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Clinical Significance of Diffusion-Weighted Brain MRI Lesions After TAVR

Results of a Patient-Level Pooled Analysis

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ABSTRACT

BACKGROUND Acute brain infarction detected by diffusion-weighted magnetic resonance imaging (DW-MRI) is common after transcatheter aortic valve replacement (TAVR), but its clinical relevance is uncertain.

OBJECTIVES The authors investigated the relationship between DW-MRI total lesion number (TLN), individual lesion volume (ILV), and total lesion volume (TLV) and clinical stroke outcomes after TAVR.

METHODS Patient-level data were pooled from 4 prospective TAVR embolic protection studies, with consistent predischarge DW-MRI acquisition and core laboratory analysis. C-statistic was used to determine the best DW-MRI measure associated with clinical stroke.

RESULTS A total of 495 of 603 patients undergoing TAVR completed the predischarge DW-MRI. At 30 days, the rate of clinical ischemic stroke was 6.9%. Acute ischemic brain injury was seen in 85% of patients with 5.5 $\pm$ 7.3 discrete lesions per patient, mean ILV of 78.2 $\pm$ 257.1 mm^3, and mean TLV of 555 $\pm$ 1,039 mm^3. The C-statistic was 0.84 for TLV, 0.81 for number of lesions, and 0.82 for maximum ILV in predicting ischemic stroke. On the basis of the TLV cutpoint as defined by receiver operating characteristic (ROC), patients with a TLV >500 mm^3 (vs TLV ≤500 mm^3) had more ischemic stroke (18.2% vs 2.3%; $P < 0.0001$), more disabling strokes (8.8% vs 0.9%; $P < 0.0001$), and less complete stroke recovery (44% vs 62.5%; $P = 0.001$) at 30 days.

CONCLUSIONS Our study confirms that the number, size, and total volume of acute brain infarction defined by DW-MRI are each associated with clinical ischemic strokes, disabling strokes, and worse stroke recovery in patients undergoing TAVR and may have value as surrogate outcomes in stroke prevention trials. (A Prospective, Randomized Evaluation of the TriGuard™ HDH Embolic Deflection Device During TAVI [DEFLECT III]; NCT02070731) (A Study to Evaluate the Neuro-embolic Consequences of TAVR [NeuroTAVR]; NCT02073864) (The REFLECT Trial: Cerebral Protection to Reduce Cerebral Embolic Lesions After Transcatheter Aortic Valve Implantation [REFLECT I]; NCT02536196) (The REFLECT Trial: Cerebral Protection to Reduce Cerebral Embolic Lesions After Transcatheter Aortic Valve Implantation [REFLECT II]; NCT02536196) (J Am Coll Cardiol 2024;84:712–722) © 2024 by the American College of Cardiology Foundation.

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All cardiac procedures, including transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR), are associated with varying degrees of embolic stroke risk.[1] Although clinical stroke rates are lower with TAVR than with SAVR,[2] stroke remains a devastating and dreaded complication of TAVR, occurring in 2% to 8% of cases despite increasing operator experience, technological advances, and a lower-risk patient population.[3-5] Most strokes occur within 48 to 72 hours of TAVR as a result of embolic debris released during aortic valve instrumentation,[6] contributing to significant morbidity and a 4- to 6-fold increased mortality at 30 days[7] and at 1 year.[6,8]

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Beyond overt stroke, covert or "silent" ischemic brain injury is a concerning consequence of TAVR occurring in the vast majority (70%-100%) of patients.[9-11] Substantial work has been undertaken to better quantify and assess the mechanisms of stroke after TAVR and to evaluate the role of cerebral embolic protection (CEP) devices designed to reduce embolic injury. Definitions of stroke have evolved from the original 2011 Valve Academic Research Consortium (VARC) consensus of reporting major and minor stroke[12] to the more recent 2017 Neurologic Academic Research Consortium (NeuroARC), which focused specifically on standardizing ascertainment and reporting of neurologic outcomes of cardiac procedures, expanding recommended endpoints for neuroprotection studies to include covert brain injury defined by neuroimaging.[13] Covert injury is also now included in the updated VARC-3 endpoints,[14] and diffusion-weighted magnetic resonance imaging (DW-MRI) is specifically recommended in evaluating the benefit of CEP devices.

MRI is an attractive surrogate endpoint, given that it can accurately and reproducibly quantify the extent of preexisting (based on T2-FLAIR) and acute (based on DW imaging) brain tissue injury,[15] providing an objective, quantifiable, and more sensitive measure than clinical evaluation alone.[16] Unfortunately, the clinical relevance of DW-MRI outcomes have been inconclusive, both in terms of their correlation with clinical and neurocognitive outcomes[17-19] and as a means of demonstrating CEP device efficacy.[20] As a necessary step in the validation of DW-MRI lesions as a surrogate endpoint in clinical trials and as a predictor of stroke outcomes in clinical care, we investigated the clinical correlates of DW-MRI lesion characteristics (total lesion number [TLN], individual lesion volume [ILV], and total lesion volume [TLV]) on clinical stroke after TAVR in a pooled analysis of 4 prospective clinical studies.

METHODS

STUDY POPULATION. Patient-level data were pooled from 4 prospective TAVR embolic protection studies, including DEFLECT III,[21] NeuroTAVR,[22] REFLECT I,[23] and REFLECT II[24] (Supplemental Table 1). All studies included patients undergoing TAVR for severe symptomatic aortic stenosis with a protocol-mandated predischarge DW-MRI (4 ± 2 days after the procedure) and serial neurologic assessments using the same standard methods and core laboratories. The population for this analysis included patients with completed DW-MRI.

PROCEDURE AND EVALUATIONS. All enrolled patients received a commercially available valve and were recommended to receive standard dual antiplatelet therapy with aspirin and clopidogrel through 6 months. All patients underwent neurologic assessments performed by a trained neurologist at baseline, after the procedure (predischarge or 2-6 days after TAVR), and at 30 days. Neurologic assessments included the National Institutes of Health Stroke Scale (NIHSS)[25] and the modified Rankin Scale (mRS) for stroke disability.[26] All studies were conducted in compliance with the protocol, U.S. Food and Drug Administration regulations, ICH GCP guidelines, and the Declaration of Helsinki. The protocols of each study were approved by the applicable Institutional Review Board or ethics committees at each center, and all patients provided written informed consent before enrollment.

IMAGING METHODS. All DW-MRIs were acquired using a standard acquisition protocol and analyzed at a single core laboratory (Buffalo Neuroimaging Analysis Center) using standard methods and definitions and blinded to clinical outcomes. DW-MRI images were acquired using 1.5-Tesla systems 4 ± 2 days after TAVR and included a 2D echo planar sequence with 1 b = 0 image and 3 orthogonal diffusion directions with b = 1,000 s/mm^2. T2-FLAIR images were acquired with a 2D spin echo inversion recovery sequence. The b = 0 (b0) and 3 orthogonal diffusion-encoded raw images were combined to create trace and apparent diffusion coefficient (ADC) images. All within-subject DW-MRI scans were coregistered to T2-FLAIR images using the FMRIB (Functional Magnetic Resonance Imaging of the Brain) linear image

ABBREVIATIONS AND ACRONYMS

ADC = apparent diffusion coefficient

CEP = cerebral embolic protection

DW-MRI = diffusion-weighted magnetic resonance imaging

ILV = individual lesion volume

NIHSS = National Institutes of Health Stroke Scale

ROC = receiver operating characteristic

SAVR = surgical aortic valve replacement

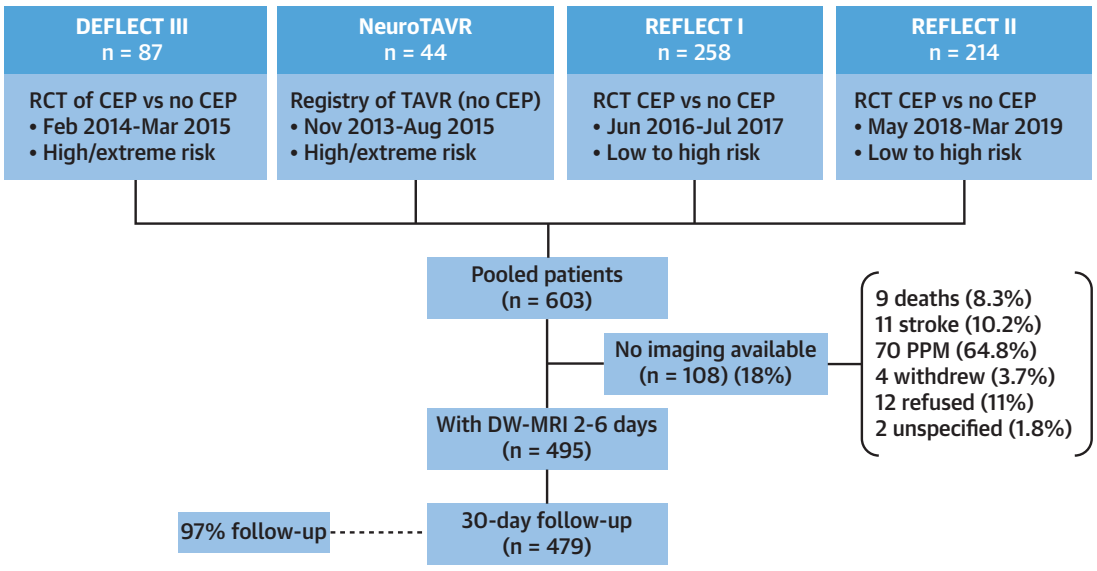
TAVR = transcatheter aortic valve replacement

TLN = total lesion number

TLV = total lesion volume

VARC = Valve Academic Research Consortium

FIGURE 1 Patient Flow and Follow-Up



CEP = cerebral embolic protection; DW-MRI = diffusion-weighted magnetic resonance imaging; PPM = permanent pacemaker; RCT = randomized controlled trial; TAVR = transcatheter aortic valve replacement.

registration tool with 6 degrees of freedom.[27] Corrected T2-FLAIR and DW-MRI trace images were standardized by applying a piecewise-linear histogram adjustment method to compensate for scan-to-scan variability in absolute intensity.[28] Lesions were delineated on corrected and aligned DW-MRI trace images and T2-FLAIR images using a semiautomated contouring technique provided by the Java Image Manipulation software package, with simultaneous reference to the ADC and T2-FLAIR images, as previously reported.[20,23,24,29] A trained operator identified each lesion individually and delineated the isocontour at the maximum local gradient using an automated algorithm. The operator viewed all images simultaneously to confirm hypointensity on ADC maps. T2-FLAIR lesions were restricted to those that were not simultaneously DW-MRI-positive to quantify a proxy for preprocedural lesion burden on postprocedural images. DW-MRI measures included the total number of lesions detected (TLN), individual lesion volume (ILV), and total lesion volume (TLV) assessed as the sum of the volumes of all detected lesions per subject. Our core laboratory inter-rater intraclass correlation of absolute agreement for lesion number was 97.4%, and for volume was 96.1% across 5 independent readers.

CLINICAL ENDPOINTS. The primary endpoints for this analysis were ischemic stroke, including ischemic stroke with hemorrhagic conversion, and disabling ischemic stroke at 30 days. All neurologic events were defined and adjudicated according to the NeuroARC recommendations.[13] Other safety outcomes including all-cause and cardiovascular mortality, myocardial infarction, acute kidney injury, and bleeding were defined according to the VARC-2 recommendations.[30] All events were adjudicated by the same independent clinical events committee (Yale Cardiovascular Research Group, New Haven, Connecticut, USA).

STATISTICAL ANALYSIS. Categorical variables are reported as frequency and percentage. Continuous variables are reported as mean ± SD, with median (Q1-Q3) where appropriate. Reported *P* values are from the Fisher exact test for categorical variables and from either Student's *t*-test or the Wilcoxon rank-sum test for continuous variables. We used logistic regression and ROC curves with the corresponding area under the curve as estimated by the C-statistic to determine the ability of DW-MRI measures, including TLN, mean ILV, maximum ILV, and TLV, to discriminate clinical stroke at 30 days. Optimal thresholds for predicting ischemic stroke or disabling stroke were identified using both Youden's J index[31] and the closest to (0,1) criteria.[32] We compared the characteristics of patients above and below a TLV threshold of 500 mm^3 based on the logistic regression ROC results. To assess the relationship between TLV and

ischemic stroke we report the predicted probability of ischemic stroke according to increasing TLV. To assess the relevance of individual lesion size to the risk of ischemic stroke, a single lesion volume threshold approach was used for individual lesions greater than each volumetric threshold from 0 to 1,000 mm^3 (in increments of 10 mm^3 up to 200 mm^3 and increments of 100 mm^3 thereafter), and TLVs were summed without including these subthreshold lesions. For example, a threshold of 100 mm^3 excludes all individual lesions ≤100 mm^3 from the calculation of TLV. The association between total suprathreshold lesion volume and stroke was assessed by logistic regression, and we report the OR, 95% CI, and logistic regression C-statistic for ischemic stroke vs suprathreshold TLV. Calibration was assessed using the Hosmer-Lemeshow test. In addition, we performed an adjusted logistic regression model limited to the 2 strongest confounders identified by univariate analysis because of the limited number of clinical strokes. The results were considered significant at $P < 0.05$. All analyses were conducted using SAS version 9.4 (SAS Institute).

RESULTS

PATIENT POPULATION. A total of 603 patients were pooled from the 4 studies, of whom 108 (18%) did not undergo DW-MRI imaging (Figure 1). Reasons for patients not undergoing DW-MRI included 9 deaths, 11 strokes, 70 permanent pacemakers, 12 refusals, 4 withdrawals, and 2 unspecified. A comparison of patients with and without DW-MRI is summarized in Supplemental Tables 2 and 3. The study population therefore included a total of 495 patients with completed DW-MRI imaging, of whom 479 (97%) had complete 30-day follow-up observation. Patients had a mean age of 81 ± 7 years and intermediate surgical risk with a mean Society of Thoracic Surgeons score of 5.2 ± 3.6 and EuroSCORE II of 4.8 ± 4.4; 30.8% had a history of atrial fibrillation, and 8.6% a prior stroke. General anesthesia was used in 48.9%, balloon aortic valvuloplasties in 44.6%, and a balloon-expandable valve in 62.7% (Table 1).

CLINICAL OUTCOMES. At 30 days, 33 (6.9%) patients had a stroke, 4 (0.8%) died, and 15 (3.1%) had a disabling stroke (Table 2). All strokes were ischemic, 45% (15 of 33) were disabling, 52% (17 of 33) were nondisabling (1 was unspecified), none were fatal, 79% (26 of 33) had some degree of recovery, and 48% (16 of 33) recovered completely. Acute brain infarction on DW-MRI was present in 85% of patients, including 100% of patients with stroke and 84% of patients without stroke ($P = 0.005$). The median (Q1-Q3) TLN per patient was 3.0 (1.0-7.0), the median (Q1-Q3) ILV was 35.9 mm^3 (18.8-68.8 mm^3), and the median (Q1-Q3) TLV per subject was 227 mm^3 (54-620 mm^3) (Table 3). Whereas all DW-MRI measures were significantly higher in patients with ischemic stroke, ILV were modestly higher, whereas the TLN was >3.5-fold higher and TLV was >7.5-fold higher than in patients without stroke (Table 3). The distribution of TLN, ILV, and TLV based on the presence or absence of ischemic stroke at 30 days is presented in Supplemental Figure 1, showing that stroke patients tend to have a greater TLN, ILV, and TLV.

DW-MRI MEASURES TO DISCRIMINATE STROKE. The C-statistic (95% CI) for ischemic stroke was 0.81 (95% CI: 0.74-0.89) for TLN (cutpoint 4-6 lesions), 0.78 (95% CI: 0.72-0.86) for average LV (cutpoint 67 mm^3), 0.82 (95% CI: 0.74-0.90) for the maximum ILV (cutpoint 216 mm^3), and 0.84 (95% CI: 0.77-0.91)

TABLE 1 Baseline Demographic and Procedural Characteristics for All Patients and Stratified by Total Lesion Volume

	Total (N = 495)	TLV >500 mm^3 (n = 144)	TLV ≤500 mm^3 (n = 351)	*P* Value
Age, y	80.6 ± 7.3	82.0 ± 6.4	80.1 ± 7.6	0.007
Male	55.8	54.2	56.4	0.69
Body mass index, kg/m^2	28.7 ± 6.5	27.6 ± 6.2	29.2 ± 6.5	0.014
Hypertension	87.4	91.0	86.0	0.14
Diabetes mellitus	35.2	34.0	35.7	0.76
Dyslipidemia	75.7	69.2	78.3	0.04
Peripheral vascular disease	12.6	14.9	11.7	0.37
Carotid artery disease	19.7	16.5	21.0	0.31
Chronic renal disease	20.2	18.9	20.7	0.71
COPD	41.9	16.9	52.2	0.18
Atrial fibrillation	30.8	29.4	31.4	0.75
Congestive heart failure	98.2	99.3	97.7	0.46
NYHA functional class III/IV	63.1	54.9	66.6	0.017
Prior PCI	28.8	27.0	29.6	0.58
Prior CABG	20.2	19.4	20.5	0.90
Previous stroke or TIA	13.3	12.1	13.8	0.66
Stroke	8.6	7.1	9.2	0.59
EuroSCORE II	4.8 ± 4.4	5.0 ± 5.4	4.7 ± 4.0	0.43
STS score	5.2 ± 3.6	5.6 ± 4.1	5.0 ± 3.4	0.08
General anesthesia	48.9	43.8	51.0	0.17
Procedure time, min	76.9 ± 40.0	86.6 ± 40.2	73.0 ± 39.3	0.0006
Total contrast, mL	118.6 ± 60.5	130.6 ± 63.4	113.6 ± 58.6	0.005
Femoral access	99.6	99.4	99.7	0.71
Balloon aortic valvuloplasty	44.6	49.3	42.6	0.19
Rapid pacing	94.8	90.7	96.5	0.013
Self-expanding TAVR	35.3	54.2	27.6	<.0001
Balloon-expandable TAVR	62.7	43.7	70.4	<.0001
TAVR not specified	2.0	2.1	2.0	>0.99

Values are mean ± SD or %. *P* values from the Fisher exact test for categorical variables and from Student's *t*-test for continuous variables.

CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement; TIA = transient ischemic attack; TLV = total lesion volume.

TABLE 2 Clinical Outcomes at 30 Days for All Patients and Stratified by Total Lesion Volume

	Total (N = 478)	TLV >500 mm³ (n = 137)	TLV ≤500 mm³ (n = 342)	*P* Value
Death or ischemic stroke	36 (7.5)	26 (19.0)	10 (2.9)	<0.0001
Stroke	33 (6.9)	25 (18.2)	8 (2.3)	<0.0001
Ischemic	33 (6.9)	25 (18.2)	8 (2.3)	<0.0001
Hemorrhagic	0 (0.0)	0 (0.0)	0 (0.0)	–
Fatal or disabling stroke	15 (3.1)	12 (8.8)	3 (0.9)	<0.0001
Fatal stroke	0 (0.0)	0 (0.0)	0 (0.0)	–
Disabling stroke	15 (3.1)	12 (8.8)	3 (0.9)	<0.0001
Nondisabling stroke	17 (3.6)	12 (8.8)	5 (1.5)	0.0003
Stroke recovery	26 (6.6)	19 (16.8)	7 (2.5)	<0.0001
Complete	16 (4.1)	11 (9.8)	5 (1.8)	0.0008
Incomplete	10 (2.5)	8 (7.1)	2 (0.7)	0.001
TIA	4 (0.8)	0 (0.0)	4 (1.2)	0.58
Stroke or TIA	37 (7.7)	25 (18.2)	12 (3.5)	<0.0001
Delirium	4 (1.0)	0 (0.0)	4 (1.4)	0.58
Death (all-cause)	4 (0.8)	2 (1.5)	2 (0.6)	0.32
Cardiovascular	4 (0.8)	2 (1.5)	2 (0.6)	0.32
Noncardiovascular	0 (0.0)	0 (0.0)	0 (0.0)	–
Myocardial infarction	8 (1.7)	3 (2.2)	5 (1.5)	0.69
Periprocedural	7 (1.5)	3 (2.2)	4 (1.2)	0.41
Spontaneous	1 (0.2)	0 (0.0)	1 (0.3)	>0.99
Any acute kidney injury	16 (3.4)	6 (4.4)	10 (2.9)	0.41
Stages 2/3	0 (0.0)	0 (0.0)	0 (0.0)	–
Any bleeding[a]	98 (20.2)	38 (27.1)	60 (17.4)	0.018
Life-threatening	15 (3.1)	7 (5.1)	8 (2.3)	0.14
Major	33 (8.4)	12 (10.6)	21 (7.5)	0.32
Minor	46 (9.6)	20 (14.5)	26 (7.6)	0.03
VARC 2 early safety	69 (14.3)	37 (26.6)	32 (9.3)	<0.0001

Values are n (%). [a]Bleeding defined according to VARC-2 criteria. *P* values from the Fisher exact test.
TIA = transient ischemic attack; TLV = total lesion volume; VARC = Valve Academic Research Consortium.

for TLV with cutpoints of 440 mm³ (Youden method) and 547 mm³ (distance to 0,1 method) (Figure 2, top). Calibration was acceptable for TLV and TLN as assessed by the Hosmer-Lemeshow test after adjustment ($P > 0.05$) but questionable for average ILV ($P = 0.001$) and maximum ILV ($P = 0.002$). After adjustment for potential confounders for ischemic stroke at 30 days, including age and self-expanding valve use, the C-statistic for discriminating ischemic stroke increased to 0.87 (95% CI: 0.81-0.93) for TLV. For disabling stroke, the C-statistic was 0.83 (95% CI: 0.72-0.94) for TLN (cutpoint 11 lesions), 0.83 (95% CI: 0.76-0.90) for average ILV (cutpoint 68 mm³ Youden and 83 mm³ distance to 0,1 method), 0.83 (95% CI: 0.75-0.93) for maximum ILV (cutpoint 222 mm³), and 0.86 (95% CI: 0.77-0.96) for TLV with cutpoints of 802 mm³ (distance to 0,1 method) and 1,156 mm³ (Youden method) (Figure 2, bottom). Calibration results were similar for disabling stroke.

Using the TLV cutpoint of 500 mm³ (midpoint between the 2 methods) determined by the logistic regression ROC curve for 30-day ischemic stroke, patients with TLV >500 mm³ were older ($P = 0.007$), had more NYHA functional class III/IV disease ($P = 0.017$) but similar surgical risk (Society of Thoracic Surgeons or EuroSCORE II), had longer procedural times ($P = 0.0006$) and more self-expanding valves ($P < 0.0001$) compared with patients with TLV ≤500 mm³ (Table 1). Patients with TLV >500 mm³ had more ischemic stroke in hospital (15.4% vs 2.3%; $P < 0.001$) and at 30 days (18.2% vs 2.3%; $P < 0.0001$), more disabling strokes at 30 days (8.8% vs 0.9%; $P < 0.0001$), and less complete stroke recovery at 30 days (44% vs 62.5%, $P < 0.0001$) (Table 2). The prevalence of TLV thresholds (<50 mm³, 50 to <100 mm³, 100 to <150 mm³, 150 to <250 mm³, 250 to <500 mm³, and >500 mm³) and associated stroke rates is presented in Figure 3. Patients with a TLV ≥500 mm³ constituted 29% of the population and had a 18.2% stroke rate, corresponding to 76% of all strokes and 80% of all disabling strokes (Table 2). The predicted probability of ischemic stroke increased in an S-shaped curve relationship with every increment in TLV, suggesting that although the risk of stroke is low at lower TLVs, any increment in ischemic brain injury is clinically relevant and that there is no TLV threshold below which there is no stroke risk (Figure 4).

Suprathreshold DW-MRI analysis. To evaluate whether there is a threshold below which individual lesions are clinically irrelevant and can be discounted, we assessed the prevalence and associated stroke rate of suprathreshold TLVs (TLV derived from all lesions above ILV thresholds of 50 mm³, 100 mm³, 150 mm³, 250 mm³, and 500 mm³) in the overall population (Supplemental Figure 2). The stroke rate remained constant across each suprathreshold TLV. There was no ILV threshold that statistically improved the prediction of ischemic stroke or its discriminatory ability based on the logistic regression of the C-statistic. The C-statistic continued to decrease and the discriminatory ability of TLV steadily worsened when any ILV threshold was excluded (Supplemental Figure 3). This suggests that excluding any ILV threshold will not improve the prediction of ischemic stroke and should therefore not be discounted.

DISCUSSION

This patient-level pooled analysis is the first extensive clinical validation of DW-MRI-defined brain injury as a potential surrogate for clinical stroke. It confirms that acute ischemic brain injury is common after TAVR, occurring in approximately 85% of patients even in the absence of clinically

apparent stroke.[9-11] This is the first study to establish that: 1) the number, size, and total volume of DW-MRI-defined acute brain infarction after TAVR are associated with clinical strokes and stroke disability; 2) based on the C-statistic, lesion number (thresholds 4-6), maximum individual lesion volume (threshold of 216 mm^3 by both methods), and total lesion volume (threshold of 440-550 mm^3) had excellent discrimination in identifying stroke; and 3) the risk of stroke was incremental with increases in TLV, and no individual lesion volume threshold could be identified that improved TLV discrimination of stroke risk; rather, exclusion of any individual lesion threshold tended to worsen discrimination (**Central Illustration**).

TAVR has had a profound impact on the treatment of patients with symptomatic severe aortic valve disease since its approval. Despite the widespread clinical adoption and the iterative improvements of TAVR over the past decade, stroke remains a devastating complication and—as confirmed in our study—strokes were common (6.9%), reflecting the systematic clinical and imaging surveillance used in these trials, and cerebral embolization occurs in the vast majority of patients (85%) including patients without acute stroke (84%). Although CEP remains a promising solution, the SENTINEL Cerebral Protection System (Boston Scientific) was approved based solely on its safety profile and evidence of debris capture in most patients.[20] The SENTINEL device has thus far failed to demonstrate benefit in preventing clinical stroke despite being evaluated in a 3,000-patient trial,[5] and the device did not significantly reduce DW-MRI infarct volume in its approval trial.[20] This has presented a major hurdle for next-generation CEP devices, particularly because demonstrating stroke reduction is exceedingly difficult because of the large sample size required. Imaging outcomes are an appealing alternative to clinical stroke in evaluating the efficacy of CEP devices, and our study adds to our understanding of DW-MRI endpoints as a surrogate outcome measure. Our study supports the use of TLV as a continuous or dichotomous surrogate measure of ischemic stroke in evaluating the treatment effect of neuroprotection therapies.

Whereas a substantial body of literature has investigated the predictive value of lesion volume for stroke outcomes in patients presenting with stroke,[33-35] few studies have reported the relationship between DW-MRI lesion size and risk of escalation from "covert" injury to overt clinical stroke.[36-38] Our pooled analysis provides the necessary clinical validity by establishing the prognostic role of DW-MRI imaging after TAVR in discriminating ischemic and disabling stroke. Although all DW-MRI measures were predictive, TLV had the highest C-statistic (0.84, which was modestly strengthened to 0.86 after adjustment for clinical confounders) to discriminate ischemic stroke. The plausibility of TLN, ILV, and TLV in predicting clinical outcomes is further supported by the excellent discrimination of disabling stroke (C-statistic >0.83-0.86). Defining the cutpoints with the highest sensitivity and specificity for TLV thresholds of 450 to 550 mm^3 for ischemic stroke and 800 to 1,100 mm^3 for disabling stroke provides practical measures that can be relevant in clinical practice as well as for future clinical trial designs. A clinically meaningful TLV threshold of ≥450 to 550 mm^3 represents a major embolic risk after TAVR that occurred in approximately 30% of patients in our study and accounted for 76% of all strokes and 80% of all disabling strokes. Although it is unreasonable to think that any surrogate can perfectly predict stroke, we show that dichotomizing TLV at a threshold ≥500 mm^3 is remarkably effective at identifying very low and very high risk of stroke such that CEP could use this threshold in a hierarchical analysis to look for a potential benefit.

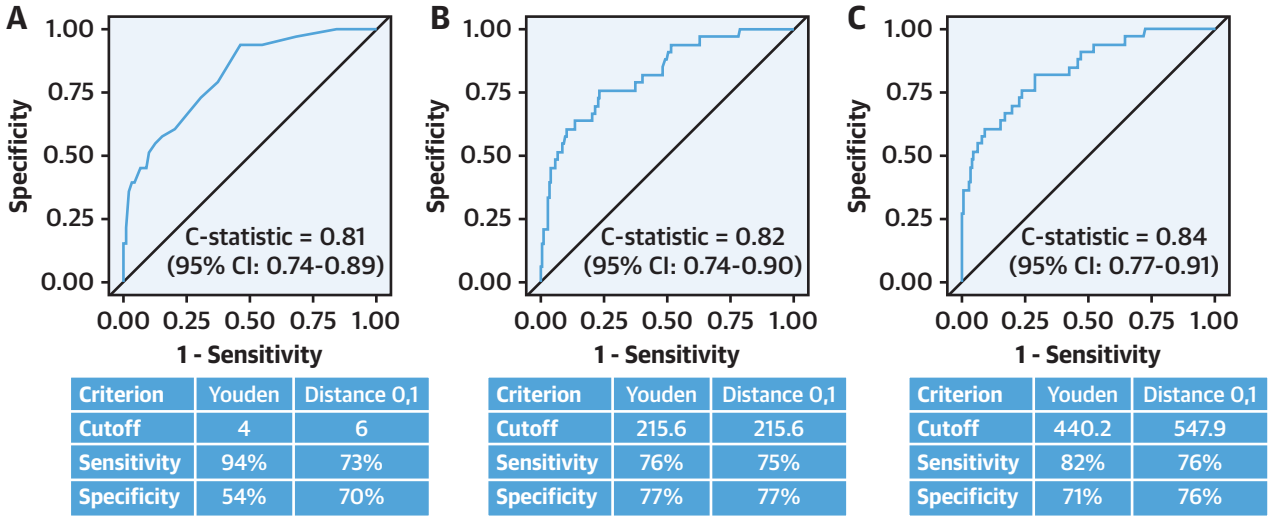
Our study also adds to our mechanistic understanding of stroke during TAVR, whereby larger showers of emboli (lesion counts were >3.5-fold higher in stroke patients) contributed more than

TABLE 3 DW-MRI Findings in Subjects With and Without Stroke at 30 Days

	Total (All MRI)	Ischemic Stroke Event	No Event	*P* Value
Any lesions	421/495 (85.1)	33/33 (100.0)	373/445 (83.8)	0.005
Total lesion number				
Median (Q1-Q3)	3.0 (1.0-7.0)	11.0 (5.0-21.0)	3.0 (1.0-7.0)	<0.0001
Mean ± SD (n)	5.5 ± 7.3 (495)	15.9 ± 14.4 (33)	4.7 ± 5.3 (445)	
(min, max)	(0.0, 63.0)	(1.0, 59.0)	(0.0, 38.0)	
Total lesion volume				
Median (Q1-Q3)	227 (54-620)	1,464 (548-3,725)	187 (45-504)	<0.0001
Mean ± SD (n)	555 ± 1,039 (495)	2,322 ± 2,294 (33)	415 ± 718 (445)	
(min, max)	(0, 10,042)	(59, 81,34)	(0, 10,042)	
Individual lesion volume				
Median (Q1-Q3)	35.9 (18.8-68.8)	52.8 (31.3-117.0)	44.9 (28.7-81.3)	0.002
Mean ± SD (n)	78.2 ± 257.1 (3,648)	146.0 ± 413.6 (525)	89.1 ± 262.5 (2,076)	
(min, max)	(3.1, 9,849.7)	(18.0, 6,894.9)	(18.6, 9,849.7)	
Average lesion volume (per patient)				
Median (Q1-Q3)	56.6 (33.9-88.6)	110.1 (74.3-172.3)	53.9 (31.4-82.7)	<0.0001
Mean ± SD (n)	82.2 ± 148.3 (495)	150.9 ± 159.3 (33)	77.3 ± 148.9 (445)	
(min, max)	(0.0, 2273.6)	(29.7, 936.9)	(0.0, 2273.6)	

P values from the Fisher exact test for categorical variables and from Student's *t*-test or Wilcoxon rank-sum test for continuous variables. Average lesion volume and individual lesion volume are patient- and lesion-level, respectively.

FIGURE 2 ROC Curves for DW-MRI Lesion Measures in Discriminating Stroke



Criterion	Youden	Distance 0,1
Cutoff	4	6
Sensitivity	94%	73%
Specificity	54%	70%

Criterion	Youden	Distance 0,1
Cutoff	215.6	215.6
Sensitivity	76%	75%
Specificity	77%	77%

Criterion	Youden	Distance 0,1
Cutoff	440.2	547.9
Sensitivity	82%	76%
Specificity	71%	76%

Criterion	Youden	Distance 0,1
Cutoff	11	11
Sensitivity	67%	67%
Specificity	88%	88%

Criterion	Youden	Distance 0,1
Cutoff	222.2	222.2
Sensitivity	80%	80%
Specificity	76%	76%

Criterion	Youden	Distance 0,1
Cutoff	1156	802.1
Sensitivity	73%	80%
Specificity	90%	83%

(Top) ROC curves and C-statistics of DW-MRI (A) lesion count, (B) individual lesion volume, and (C) total lesion volume in discriminating ischemic stroke. (Bottom) ROC curves and C-statistics of DW-MRI (D) lesion count, (E) individual lesion volume, and (F) total lesion volume in predicting disabling stroke. DW-MRI = diffusion-weighted magnetic resonance imaging; ROC = receiver operating characteristic.

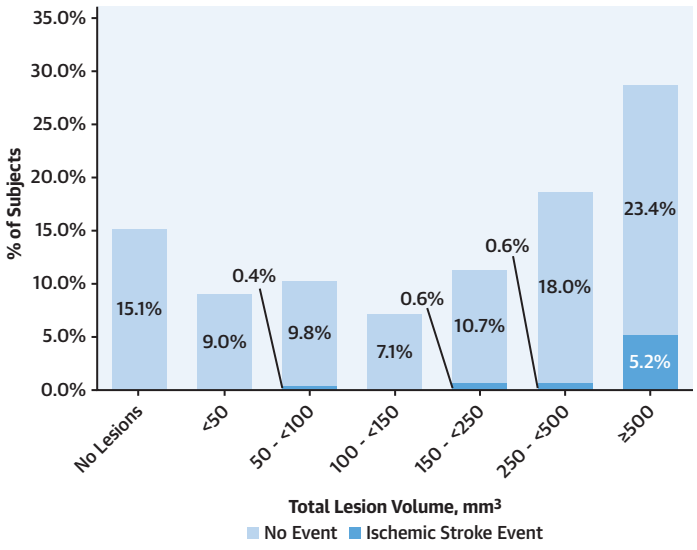
larger individual lesions to the overall >5.5-fold increase in TLV associated with stroke (Table 3). Although risk factors for identifying patients at high risk of embolic stroke after TAVR are challenging because of the low frequency of stroke events, our observation supports measures to limit the total number and ultimately the total volume of brain injury.

Another important aspect of our study is determining whether there is a threshold below which ILV or TLV is not clinically meaningful. This is of clinical relevance after cardiovascular procedures with or without CEP, inasmuch as any instrumentation across the aortic arch and into the left ventricle can result in embolization of small debris. In fact, imaging evaluations of a CEP device demonstrated a reduction in large individual brain lesions at the expense of a greater number of smaller lesions, and this remains a potential concern for any device that is positioned in the aortic arch.[23,24] Our analysis suggests that increasing TLV is associated with increasing stroke risk, and the exclusion of any individual lesion

threshold, no matter how small, worsened the discriminatory ability of TLV in identifying ischemic stroke. Our data support the argument by Goyal et al[39] that there is a strong a priori rationale to presume that any brain infarction should be avoided, given that even a very small lesion in a highly eloquent brain region can result in substantial clinical deficits.[40] This data also justifies using TLV as a continuous measure in stroke prevention trials.

It should be acknowledged that DW-MRI after TAVR can be difficult to implement in clinical trials. DW-MRI adds substantially to the cost of a trial and risks poor protocol adherence because patients may not tolerate the study after the procedure or may have pacer wires or pacemakers placed that would be a contraindication. Differences in acquisition and analysis methods can make it difficult to generalize results unless standardized acquisition and analysis methods are implemented. Our study represents the largest patient-level TAVR cohort that ties together imaging and clinical stroke examinations using the same methodology and acquisition-harmonization used to offset any differences across the studies. Recently, Indja et al[41] pointed out the need for standardizing DW-MRI endpoints after interventions as well as the lack of common reporting of ILV or even TLV. On the basis of our study results, a candidate set of endpoints should include TLN, maximum ILV, TLV, and at a minimum reporting a TLV threshold of >450 to 550 mm^3 and >1,000 mm^3. Reporting these outcomes would provide a clearer picture of iatrogenic harm from procedures and harm reduction from CEP devices.

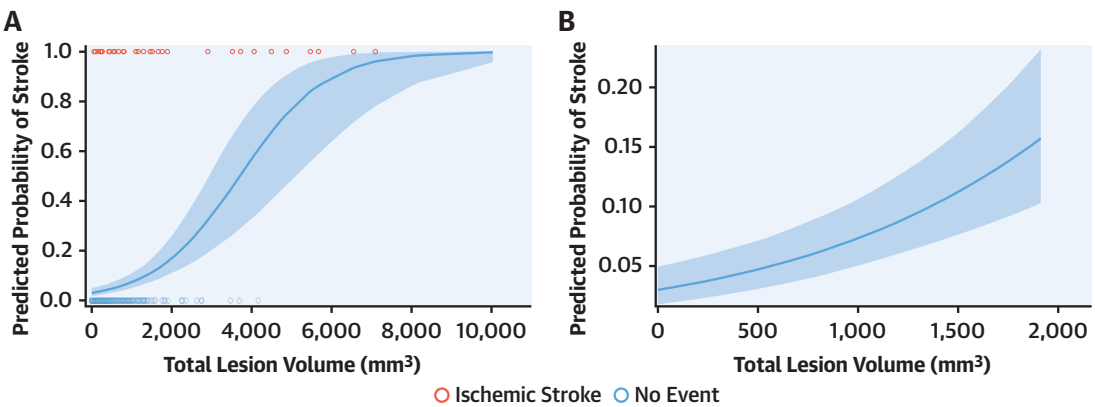
FIGURE 3 Frequency of TLV Ranges in the Population and Associated Absolute Stroke Rates by TLV Range



Frequency of TLV ranges and percent of patients with (dark blue) and without (light blue) ischemic stroke for each. TLV = total lesion volume.

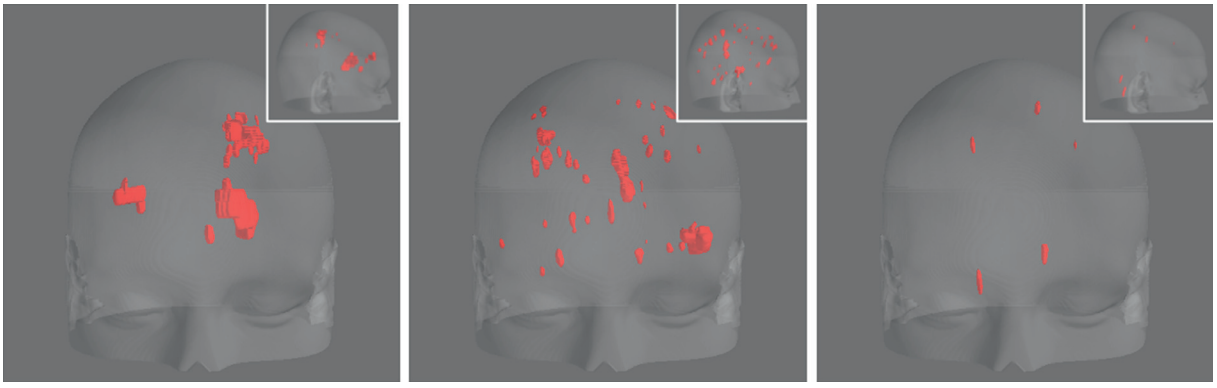
STUDY LIMITATIONS. The substantial DW-MRI dropout rate (18% in our study) will remain a major limitation of using this surrogate in clinical

FIGURE 4 Predicted Probability of Ischemic Stroke at 30 Days Based on Increasing TLV



(A) Distribution of TLV among those with (red) and without (blue) stroke are plotted on the horizontal axis above and below the chart. (B) Magnified view of lower range of TLV. The blue shaded area shows the 95% CI. TLV = total lesion volume.

CENTRAL ILLUSTRATION **DW-MRI and Stroke After Transcatheter Aortic Valve Replacement**



TLN: 11
TLV: 6,612.5 mm^3

TLN: 44
TLV: 5,525.0 mm^3

TLN: 5
TLV: 245.0 mm^3

	Stroke		Disabling Stroke	
	C-Statistic (95% CI)	Cutpoint	C-Statistic (95% CI)	Cutpoint
Total lesion volume, mm^2	0.84 (0.77-0.91)	440-548	0.86 (0.77-0.96)	802-1156
Total lesion number, N	0.81 (0.74-0.89)	4-6	0.83 (0.72-0.93)	11
Max individual lesion volume, mm^2	0.82 (0.74-0.90)	215	0.84 (0.75-0.93)	222

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Illustration of 3 patients with ischemic stroke from the pooled analysis and summary of DW-MRI measures and cutpoints to discriminate stroke and disabling stroke. The TLV and TLN of each patient predicted stroke. DW-MRI = diffusion-weighted magnetic resonance imaging; TLN = target lesion number; TLV = target lesion volume.

evaluation. The leading reasons for MRI dropout were the implantation of permanent pacemakers after TAVR, patient instability, and patient refusal. In our study, patients without DW-MRI had similar demographics but had substantially worse outcomes, including higher rates of cardiovascular death, acute kidney injury, and bleeding complications, although the rate of ischemic stroke was similar between the groups. It is likely that complete DW-MRI ascertainment would affect our results, but it is unlikely to invalidate our overall findings and conclusion. The similar rates of ischemic stroke between the DW-MRI dropouts and our study cohort reduce the likelihood that our conclusions would be different. Head CT may also be used to assess acute strokes in patients who do not tolerate MRI, although with reduced sensitivity.[42] In the future, use of portable bedside MRI systems will reduce dropout rates; however, validation will be needed because of the lower resolution of current systems. Another important limitation includes the lack of baseline MRI and the potential underestimation of MRI lesions that may be below the threshold of visibility on MRI, leading to possible brain injury underestimation.[43] Similarly, smaller lesions may be more affected by interpolation from coregistration, partial volume, and other methodological issues, leading to overestimation of brain injury.[44] We did not standardize the MRI manufacturer, for acquisition which may have introduced measurement variability, and we did not evaluate the impact of location on stroke outcomes in this analysis; this will be the focus of subsequent work. Although anatomical location clearly influences clinical symptoms, it is challenging to integrate both size and location in a reproducible and reportable methodology. Our aim in this study was to evaluate whether size alone was a clinically meaningful measure. Finally, detailed neurocognitive data were not available across all studies and are therefore not reported, and despite this being the largest report to

date, the number of strokes was still small, and the ability to adjust for additional potential confounders was limited.

CONCLUSIONS

This patient-level pooled analysis confirms that number, size, and total volume of acute brain infarction defined by DW-MRI are each associated with clinical ischemic strokes, disabling strokes, and worse recovery in patients undergoing TAVR. DW-MRI lesion number (4-6), maximum ILV (with a threshold of 216 mm^3), and TLV (with a threshold of 440-550 mm^3) had excellent discrimination in identifying ischemic and disabling stroke.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The number, size, and total volume of DW-MRI–defined acute brain infarction after TAVR are associated with clinical strokes and stroke disability.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: There is a strong rationale to presume that any brain infarction should be avoided.

TRANSLATIONAL OUTLOOK: There is a need for standardized DW-MRI endpoints after TAVR interventions; this will provide a clearer picture of iatrogenic harm from procedures and harm reduction from CEP devices.

REFERENCES

1. Gress DR. The problem with asymptomatic cerebral embolic complications in vascular procedures: what if they are not asymptomatic? *J Am Coll Cardiol*. 2012;60(17):1614–1616.

2. Siontis GCM, Overtchouk P, Cahill TJ, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. *Eur Heart J*. 2019;40(38):3143–3153.

3. Carroll JD, Mack MJ, Vemulapalli S, et al. STS-ACC TVT registry of transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2020;76(21):2492–2516.

4. Auffret V, Lefevre T, Van Belle E, et al. Temporal trends in transcatheter aortic valve replacement in France: FRANCE 2 to FRANCE TAVI. *J Am Coll Cardiol*. 2017;70(1):42–55.

5. Kapadia SR, Makkar R, Leon M, et al. Cerebral embolic protection during transcatheter aortic-valve replacement. *N Engl J Med*. 2022;387(14):1253–1263.

6. Kapadia S, Agarwal S, Miller DC, et al. Insights into timing, risk factors, and outcomes of stroke and transient ischemic attack after transcatheter aortic valve replacement in the PARTNER trial (placement of aortic transcatheter valves). *Circ Cardiovasc Interv*. 2016;9(9):e002981.

7. Huded CP, Tuzcu EM, Krishnaswamy A, et al. Association between transcatheter aortic valve replacement and early postprocedural stroke. *JAMA*. 2019;321(23):2306–2315.

8. Bjursten H, Norrving B, Ragnarsson S. Late stroke after transcatheter aortic valve replacement: a nationwide study. *Sci Rep*. 2021;11(1):9593.

9. Woldendorp K, Indja B, Bannon PG, Fanning JP, Plunkett BT, Grieve SM. Silent brain infarcts and early cognitive outcomes after transcatheter aortic valve implantation: a systematic review and meta-analysis. *Eur Heart J*. 2021;42(10):1004–1015.

10. Arnold M, Schulz-Heise S, Achenbach S, et al. Embolic cerebral insults after transapical aortic valve implantation detected by magnetic resonance imaging. *JACC Cardiovasc Interv*. 2010;3(11):1126–1132.

11. Kahlert P, Knipp SC, Schlamann M, et al. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. *Circulation*. 2010;121(7):870–878.

12. Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. *J Am Coll Cardiol*. 2011;57(3):253–269.

13. Lansky AJ, Messe SR, Brickman AM, et al. Proposed standardized neurological endpoints for cardiovascular clinical trials: an Academic Research Consortium initiative. *J Am Coll Cardiol*. 2017;69(6):679–691.

14. Généreux P, Piazza N, Alu MC, et al. Valve Academic Research Consortium 3: updated endpoint definitions for aortic valve clinical

research. *J Am Coll Cardiol*. 2021;77(21):2717-2746.

15. Sotak CH. The role of diffusion tensor imaging in the evaluation of ischemic brain injury: a review. *NMR Biomed*. 2002;15(7-8):561-569.

16. Lovblad KO, Pluschke W, Remonda L, et al. Diffusion-weighted MRI for monitoring neurovascular interventions. *Neuroradiology*. 2000;42(2):134-138.

17. Cosottini M, Michelassi MC, Puglioli M, et al. Silent cerebral ischemia detected with diffusion-weighted imaging in patients treated with protected and unprotected carotid artery stenting. *Stroke*. 2005;36(11):2389-2393.

18. Knipp SC, Matatko N, Wilhelm H, et al. Cognitive outcomes three years after coronary artery bypass surgery: relation to diffusion-weighted magnetic resonance imaging. *Ann Thorac Surg*. 2008;85(3):872-879.

19. Lazar RM, Pavol MA, Bormann T, et al. Neurocognition and cerebral lesion burden in high-risk patients before undergoing transcatheter aortic valve replacement: insights from the SENTINEL trial. *JACC Cardiovasc Interv*. 2018;11(4):384-392.

20. Kapadia SR, Kodali S, Makkar R, et al. Protection against cerebral embolism during transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2017;69(4):367-377.

21. Lansky AJ, Schofer J, Tchetche D, et al. A prospective randomized evaluation of the TriGuard™ HDH embolic DEFLECTion device during transcatheter aortic valve implantation: results from the DEFLECT III trial. *Eur Heart J*. 2015;36(31):2070-2078.

22. Lansky AJ, Brown D, Pena C, et al. Neurologic complications of unprotected transcatheter aortic valve implantation (from the Neuro-TAVI trial). *Am J Cardiol*. 2016;118(10):1519-1526.

23. Lansky AJ, Makkar R, Nazif T, et al. A randomized evaluation of the TriGuard™ HDH cerebral embolic protection device to Reduce the Impact of Cerebral Embolic LEsions after TransCatheter Aortic Valve ImplanTation: the REFLECT I trial. *Eur Heart J*. 2021;42(27):2670-2679.

24. Nazif TM, Moses J, Sharma R, et al. Randomized evaluation of TriGuard 3 cerebral embolic protection after transcatheter aortic valve replacement: REFLECT II. *JACC Cardiovasc Interv*. 2021;14(5):515-527.

25. Brott T, Adams HP Jr, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*. 1989;20(7):864-870.

26. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19(5):604-607.

27. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 2002;17(2):825-841.

28. Nyúl LG, Udupa JK, Zhang X. New variants of a method of MRI scale standardization. *IEEE Trans Med Imaging*. 2000;19(2):143-150.

29. Haussig S, Mangner N, Dwyer MG, et al. Effect of a cerebral protection device on brain lesions following transcatheter aortic valve implantation in patients with severe aortic stenosis: the CLEAN-TAVI randomized clinical trial. *JAMA*. 2016;316(6):592-601.

30. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *Eur Heart J*. 2012;33(19):2403-2418.

31. Youden WJ. Index for rating diagnostic tests. *Cancer*. 1950;3(1):32-35.

32. Pepe MS. *The Statistical Evaluation of Medical Tests for Classification and Prediction*. Oxford University Press; 2003.

33. Beaulieu C, de Crespigny A, Tong DC, Moseley ME, Albers GW, Marks MP. Longitudinal magnetic resonance imaging study of perfusion and diffusion in stroke: evolution of lesion volume and correlation with clinical outcome. *Ann Neurol*. 1999;46(4):568-578.

34. Schroder J, Cheng B, Ebinger M, et al. Validity of acute stroke lesion volume estimation by diffusion-weighted imaging: Alberta stroke program early computed tomographic score depends on lesion location in 496 patients with middle cerebral artery stroke. *Stroke*. 2014;45(12):3583-3588.

35. Yoo AJ, Barak ER, Copen WA, et al. Combining acute diffusion-weighted imaging and mean transmit time lesion volumes with National Institutes of Health stroke scale score improves the prediction of acute stroke outcome. *Stroke*. 2010;41(8):1728-1735.

36. Almekhlafi MA, Demchuk AM, Mishra S, et al. Malignant emboli on transcranial Doppler during carotid stenting predict postprocedure diffusion-weighted imaging lesions. *Stroke*. 2013;44(5):1317-1322.

37. Barber PA, Hach S, Tippett LJ, Ross L, Merry AF, Milsom P. Cerebral ischemic lesions on diffusion-weighted imaging are associated with neurocognitive decline after cardiac surgery. *Stroke*. 2008;39(5):1427-1433.

38. Messe SR, Acker MA, Kasner SE, et al. Stroke after aortic valve surgery: results from a prospective cohort. *Circulation*. 2014;129(22):2253-2261.

39. Goyal M, Ganesh A, Tymianski M, Hill MD, Ospel JM. Iatrogenic diffusion-weighted imaging lesions: what is their impact and how can it be measured? *Stroke*. 2021;52(5):1929-1936.

40. Axer H, Grassel D, Bramer D, et al. Time course of diffusion imaging in acute brainstem infarcts. *J Magn Reson Imaging*. 2007;26(4):905-912.

41. Indja B, Woldendorp K, Vallely MP, Grieve SM. Silent brain infarcts following cardiac procedures: a systematic review and meta-analysis. *J Am Heart Assoc*. 2019;8(9):e010920.

42. Mullins ME, Schaefer PW, Sorensen AG, et al. CT and conventional and diffusion-weighted MR imaging in acute stroke: study in 691 patients at presentation to the emergency department. *Radiology*. 2002;224(2):353-360.

43. Smith EE, Schneider JA, Wardlaw JM, Greenberg SM. Cerebral microinfarcts: the invisible lesions. *Lancet Neurol*. 2012;11(3):272-282.

44. van Veluw SJ, Zwanenburg JJ, Rozemuller AJ, Luijten PR, Spliet WG, Biessels GJ. The spectrum of MR detectable cortical microinfarcts: a classification study with 7-tesla postmortem MRI and histopathology. *J Cereb Blood Flow Metab*. 2015;35(4):676-683.

KEY WORDS cerebral embolic protection, covert brain ischemia, transcatheter aortic valve replacement

APPENDIX For supplemental figures and tables, please see the online version of this paper.