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Evolution, Predictors, and Neurocognitive Effects of Silent Cerebral Embolism During Transcatheter Aortic Valve Replacement

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ABSTRACT

OBJECTIVES The aim of this study was to assess the characteristics, predictors, evolution, and neurocognitive effects of silent cerebral ischemic lesions (SCILs).

BACKGROUND Most patients undergoing transcatheter aortic valve replacement (TAVR) develop SCILs detectable on magnetic resonance imaging (MRI). The natural history and clinical relevance of SCILs are not well established.

METHODS Cerebral MRI was performed within 7 days before TAVR to assess baseline status and age-related white matter change score. MRI was repeated post-operatively to assess the occurrence, location, number, and dimensions of SCILs. Patients developing SCILs underwent a third MRI examination at 3- to 5-month follow-up. A neurocognitive evaluation was performed before TAVR, at discharge, and at 3-month follow-up.

RESULTS Of the 117 patients enrolled, 96 underwent post-procedural MRI; SCILs were observed in 76% of patients, distributed in all vascular territories, with a median number of 2 lesions, a median diameter of 4.5 mm, and a median total volume of 140 mm^3. Independent predictors of SCIL occurrence were higher baseline age-related white matter change score and the use of self-expanding or mechanically expanded bioprostheses. Among 47 patients who underwent follow-up MRI, only 26.7% of post-procedural SCILs evolved into gliotic scar. SCIL occurrence was associated with a more pronounced transient neurocognitive decline early after TAVR and with lower recovery at follow-up.

CONCLUSIONS SCILs occur in the vast majority of patients undergoing TAVR and are predicted by more diffuse white matter damage at baseline and by the use of non-balloon-expandable prostheses. Although most SCILs disappear within months, their occurrence has a limited but significant impact on neurocognitive function.
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ABBREVIATIONS AND ACRONYMS

ARWMC = age-related white matter change

CI = confidence interval

DWI = diffusion-weighted magnetic resonance imaging

HR = hazard ratio

IQR = interquartile range

MMSE = Mini Mental State Examination

MoCA = Montreal Cognitive Assessment

MRI = magnetic resonance imaging

SCIL = silent cerebral ischemic lesion

TAVR = transcatheter aortic valve replacement

The rate of periprocedural stroke after transcatheter aortic valve replacement (TAVR) is about 3% to 4% in patients at intermediate or high surgical risk (1), decreasing to 0.5% in those at low surgical risk (2). However, in studies with accurate neurological evaluation, the 30-day stroke rate can be as high as 10% (3,4), and cerebral adverse event rates may reach 100% when including clinically silent cerebral ischemic lesions (SCILs) detected on diffusion-weighted magnetic resonance imaging (DWI) (5–7). The rate of new SCILs following TAVR is almost double that reported after aortic valve surgery (8). The predictors and temporal course of SCILs are disputed, with conflicting evidence regarding their reversibility.

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Although neurologically silent, SCILs can alter the neurocognitive profile of patients and are associated with a >2-fold risk for developing dementia (9). In addition, elderly subjects are at higher risk for progressive neurocognitive deterioration because of concomitant factors, such as previous cerebrovascular accidents, atrial fibrillation, and neurodegenerative diseases. The progressive extension of TAVR to younger patients reinforces the need for a careful evaluation of the impact of SCILs on neurocognitive function. Studies assessing the cognitive trajectory over a short period following TAVR reported preserved or improved cognition in the majority of patients (6,10,11), while studies extending follow-up to 1 or 2 years demonstrated cognitive decline in about 10% of patients (12,13).

Our aim was to prospectively determine the incidence, time course, and predictors of SCILs and their impact on neurocognition.

METHODS

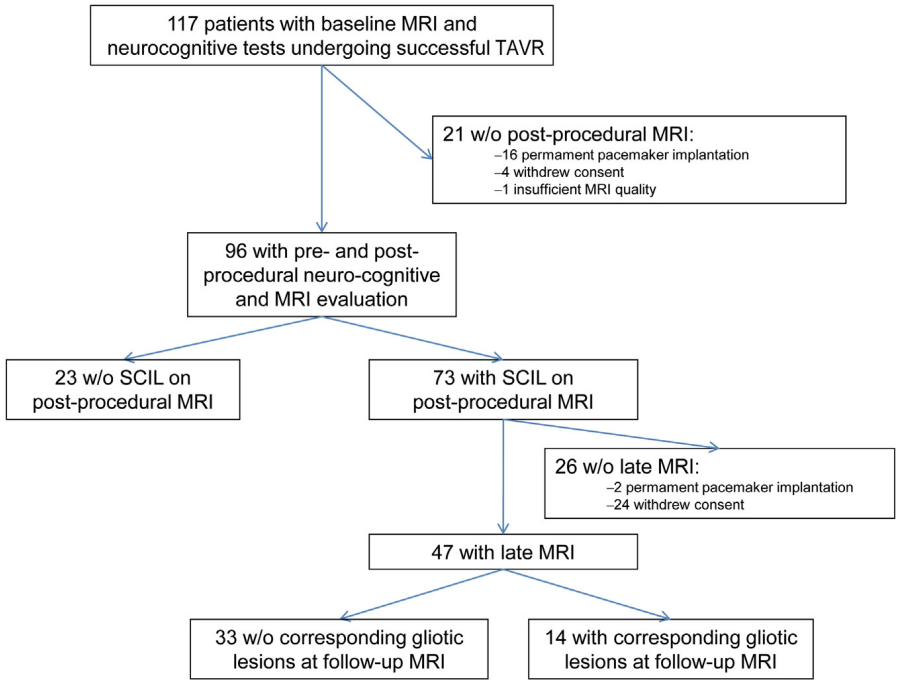
Patients with severe symptomatic aortic stenosis, either inoperable or at high or intermediate surgical risk by heart team evaluation and scheduled for TAVR at 5 Italian centers, were screened. Patients were enrolled after providing written informed consent to undergo serial magnetic resonance imaging (MRI) and neurocognitive examination. Patients with baseline severe neurological or neurocognitive impairment and those with contraindications to MRI were excluded. All baseline, procedural, and follow-up data were prospectively entered in a dedicated online database. The study protocol was approved by the ethics committee of each participating site.

NEUROLOGICAL EXAMINATION. All patients underwent evaluation by a neurologist unaware of the results of MRI scans within 2 weeks before TAVR, with assessment of focal neurological deficits through the National Institutes of Health Stroke Scale, degree of autonomy through the modified Rankin Scale, and cognitive status through the Montreal cognitive Assessment (MoCA) (14) and the Mini Mental State Examination (MMSE) (15). Patients with baseline severe neurological or neurocognitive impairment, defined by a National Institutes of Health Stroke Scale score ≥1, a modified Rankin Scale score ≥2, a MoCA score <15, or an MMSE score <15, were excluded. Patients with post-procedural stroke were excluded from further neurocognitive assessments. The neurological evaluation was repeated before discharge and at 3-month follow-up. Cognitive deterioration or improvement was defined as a change of ≥3 points in either MoCA or MMSE score between baseline and follow-up (13).

MRI. All MRI examinations were performed with 1.5-T systems according to a standard protocol that included 2-dimensional axial fluid-attenuated inversion recovery, DWI, and T2* sequences for the assessment of SCILs (16). All scans were read by 2 experienced neuroradiologists in a core laboratory, blinded to the clinical, procedural, and neurocognitive data of the patients. In case of discrepancy, a consensus reading was held. Pre-procedural MRI was performed 1 to 7 days before TAVR. The extent of white matter damage was assessed semiquantitively using the age-related white matter change (ARWMC) score, which grades changes from absent to severe on a 4-point scale (from 0 to 3) (17). If a pacemaker was not implanted post-operatively, MRI was performed before discharge (2 to 7 days after TAVR) to assess the presence of new SCILs, defined as new hyperintense lesions on DWI. Patients who developed new SCILs at post-procedural MRI repeated the examination at 3 to 5 months after discharge. New SCILs detected at post-procedural imaging were considered completely resolved if neither DWI nor fluid-attenuated inversion recovery lesions were detected at the same location at follow-up; they were considered as evolved into gliotic scar if a fluid-attenuated inversion recovery cerebral lesion was found at the same location of post-procedural DWI hyperintensity. Microhemorrhagic events were defined as punctate hypointense findings on T2*-weighted images.

The number and mean diameter of new SCILs were measured; lesions were classified as small (maximum diameter ≤3 mm), medium (maximum diameter 4 to

FIGURE 1 Study Flow



The study enrolled consecutive patients scheduled for transcatheter aortic valve replacement (TAVR) who underwent pre-procedural magnetic resonance imaging (MRI) and neurocognitive testing. Post-procedural MRI was performed to detect silent cerebral lesions (SCILs); patients with SCILs underwent follow-up MRI.

9 mm), or large (maximum diameter ≥10 mm) (18). For volume quantification, planimetry of each lesion was performed by manual contouring, and the lesion volume was calculated by multiplying the surface by the slice thickness and slice gap. Total SCIL volume was defined as the sum of all new SCIL volumes in post-procedural scans. We also assessed the percentage changes in the number, mean diameter, and volume of ischemic lesions between post-procedural and follow-up MRI.

COMPUTED TOMOGRAPHIC ANALYSIS. All patients underwent pre-procedural computed tomography of the heart, thoracoabdominal aorta, and iliofemoral arteries. Two physicians graded the calcification of the aortic valve, ascending aorta, and aortic arch as mild, moderate, or severe. A quantitative assessment of calcium volume in the aortic valve was performed using 3mensio software (3mensio Medical Imaging, Bilthoven, the Netherlands), defining calcium as 2 adjacent pixels with attenuation ≥130 Hounsfield units at 120 kVp (19).

TAVR PROCEDURE. Bioprostheses were implanted using standard technique. The transfemoral route was used preferentially; the trans-subclavian access route was the second choice (20). The use of embolic protection devices was not allowed. Adverse events were defined according to Valve Academic Research Consortium-2 definitions (21).

STATISTICAL ANALYSIS. Quantitative variables are presented as mean ± SD or as median (interquartile range [IQR]). We compared baseline and procedural characteristics between patients developing and those not developing SCILs. Differences were assessed using the chi-square test or Fisher exact test for categorical variables and Student's *t*-test or the Mann-Whitney *U* test for continuous variables. Change differences were assessed using a paired Wilcoxon signed rank test. Repeated-measures analysis of variance was performed to evaluate changes in neurocognition over time; pairwise differences were assessed using Duncan's multiple-comparison test. We used multivariate logistic regression models to investigate predictors of SCIL occurrence among baseline and procedural characteristics with p values of <0.10 at univariate analysis.

Sample size calculation was made with respect to the prevalence of SCILs, assuming a 2-tailed probability of type I error of 0.05. The design of the study being experimental, patient population size could

TABLE 1 Baseline Clinical Profile

	Overall Population (N = 96)	No SCILs (n = 23)	SCILs (n = 73)	p Value
Age, yrs	83 ± 5	82 ± 5	83 ± 5	0.97
Male	40 (41.7)	6 (26.1)	34 (46.6)	0.08
Diabetes	24 (25.0)	3 (13.0)	21 (28.8)	0.13
Coronary artery disease	37 (39.0)	5 (21.7)	32 (44.4)	0.05
Carotid artery disease	13 (13.5)	4 (17.4)	9 (12.3)	0.54
Previous stroke/TIA	5 (5.2)	0 (0.0)	6 (8.4)	0.35
Atrial fibrillation	24 (25.0)	7 (30.4)	17 (23.3)	0.49
Paroxysmal	11 (11.5)	3 (13.0)	8 (11.0)	0.78
Permanent	13 (13.5)	4 (17.4)	9 (12.3)	0.54
Chronic kidney disease	68 (70.8)	15 (65.2)	53 (72.6)	0.50
eGFR <30 ml/min	10 (10.4)	3 (13.0)	7 (9.6)	0.70
Left ventricular ejection fraction, %	52 ± 11	51 ± 10	52 ± 11	0.25
Antiplatelets	65 (67.7)	15 (65.2)	50 (68.5)	0.97
Anticoagulants	13 (13.5)	5 (21.7)	8 (11.0)	0.33

Values are mean ± SD or n (%).

eGFR = estimated glomerular filtration rate; SCIL = silent cerebral ischemic lesion; TIA = transient ischemic attack.

only be estimated. On the basis of published research, we hypothesized an 80% prevalence of SCILs, with an 80% rate of resolution at follow-up. To assess the time course of SCIL, we considered needing at least 15 patients with persisting lesions at follow-up. Forecasting a 15% attrition rate for follow-up MRI, we expected that by enrolling 115 patients, 98 would complete the study protocol, 78 would develop SCIL, and 16 would show permanent lesions at follow-up.

Statistical analysis was performed using NCSS 11 (NCSS, Chicago, Illinois). All tests were 2-sided with a 0.05 significance level.

TABLE 2 Baseline CT Angiographic, Cerebral MRI, and Neurocognitive Data

	Overall Population (N = 96)	No SCILs (n = 23)	SCILs (n = 73)	p Value
CT angiography				
Severe ascending aorta calcifications	17 (17.7)	3 (13.0)	14 (19.2)	0.74
Severe aortic arch calcifications	15 (15.6)	3 (13.0)	12 (16.4)	0.99
Severe aortic valvular calcification	20 (20.8)	3 (13.0)	17 (23.3)	0.39
Valvular calcium, Agatston units	3,273 ± 1,916	3,084 ± 1,798	3,325 ± 1,962	0.72
Valvular calcium volume, mm^3	2,510 ± 1,434	2,327 ± 1,277	2,560 ± 1,483	0.62
Cerebral MRI				
Previous ischemic injury	15 (15.6)	2 (8.7)	13 (17.8)	0.51
Previous microhemorrhagic lesion	15 (15.6)	1 (4.4)	14 (19.2)	0.11
ARWMC score	1.5 ± 1.0	1.1 ± 0.9	1.7 ± 1.0	0.01
Neurocognitive evaluation				
MMSE score	26.1 ± 3.4	25.7 ± 3.8	26.2 ± 3.3	0.59
MoCA score	24.6 ± 4.1	23.2 ± 4.5	25.0 ± 3.9	0.07

Values are n (%) or mean ± SD.

ARWMC = age-related white matter changes; CT = computed tomographic; MMSE = Mini Mental State Examination; MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; SCIL = silent cerebral ischemic lesion.

RESULTS

POPULATION. Between 2014 and 2017, 117 patients scheduled for TAVR were enrolled. Following TAVR, 16 patients required permanent pacemaker implantation, 4 withdrew their consent, and 1 had an inadequate-quality MRI study. The remaining 96 patients who fulfilled the study protocol with both baseline and post-procedural MRI formed the final study population (Figure 1). The baseline clinical profile of the overall population and of patients developing or not developing post-procedural SCIL is summarized in Table 1. The mean age was 83 ± 5 years; 5.2% of patients had previous strokes or transient ischemic attacks, and 25.0% had histories of atrial fibrillation.

BASELINE IMAGING. On pre-procedural computed tomography, 20.8% of patients showed severe aortic valve calcifications; average valvular calcium volume was 2,510 ± 1,434 mm^3 (Table 2). On pre-procedural MRI, 15.6% of showed signs of previous ischemic injuries, and 15.6% showed microhemorrhages. The ARWMC score was 1.5 ± 1.0, reflecting mild to moderate baseline white matter changes.

PROCEDURAL RESULTS. The transfemoral access was used in 81 patients (83.3%), while in 15 (16.7%) trans-subclavian access was used (Table 3). Self-expanding bioprostheses were used in 62 patients (64.6%): CoreValve Evolut R (44.8%) and CoreValve Evolut (15.6%) (Medtronic, Minneapolis, Minnesota) and ACURATE-neo (4.2%) (Symetis, Lausanne, Switzerland). The balloon-expandable SAPIEN 3 was used in 24 (25.0%) (Edwards Lifesciences, Irvine, California) and the mechanically expanded Lotus in 10 (10.4%) (Boston Scientific, Marlborough, Massachusetts). Pre-dilatation was performed in 72 patients (75.0%), while 6 bioprostheses (6.3%) were post-dilated. The rate of pre-dilatation was 95.8% for balloon-expandable prostheses and 68.1% for non-balloon-expandable prostheses ($p = 0.006$); the rate of post-dilatation was 7.0% versus 4.2%, respectively ($p = 0.83$). In 1 case, implantation of a second bioprosthesis was required because of severe paravalvular leak. Two patients (2.1%) had post-procedural strokes. Ten patients (10.4%) had vascular access-site complications, requiring surgical or endovascular repair in 2 cases. Ten patients

(10.4%) received transfusion of at least 1 unit of packed red blood cells, in 4 cases because of vascular complications. Five patients (5.2%) developed post-procedural atrial fibrillation.

POST-PROCEDURAL AND LATE MRI. Among 96 enrolled patients, 73 (76.0%) showed a total of 238 new SCILs at post-procedural MRI (SCIL group) (Figure 1). Median time from TAVR to post-procedural MRI was 7 days (IQR: 5 to 8 days). Because of MRI availability and procedural complications, 29 patients underwent post-procedural MRI 8 to 10 days following TAVR; their rate of SCIL development was similar to that of patients undergoing MRI within 7 days (79.3% vs. 74.6%; p = 0.62). Among patients with SCILs, the median number of lesions was 2 (IQR: 1 to 4), with a median diameter of 4.5 mm (IQR: 3.5 to 7.0 mm) per lesion and a median total volume of 140 mm^3 (IQR: 34 to 511 mm^3) (Table 4). A single ischemic lesion was evident in only 24 patients (32.9%); large lesions (diameter >9 mm) were observed in 24.7% of patients. Regarding anatomic distribution, supratentorial lesions were observed in 87.7% of patients with SCILs; 76.7% showed lesions in the cortical layer or at the cortical-subcortical junction, while deep-located lesions were observed in 39.7%, mainly within the coronae radiatae and thalami. Infratentorial lesions were observed in 48.0%, always within the cerebellum, while the brain stem was spared. Supplemental Table 1 summarizes the distribution of the 238 SCILs; 24.8% were located in the vertebrobasilar territory (Supplemental Figure 1). Median total lesion volume was numerically smaller in patients receiving balloon-expandable prostheses (49 mm^3 [IQR: 14 to 252 mm^3] vs. 179 mm^3 [IQR: 48 to 520 mm^3]; p = 0.06).

Among 73 patients with post-procedural SCILs, 47 underwent a third MRI examination a median of 3.7 months (IQR: 3.1 to 4.5 months) following TAVR. Among the 146 post-procedural SCILs, only 39 (26.7%) evolved into gliotic lesions at the same site, with 33 patients (70.2%) being free of lesions at the sites of all post-procedural SCILs. One patient showed a new ischemic lesion, not present post-procedure. The overall ischemic burden decreased significantly in terms of the absolute number of lesions per patient (−79%) (Figure 2), mean lesion diameter (−70%), and total lesion volume (−84%) (Table 4, Supplemental Figure 2).

PREDICTORS OF SCILs. Baseline demographic and clinical parameters were comparable between groups, but patients experiencing SCILs showed a trend toward a higher prevalence of male sex, diabetes, and coronary artery disease (Table 1). No significant differences were found regarding computed tomographic angiographic parameters, including qualitative and quantitative assessment of aortic valve calcification (Table 2). At baseline MRI, the SCIL group showed a higher ARWMC score (Central Illustration) and a trend toward a higher prevalence of micro-hemorrhagic injuries. At neurocognitive examination,

TABLE 3 Procedural Details

	Overall Population (N = 96)	No SCILs (n = 23)	SCILs (n = 73)	p Value
Vascular access				0.10
Femoral	81 (84.4)	22 (95.7)	59 (80.8)	
Subclavian	15 (15.6)	1 (4.3)	14 (19.2)	
Bioprosthesis type				0.001
CoreValve Evolut R	43 (44.8)	9 (39.1)	34 (46.6)	
CoreValve Evolut	15 (15.6)	2 (8.7)	13 (17.8)	
ACURATE-neo	4 (4.2)	0 (0.0)	4 (5.5)	
SAPIEN 3	24 (25.0)	12 (52.2)	12 (16.4)	
Lotus	10 (10.4)	0 (0.0)	10 (13.7)	
Bioprosthesis size range				0.30
≤23 mm	22 (22.9)	7 (30.4)	15 (20.6)	
24–28 mm	36 (37.5)	10 (43.5)	26 (35.6)	
≥29 mm	38 (39.6)	6 (26.1)	32 (43.8)	
Bioprosthesis size, mm	26.7 ± 2.6	25.9 ± 2.3	26.9 ± 2.7	0.09
Pre-dilatation	72 (75.0)	17 (73.9)	55 (75.3)	0.89
Post-dilatation	6 (6.3)	0 (0.0)	6 (8.3)	0.33

Values are n (%) or mean ± SD.
SCIL = silent cerebral ischemic lesion.

TABLE 4 Details of Post-Procedural and Late MRI of Patients Who Developed SCILs

Post-procedural MRI (n = 73)	
Number of lesions	2 (1–4)
Supratentorial lesions	64 (87.7)
Cortical-subcortical lesions	56 (76.7)
Deep lesions	29 (39.7)
Infratentorial lesions	35 (48.0)
Median SCIL diameter, mm	4.5 (3.5–7.0)
Lesions with diameter <3 mm	37 (50.7)
Lesions with diameter 4–9 mm	57 (78.1)
Lesions with diameter >9 mm	18 (24.7)
Median total SCIL volume, mm^3	140 (34–511)
Mean total SCIL volume, mm^3	487 ± 994
Late MRI (n = 47)	
Patients with gliotic evolution of postprocedural SCILs	14 (29.8)
Number of lesions	2 (1–4)
Reduction in the number of SCILs, %	79 ± 35
Median SCIL diameter, mm	3.5 (2.8–5.4)
Reduction in median SCIL diameter, %	70 ± 46
Lesions with diameter <3 mm	10 (21.3)
Lesions with diameter 4–9 mm	7 (14.9)
Lesions with diameter >9 mm	3 (6.4)
Median total SCIL volume, mm^3	171 (14–446)
Reduction in the volume of lesions, %	84 ± 35

Values are median (interquartile range), n (%), or mean ± SD.
Abbreviations as in Tables 1 and 2.

TABLE 5 Serial Neurocognitive Assessments

	Overall Population (N = 83)	No SCILs (n = 19)	p Value vs. Baseline	SCILs (n = 64)	p Value vs. Baseline
Baseline					
MMSE score	26.1 ± 0.4	25.8 ± 0.9		26.2 ± 0.4	
MoCA score	24.5 ± 0.5	23.1 ± 1.1		25.0 ± 0.5	
Discharge					
MMSE score	25.4 ± 0.4	25.2 ± 0.8	0.02	25.5 ± 0.4	0.003
MoCA score	24.2 ± 0.5	23.2 ± 1.0	>0.20	24.5 ± 0.5	0.02
Follow-up					
MMSE score	25.6 ± 0.4	25.6 ± 0.9	>0.20	25.6 ± 0.5	0.02
MoCA score	24.5 ± 0.5	23.4 ± 1.0	>0.20	24.8 ± 0.5	>0.20

Values are mean ± SE.
Abbreviations as in Tables 1 and 2.

patients with SCILs showed a trend toward a higher baseline MoCA score. Regarding procedural details, the use of non-balloon-expandable bioprostheses (**Central Illustration**) was strongly associated with the occurrence of SCILs, while a trend was observed with larger bioprosthesis diameter and subclavian access route.

At multivariate analysis, among all variables examined, the only independent predictors of post-procedural SCILs were a higher baseline ARWMC score (hazard ratio [HR]: 2.2; 95% confidence interval [CI]: 1.1 to 4.4; p = 0.023) and the use of non-balloon-expandable bioprostheses (HR: 5.2; 95% CI: 1.5 to 18.7; p = 0.011) (Supplemental Table 2).

An additional analysis was performed comparing patients without SCILs versus patients with healed SCILs versus patients developing gliotic scars (Supplemental Table 3). Diabetes (HR: 17.0; 95% CI: 2.2 to 133; p = 0.007), ARWMC score (HR: 2.6; 95% CI: 1.0 to 6.6; p = 0.049), and the use of non-balloon-expandable bioprostheses (HR: 17.6; 95% CI: 1.2 to 251; p = 0.03) were independent predictors of gliotic scar occurrence.

NEUROCOGNITIVE FUNCTION. Eighty-three patients had complete serial assessments, 64 with post-procedural SCILs and 19 without (**Table 5**). Before intervention, 6.0% of the patients showed impaired neurocognitive function on the basis of MMSE score and 28.9% on the basis of MoCA score; no significant differences were present between groups (Supplemental Table 4). Although on repeated-measures analysis of variance the changes in neurocognitive testing though time were not statistically different between groups both for MMSE score (p = 0.67) and MoCA score (p = 0.37), among patients with SCILs, the worsening of neurocognition over time was significant for MMSE score (p = 0.001) and borderline significant for MoCA (p = 0.05). Pairwise comparisons showed significant reductions in MMSE and MoCA scores at discharge in patients with SCILs (p = 0.003 and p = 0.02, respectively) and a reduction in MMSE score in patients without SCILs (p = 0.02) (**Figure 3**). The changes in MMSE and MoCA scores at discharge were inversely correlated with median SCIL volume (p = 0.03, r = −0.229, and p = 0.001, r = −0.334, respectively). At 3-month follow-up, only patients with SCILs still showed a persisting significant decrease in MMSE compared with baseline (p = 0.02) (**Figure 3**).

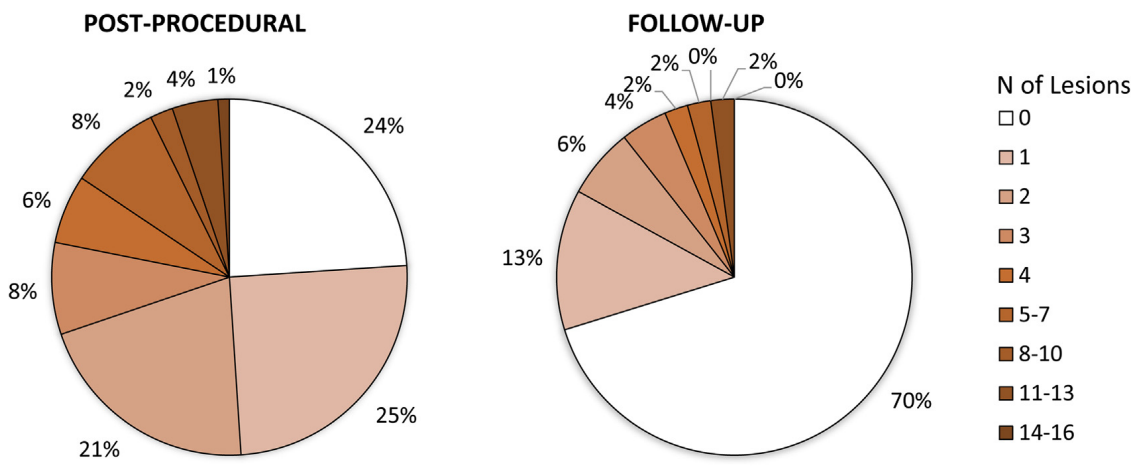
DISCUSSION

We enrolled the largest population of TAVR patients undergoing baseline and post-procedural cerebral MRI in an investigator-driven study and the largest population ever undergoing 3 MRI examinations to assess the natural history of SCILs. The main findings of our study are as follows: 1) post-procedural SCILs were observed in 76% of patients after a median of 7 days; 2) a higher degree of age-related white matter damage at baseline and the use of non-balloon-expandable bioprostheses were independent predictors of SCIL occurrence; 3) only 26.7% of SCILs evolve into gliotic scar at 3- to 5-month follow-up; and 4) the occurrence of SCILs is associated with a more pronounced decrease in MMSE score after TAVR and with lower recovery at 3-month follow-up.

STROKE FOLLOWING TAVR. The occurrence of stroke following TAVR is multifactorial (22), but embolization certainly plays a major role, prompting the investigation of cerebral embolic protection devices in randomized trials. However, the low rate of clinically evident stroke requires large study populations to demonstrate a significant reduction in stroke with embolic protection devices, thus explaining the failure of all randomized trials so far (3,4,6,7). Only recently, a propensity-matched comparison of 1,066 patients demonstrated for the first time a significant 65% reduction in periprocedural stroke with a dual-filter device (23). Because silent cerebral embolization is definitely more frequent than stroke, and given the lack of evidence regarding its natural history and clinical relevance, we chose to investigate SCILs by means of serial MRI and neurocognitive assessment.

SCILs: PREVALENCE AND PREDICTORS. The rate of post-procedural SCILs ranges from 60% (24) to 100% (11), with a median number of lesions ranging from 1

FIGURE 2 Distribution of the Number of Cerebral Lesions



The pie charts depict the proportion of patients showing a specific range of silent cerebral lesions (SCILs) at post-procedural magnetic resonance imaging **(left)** and of gliotic lesions at follow-up at the same site of a post-procedural SCIL **(right)**.

(24) to 10 (4). Such variability depends on a number of factors, including MRI equipment and acquisition protocols and the shrinking of SCIL volume during the first few days after TAVR (4). Our rate of 76% SCIL-positive patients, as well as the median SCIL number and volume, fall at the lower margin of previously reported rates, possibly because of the slightly longer median time between TAVR and post-procedural MRI.

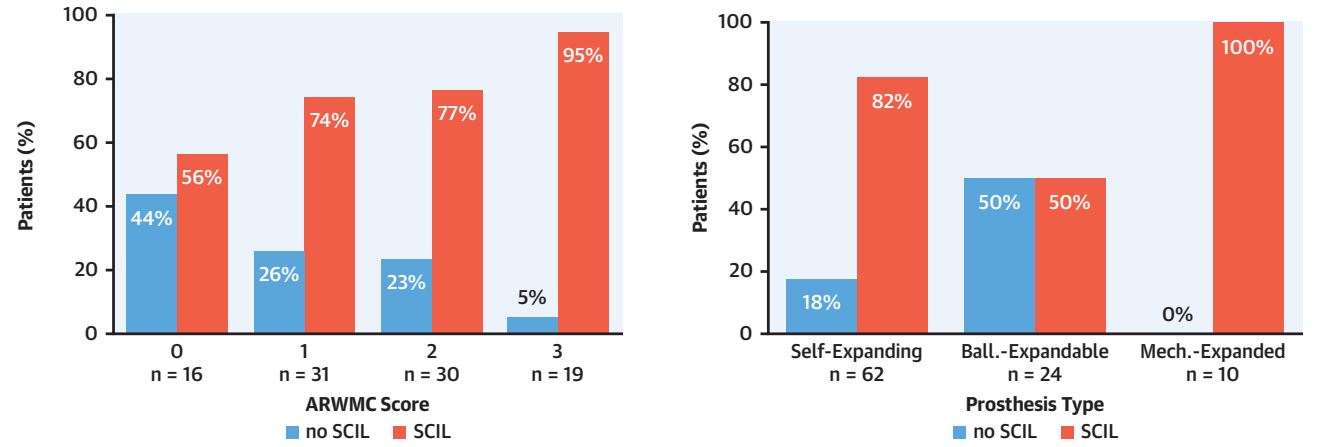
The embolic nature of SCILs after TAVR is supported by the presence of embolic debris in carotid filters deployed during TAVR (25). Of note, one-fourth of our patients had lesions in the vertebrobasilar territory, at least partially resulting from embolization through the left vertebral artery, which is not guarded by dual-filter embolic protection devices.

In our study, the use of non-balloon-expandable prostheses was an independent predictor of SCILs, with SCIL rates of 100% and 82% in patients receiving mechanically expanded prostheses and self-expanding prostheses, respectively, compared with 50% in those receiving balloon-expandable prostheses. These results are in agreement with previous findings showing a trend toward a lower number and volume of SCILs with balloon-expandable prostheses (3,6,7). In our population, the difference among valve types cannot be related either to post-dilatation, performed in a similarly low proportion of patients, or to pre-dilatation, significantly more common with balloon-expandable prostheses. On the contrary, the difference in SCIL rate may be related to the different prosthesis implantation modalities: a short-lasting balloon inflation for balloon-expandable valves versus prolonged friction of the prosthesis against a beating heart for non-balloon-expandable prostheses.

Importantly, crushing of the native aortic valve does not seem to be the primary source of embolization, as the histopathologic evaluation of embolic debris showed aortic valve tissue only in one-third of the cases (26). In contrast, arterial wall fragments were present in 94% of patients (3), suggesting that navigation of the prosthesis delivery system through an atheromatous aortic arch may be an important source of cerebral embolization. In our study, a higher ARWMC score was an independent predictor of SCILs, confirming the finding that baseline cerebral lesion volume was the only independent predictor of SCIL volume in the SENTINEL (Cerebral Protection in Transcatheter Aortic Valve Replacement) trial (3). The ARWMC score is a validated index of white matter damage, correlating with cognitive impairment in patients with stroke and associated with stroke risk during carotid revascularization (27). A possible explanation could be that white matter changes are at least partially related to chronic microembolization from the ascending aorta and aortic arch (16). Therefore, more advanced atherothrombotic disease of the aorta may represent the causal link between a higher ARWMC score and a higher rate of SCILs.

TIME COURSE OF SCIL. A very high rate of complete resolution of post-procedural SCIL has consistently been reported, ranging between 80% at 3 months (5,10) and 100% at 1 month (3,11). In our study, 73.3%

CENTRAL ILLUSTRATION Predictors of SCILs



De Carlo, M. et al. J Am Coll Cardiol Intv. 2020;13(11):1291–300.

(A) The age-related white matter change (ARWMC) score was an independent predictor of silent cerebral ischemic lesions (SCILs). **(B)** SCIL prevalence was related to prothesis types, being lowest in patients receiving balloon-expandable valves. Ball. = balloon; Mech. = mechanically.

of SCILs disappeared at follow-up, with 70.2% of patients showing resolution of all post-procedural lesions; we may have underestimated the resolution rate because of the slightly longer delay between TAVR and post-procedural MRI, allowing spontaneous resolution of some SCILs before they could be detected. Among patients with persisting SCILs, the number, diameter, and volume of lesions decreased by 70% to 80%, further reducing the overall ischemic burden at follow-up.

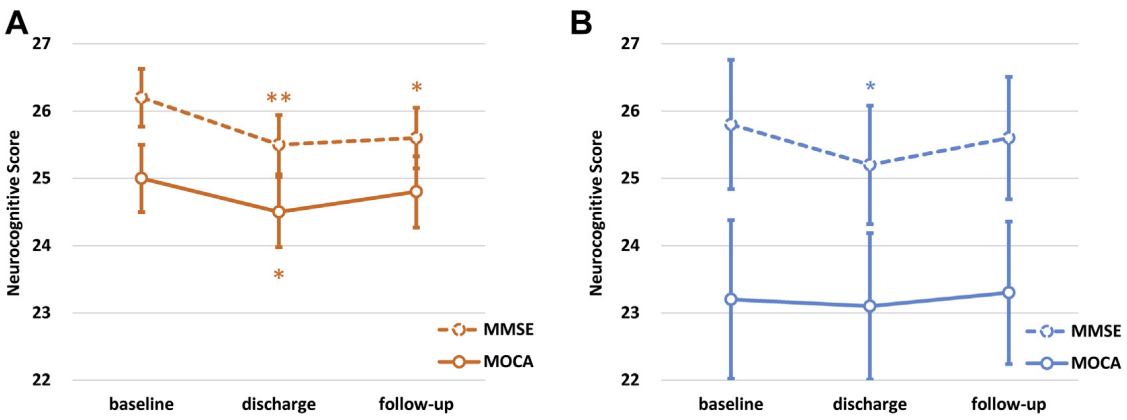
NEUROCOGNITIVE TRAJECTORY FOLLOWING TAVR. Neuropsychological testing has been used in patients undergoing TAVR, with conflicting results regarding changes in neurocognitive function early after the procedure. Small studies described significant worsening in MoCA scores in 33% to 41% of patients at 30 days (6,8); a larger study reported cognitive deterioration in 13% of patients, while cognitive improvement was observed in 38% of patients with impaired baseline cognition, possibly related to improved hemodynamic status (13). The potential relationship between the occurrence of SCILs and a post-operative neurocognitive decline has also been investigated with conflicting results. Initial reports described no association between SCILs and cognitive trajectory (8), while the SENTINEL trial reported a significant correlation between the change in neurocognitive scores and median SCIL volume (3).

In our study, 30% of patients showed impaired cognitive function at baseline, in agreement with previous studies (12). A mild, transient post-procedural decrease in MMSE score was observed in patients not developing SCILs, possibly related to the impact of hospitalization and temporary immobilization on elderly patients. However, patients developing SCILs showed a larger decrease in MMSE score, persisting at 3-month follow-up, as also described in the most recent studies (3,24). Importantly, in our study 56% of SCILs were cortical-subcortical in location. In agreement with the most recent studies (3,24), patients developing SCILs had significant worsening of neurocognitive function at discharge, with incomplete recovery at follow-up; we also found a correlation between the decrease in neurocognitive scores and SCIL volume. The clinical relevance of such mild transient decrease in neurocognitive function appears limited in very elderly patients but may be not negligible when expanding TAVR to younger, lower risk patients.

STUDY LIMITATIONS. First, post-procedural MRI was slightly more delayed compared with previous studies, making a direct comparison of SCIL number and volume among studies not feasible.

Second, a significant proportion of patients refused to undergo the third MRI and/or neurocognitive assessment; in particular, we cannot exclude that

FIGURE 3 Changes in Neurocognition



Neurocognitive examination results in the 83 patients with serial assessments. **(A)** Patients developing silent cerebral lesions (SCILs): the change over time was significant for the Mini Mental State Examination (MMSE) score ($p = 0.001$) and borderline significant for the Montreal Cognitive Assessment (MoCA) score ($p = 0.05$); the decrease was significant at discharge for both scores, persisting at follow-up for MMSE score. **(B)** Patients without SCILs: a trend toward a decrease was observed only for MMSE score ($p = 0.06$); the decrease was significant at discharge. **Circles** and **bars** represent means and SEs, respectively. *$p = 0.02$ versus baseline (Duncan's test); **$p = 0.003$ versus baseline (Duncan's test).

cerebral injury and/or neurocognitive decline rates could be higher in patients lost to follow-up.

Third, the enrollment of patients was slower than expected, leading to potential time-related bias in procedural technique and operator skills; however, the distribution of valve types was substantially constant through time.

Finally, our findings cannot be extrapolated to the latest versions of commercially available bioprostheses.

CONCLUSIONS

Our study showed that SCILs occur in the vast majority of patients undergoing TAVR and are evenly distributed across all cerebral vascular territories. Baseline white matter damage is an independent predictor of the occurrence of SCILs, together with the use of non-balloon-expandable prostheses. By means of serial MRI, we also demonstrated that 73% of SCILs disappear during follow-up, without leaving permanent cerebral lesions. Finally, we observed a correlation between the occurrence and volume of SCILs and the worsening of neurocognition after TAVR.

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PERSPECTIVES

WHAT IS KNOWN? SCILs occur in most patients undergoing TAVR.

WHAT IS NEW? Diffuse age-related white matter damage at baseline and the use of non-balloon-expandable prostheses are independent predictors of SCILs, possibly identifying patients who may benefit from embolic protection strategies. Although only 27% of SCILs evolve into gliotic scars, they are associated with a limited but significant post-procedural decrease in neurocognition, persisting at follow-up.

WHAT IS NEXT? Studies are needed to identify strategies to prevent cerebral embolization and cognitive deterioration, particularly when extending TAVR to younger patients.

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KEY WORDS cerebral magnetic resonance imaging, neurocognitive function, silent cerebral ischemic lesions, transcatheter aortic valve replacement

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