon et al. (2017) revealed a relatively high prevalence of stroke for next-generation devices (39.2% vs. 12.6%; P<0.001). The authors hypothesized that this is probably due to the TA access and complex procedures applied. Similarly, Stachon et al. (2020) showed a higher stroke rate in TA- than in TF-TAVR (2.82% vs. 1.47%). However, these findings were refuted by multiple registries that revealed no significant difference in symptomatic stroke or asymptomatic stroke between the TF and TA approaches (Astarci et al., 2011; Huded et al., 2019; Guo et al., 2021). A well-conducted meta-analysis published by Wernly et al. (2019) summarized that symptomatic stroke occurred in 2.8% of patients with second-generation "on-label" devices and in 2.6% with other second-generation "off-label" devices.

TF-TAVR involves excessive interaction with the aorta wall and retrograde crossing of the calcified aortic valve, which might contribute to the occurrence of dislodged particles (Omran et al., 2003). However, TA-TAVR is more complicated and traumatic, which may involve a higher risk of air embolism due to the direct puncture of apex and could increase the risk of cerebral embolism (Yoon et al., 2017; Guo et al., 2021). The similar results of DW-MRI between the two approaches in pure AR also suggested the complexity of the mechanism of TAVR-related cerebral embolism (Kahlert et al., 2012; Athappan et al., 2014).

With regard to baseline predictors, smoking history, higher creatinine level, and aortic valve plaque at the threshold of 50 to 130 Hounsfield units (HU) have been identified as predictors of ischemic injury in AS patients (Kajio et al., 2019). However, independent predictors of ischemic stroke in pure AR patients have not been explored in previous studies. Our findings demonstrated that smoking history, CKD 4/5, and calcification of LVOT were effective predictors in pure AR patients. Smoking history and CKD 4/5, widely considered as cardiovascular risk factors and linked with an increased atherosclerotic burden, have been noted to be independent predictors of stroke after TAVR by prior investigators (Ambrose and Barua, 2004; Auffret et al.,

2016). The calcification of LVOT was identified by Pollari et al. (2020) to contribute to an increasing risk of peri-procedural stroke and mortality. It is remarkable that calcification of LVOT was determined as one of the predictors of cerebral lesion in the pure AR population in our analysis, even though calcification around the aortic valve was scarce. Considering the small sample size of pure AR patients in our study and the complexity of the TAVR procedure, larger-scale studies are needed to establish a more reliable risk prediction model for cerebral ischemic injury.

As widely known, new ischemic lesions detected on DW-MRI are related to cognitive decline and long-term dementia (Vermeer et al., 2003; Barber et al., 2008; Kahlert et al., 2010). Although this has been studied extensively, a knowledge gap exists with regard to the pathogenesis of cognitive decline after cerebral ischemic injury. The following points have been established in this regard: (1) Cognitive function is a high-level functional activity coordinated by cerebral multiple functional regions and the nervous system. The ischemia-hypoxia injury in the cerebral eloquent area may lead to cognitive decline. (2) Cerebral atrophy, probably caused by ischemia-related cortical neurodegeneration, especially in the cortical and subcortical areas, can exacerbate cognitive decline (Duering et al., 2012). (3) Cerebral ischemic injury may induce sustained inflammation, leading to secondary disorders of the internal environment and blood-brain barrier damage (Kliper et al., 2013). (4) There exists a complex interaction between cerebral ischemic injury and Alzheimer's disease (Hénon et al., 2001). New-onset cerebral ischemic injury may accelerate the progression of Alzheimer's disease and cerebral microvascular dysfunction. (5) Accumulating evidence shows that cognitive decline after stroke is an independent risk factor for vascular dementia (Hénon et al., 2001). In addition, there is proof that vascular abnormalities play a role in the development of dementia and cognitive dysfunction (Barber et al., 2008).

In our study, 85.0% of AS patients and 83.1% of the pure AR population had cerebral ischemic injury. Given that pure AR patients are usually younger than AS patients and the rate of cerebral ischemic lesions between two groups is similar, the risk of cerebral ischemic injury for pure AR patients undergoing TAVR cannot be ignored and attention must be paid to the safe peri-procedural management of these patients. Therefore, cerebral embolic protection devices might be recommended for pure AR patients scheduled for TAVR to reduce the incidence of stroke.

The main limitations of our single-center observational study have been elaborated as follows: first, we found many differences in the baseline characteristics between the AS and pure AR groups, yet we did not explore the predictors of stroke in the total study population; second, our findings should be interpreted with caution because the number of patients in the two groups was not balanced due to the selection of patients in clinical practice; third, prosthesis valve selection is based on operator discretion rather than randomization; finally, this study cannot determine the exact mechanism of cerebral ischemic lesions. Long-term follow-up research should be considered to further evaluate the impact of ischemic lesions on cognitive function.

Overall, cerebral ischemic lesions after TAVR were highly prevalent and no differences were found between pure AR patients and AS patients, which provides critical information for clinicians to help with patient management.

Materials and methods

Detailed methods are provided in the electronic supplementary materials of this paper.

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Author contributions

Xianbao LIU, Hanyi DAI, and Jiaqi FAN designed the study and edited the manuscript. Dao ZHOU and Gangjie ZHU performed the data analysis. Abuduwufuer YIDILISI and Jun CHEN reviewed and revised this manuscript. Yeming XU and Lihan WANG collected and checked the study data. Jian'an WANG contributed to the study design, reviewing and checking the manuscript. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Xianbao LIU, Hanyi DAI, Jiaqi FAN, Dao ZHOU, Gangjie ZHU, Abuduwufuer YIDILISI, Jun CHEN, Yeming XU, Lihan WANG, and Jian'an WANG declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. The ethical approval institution is the Second Affiliated Hospital of Zhejiang University School of Medicine (No. 2014-159). Informed consent was obtained from the patient for being included in the report.

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Supplementary information

Materials and methods; Fig. S1; Table S1