Stroke

Silent and Apparent Cerebral Ischemia After Percutaneous Transfemoral Aortic Valve Implantation

A Diffusion-Weighted Magnetic Resonance Imaging Study

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Background—The risk of stroke after transfemoral aortic valve implantation (TAVI) due to dislodgement and subsequent embolization of debris from aortic arch atheroma or from the calcified valve itself ranges between 2% and 10%. The rate of clinically silent cerebral ischemia is unknown but may be even higher.

Methods and Results—Thirty-two patients who underwent TAVI with the use of a balloon-expandable (n=22) or self-expandable (n=10) stent valve prosthesis were included in this descriptive study and compared with a historical control group of 21 patients undergoing open surgical aortic valve replacement. Periprocedural apparent and silent cerebral ischemia was assessed by neurological testing and serial cerebral diffusion-weighted magnetic resonance imaging at baseline, at 3.4 (2.5 to 4.4) days after the procedure, and at 3 months. TAVI was successful in all patients. After the procedure, new foci of restricted diffusion on cerebral diffusion-weighted magnetic resonance imaging were found in 27 of 32 TAVI patients (84%) and were more frequent than after open surgery (10 of 21 patients [48%]; P=0.011). These lesions were usually multiple (1 to 19 per patient) and dispersed in both hemispheres in a pattern suggesting cerebral embolization. Volumes of these lesions were significantly smaller after TAVI than after surgery (77 [59 to 94] versus 224 [111 to 338] mm³; P<0.001). There were neither measurable impairments of neurocognitive function nor apparent neurological events during the in-hospital period among TAVI patients, but there was 1 stroke (5%) in the surgical patient group. On 3-month follow-up diffusion-weighted magnetic resonance imaging, there were no new foci of restricted diffusion, and there was no residual signal change associated with the majority (80%) of the foci detected in the periprocedural period.

Conclusions—Clinically silent new foci of restricted diffusion on cerebral magnetic resonance imaging were detected in almost all patients (84%) undergoing TAVI. Although typically multiple, these foci were not associated with apparent neurological events or measurable deterioration of neurocognitive function during 3-month follow-up. Further work needs to be directed to determine the clinical significance of these findings in a larger patient population. (Circulation. 2010;121:870-878.)

Key Words: cerebral ischemia ■ magnetic resonance imaging ■ stenosis ■ heart valve prosthesis implantation ■ bioprosthesis ■ valves

Transfemoral aortic valve implantation (TAVI) is increasingly embraced as a viable alternative to conventional open heart surgery for selected elderly high-risk patients with severe symptomatic aortic valve stenosis.1–4 The retrograde TAVI approach involves advancement of semirigid, large-bore delivery catheters up to 24F in size through the aortic arch as well as direct manipulation of the usually heavily calcified aortic valve during passage and prior balloon valvuloplasty. This may result in dislodgement of microdebris from arch atheroma or from the valve itself with a risk of subsequent embolic stroke. Finally, crushing of the stenosed native leaflets by implantation of the metallic stent frame containing the xenopericardial tissue valve into the aortic annulus increases the risk of cerebral embolism even more. As a consequence, periprocedural stroke rates of TAVI are reported to range between 2.9% and 10%.1,4
Patients were excluded from TAVI in the presence of any of the following conditions: bicuspid aortic valve, aortic annulus diameter $\leq 18$ or $\geq 26$ mm, severe iliofemoral artery disease, unprotected left main disease, recent myocardial infarction or cerebrovascular event, sepsis or active endocarditis, severe aortic atheroma, left ventricular or atrial thrombus, active peptic ulcer, bleeding diathesis, or hyper-sensitivity to antiplatelet therapy.

**Percutaneous TAVI Procedure**

Technical aspects of the TAVI procedures with the use of the balloon-expandable, trileaflet bovine and the self-expandable, trileaflet pericardial tissue stent valve have been described in detail previously. In brief, first valvuloplasty of the aortic valve was performed with a 20- to 23-mm balloon catheter under rapid right ventricular pacing to facilitate later passage of the stent valve prosthesis. After manual crimping of the balloon-expandable valve onto a delivery balloon catheter or loading of the self-expandable prosthesis into the sheathed delivery system, the stent valve was advanced into the left ventricle with retrograde passage of the aortic valve. After positioning with the use of fluoroscopic and angiographic guidance, the balloon-expandable stent valve was deployed by balloon inflation under rapid right ventricular pacing at 160 to 220 bpm, and the self-expandable prosthesis was deployed stepwise and under guidance by several small-volume angiograms without rapid pacing. All procedures were performed in a dedicated hybrid operating room offering full functionality for cardiac catheterization, anesthesiology, and cardiac surgery.

Before the procedure, all patients received pretreatment with acetylsalicylic acid (100 mg/d), clopidogrel (75 mg/d after a loading dose of 300 mg/d), and ceftriaxone (2 g) as single-shot antibiotic prophylaxis. During the procedure, intravenous heparin was administered to achieve an activated clotting time $>250$s for the entire procedure with the activated clotting time being measured every 30 minutes. Catheters were flushed carefully with saline to avoid air embolism, and guidewires were cleaned thoroughly before catheter insertion to avoid formation of thrombi on their surface. Hemodynamic stability during the entire procedure was ensured by the attending cardiac anesthetist using a pulmonary artery catheter for invasive hemodynamic monitoring in all patients. Particular care was taken to avoid hypotensive periods and maintain a systolic blood pressure $>100$ mm Hg to prevent myocardial ischemia, which may increase the risk of ventricular fibrillation during or after rapid pacing. Therefore, colloidal or crystalloid solutions or catecholamines were administered rather liberally. After the procedure, acetylsalicylic acid was continued indefinitely, and clopidogrel was discontinued after 6 months. Phenprocoumon was substituted for clopidogrel in patients with atrial fibrillation.

**Clinical Examination, Neurological Assessment, and Assessment of Cognitive Function**

All patients underwent careful neurological examination performed by an experienced neurologist, including National Institutes of Health Stroke Scale (NIHSS) rating, before TAVI as well as shortly after the procedure when anesthetist-controlled conscious sedation or general anesthesia was completely reversed and 3 months after TAVI. The NIHSS is a 15-item impairment scale assessing level of consciousness, gaze, vision, facial palsy, extremity weakness, limb ataxia, sensory loss, language, and dysarthria. It was originally designed as a research tool to measure stroke severity by providing a numeric score from 0 to 42.14,15 It has now developed into the gold standard for the assessment of stroke and for monitoring changes in a patient’s condition in routine clinical practice. The NIHSS is currently also used to determine treatment options, anticipate discharge planning, and measure treatment.16–18 Furthermore, NIHSS rating is proposed as a diagnostic strategy in the clinical setting of periprocedural stroke during cardiac catheterization.19 In addition, the Mini Mental State Examination (MMSE) was performed to assess global cognitive function. The MMSE is a 30-point questionnaire test for evaluation of cognitive impairment briefly sampling orientation, registration, attention, calculation, re-
call, and language. It was developed as a quick screening tool to provide quantitative information on cognitive impairment and to record cognitive changes over time. Although this test was originally used to detect dementia within a psychiatric setting, its use has become widespread as a simple measure for global cognitive function and has even been used for assessment of early postoperative cognitive dysfunction after coronary artery bypass grafting.

At 3 months, the modified Rankin Scale (mRS) was used to describe the degree of the patient’s disability. The mRS is a single-item, global outcome score for stroke patients used to categorize the patient’s level of functional independence during daily activities with reference to prestroke activities by grading no (0), no significant (1), slight (2), moderate (3), moderately severe (4), and severe (5) disability and death (6). Postprocedurally clinically apparent neurological events were defined according to the guidelines for reporting morbidity and mortality after cardiac valvular operations as any new, temporary, or permanent focal or global neurological deficit occurring after anesthesia-induced unconsciousness was completely reversed.

Preoperative Assessment of Potential Sources of Embolism

Before the procedure, all patients were evaluated carefully for possible sources of embolism with the use of ECG, echocardiography, and carotid artery and transcranial Doppler ultrasonography. History of any previous embolism was taken.

Transesophageal echocardiography and transesophageal echocardiography were mandatory in all patients as part of the preinterventional TAVI evaluation protocol. In addition to evaluation of the aortic valve stenosis and measurements of the aortic annulus diameter, transesophageal echocardiography was also used to detect potential sources of cerebral embolism, such as spontaneous echo contrast, presence of intracardiac thrombi, low left atrial appendage peak velocities of <55 cm/s as measured by pulsed-wave Doppler, patent foramen ovale or other intracardiac shunts, and atheromatous disease of the aorta. Aortic atheroma, thickness of the atheroma, and the characteristics of the atheroma (mobile/protruding/sessile) in the ascending aorta, aortic arch, and descending thoracic aorta were determined. Aortic atheromas were graded as absent, mild (<4 mm without complex features), moderate (>4 mm without complex features), and severe (any size with protruding or mobile components). Carotid duplex ultrasound was performed for detection of atherosclerotic plaque burden and possible stenoses of the carotid arteries. Stenoses of common, internal, and external carotid artery were measured as a reduction of luminal area and graded with consideration of all information from B-mode, pulsed-wave, and color-flow Doppler according to established criteria. Anterior, middle, and posterior cerebral artery, vertebral and basilar arteries, and distal internal carotid artery were evaluated on the basis of peak systolic flow velocities by transcranial Doppler. Identification of the arteries and definition of normal velocities were based on published criteria.

Cerebral MRI

MRI was performed on a 1.5-T Avanto whole body imaging system (Siemens Medical Systems, Erlangen, Germany). Patients were imaged before the procedure, after the procedure when anesthetist-controlled conscious sedation or general anesthesia was completely reversed, and at 3 months. The protocol included the following 2 sequences: (1) transversal fluid-attenuated inversion recovery (repetition time, 9000 ms; echo time, 115 ms; matrix, 256×208; slice thickness, 6 mm) and (2) transversal DW images of the whole brain (repetition time, 4600 ms; echo time, 137 ms; matrix, 128×128; slice thickness, 5 mm; gradients of b volume, 0, 500, 1000 s/mm²). Diffusion images were processed to generate isotropic apparent diffusion coefficient maps with the use of the scanner’s dedicated software, allowing proper temporal classification of the lesions. Scans were read by 2 experienced neuroradiologists, blinded to the data of the patient, who looked for the presence of focal diffusion abnormalities in a pattern consistent with embolic lesions. Diffuse alterations and watershed ischemia were not regarded as embolic lesions. For volumetric quantification of new DW imaging abnormalities on postoperative scans, the area of lesion was delineated manually in each slice, and volume was calculated with the use of standard scanner software (Syngo, Siemens Medical Systems, Erlangen, Germany).

Definitions

A transient ischemic attack was defined as a fully reversible neurological event that lasted <24 hours. Stroke was defined as a neurological deficit that lasted >24 hours. Spontaneous echo contrast was defined as “smoke” in the cardiac cavities presenting on transesophageal echocardiography with a swirling motion distinguishing it from pure noise at too high gain level. Carotid stenosis was considered significant if >70%, and transcranial Doppler was considered pathological if normal flow velocities were exceeded.

Statistical Analysis

Categorical data are presented as frequencies and percentages; continuous variables are expressed as mean and 95% confidence interval. Comparisons were made with the 2-sided χ² test or, when appropriate, the 2-sided Fisher exact test for categorical variables and 1-way ANOVA for continuous variables, with the use of the Bonferroni correction for post hoc analysis to adjust for multiple testing. Repeated measurements were compared with the nonparametric Wilcoxon signed rank test. Multivariable logistic regression model was used to derive independent predictors of DW MRI lesions after TAVI. Initial modeling used variables marginally suggestive of unadjusted association with DW MRI lesions after TAVI (P<0.20). Variables were reviewed for clinical significance before testing. A P value <0.05 was considered statistically significant. All statistical analyses were performed with the use of the SPSS software package (version 17.0, SPSS, Chicago, Ill.). The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Characteristics

Patients undergoing TAVI were significantly older than those undergoing open cardiac surgery (80.0 [78.0 to 82.1] versus 67.4 [63.9 to 70.8] years; P<0.001). In addition, patients in groups 1 and 2 had significantly higher logistic EuroSCOREs and significantly more comorbidities than patients in group 3. Comparison of patient characteristics between TAVI patients and the surgical control group is summarized in Table 1.

Preinterventional Screening for Potential Sources of Embolism

Preinterventional screening for potential sources of embolism revealed the presence of aortic atheroma in all TAVI patients with involvement of the aortic arch in half of them. Atheromas were graded as mild in 27 of 32 patients (84%) (group 1, n=19; group 2, n=8) and moderate in the remaining 5 patients (16%) (group 1, n=3; group 2, n=2). Severe atheroma was considered an exclusion criterion for TAVI and thus not present in any patient. Six TAVI patients (group 1, n=4; group 2, n=2) were in permanent atrial fibrillation, and 16 patients (group 1, n=10; group 2, n=6) had reduced left atrial appendage peak velocities. Spontaneous echo contrast was found in 2 patients of group 2, but no intracardiac thrombi were observed in any patient. A patent foramen ovale was present in a single patient of group 1, and only 2 patients had a history of a previous stroke. Preprocedure carotid artery ultrasound revealed carotid artery stenosis >70% in 1 patient.
(group 1, n = 1; group 2, n = 0), luminal narrowing between 30% and 70% in 11 patients (group 1, n = 7; group 2, n = 4), and <30% in the remaining 20 patients (group 1, n = 14; group 2, n = 6). Transcranial Doppler showed occlusion of the left vertebral artery in 1 patient in group 1 and pathological flow in the left vertebral artery in 1 patient of group 2.

### Procedural Results

TAVI was technically successful in all patients. Implantation of the stent valve prostheses resulted in a postinterventional mean transaortic gradient of 11.2 (7.8 to 14.6) mm Hg and an aortic valve area of 1.81 (1.62 to 2.00) cm² (P < 0.001 versus baseline). Procedural complications included pericardial tamponade due to wire perforation requiring surgical repair in 1 patient (3%) and vascular access complications requiring endovascular or surgical repair in 8 patients (25%). In 2 patients of group 1, defibrillation with short-term mechanical resuscitation (<1 minute) became necessary for ventricular fibrillation after rapid pacing in 1 patient and due to ventricular “stunning” after valve implantation in the other. Both patients recovered after short-term external cardiac massage. The other patients remained hemodynamically stable throughout the TAVI procedure, but 9 (28%) of them required low-dose vasoactive support (<0.1 μg/kg per minute) at the conclusion of the procedure.

### Immediate Neurological Outcome

At baseline, no patient had any global or focal neurological deficit. NIHSS rating was 0 in all patients except for 1 patient in group 1 with a score of 3 because of preexisting anopia as a result of diabetic retinopathy. Assessment of global cognitive function by MMSE at baseline did not reveal major impairments with a score of 28.4 (27.4 to 29.3) (Table 2, Figure 1).

Postinterventional neurological evaluation was performed 3.4 (2.5 to 4.4) days after TAVI and showed no differences compared with baseline examination. There were no acute clinically apparent neurological complications in any patient with no change in NIHSS scoring, and there was no decline in cognitive function as indicated by a postoperative MMSE score of 28.2 (27.3 to 29.1) (Table 2, Figure 1). In the surgical control group, 1 clinically apparent, left-hemispheric stroke was diagnosed at the second postoperative day.

### Cerebral MRI

Baseline MRI scans showed various degrees of microangiopathy in all TAVI patients and signs of a previous infarction
in the 2 patients with a history of prior stroke. In group 3, preexisting brain abnormalities were found less frequently (8 of 21 patients [38%]; P < 0.001 versus TAVI patients). No acute diffusion abnormalities were found in any patient at baseline. Postprocedural DW MRI findings are shown in Table 3. After TAVI, new hyperintense lesions on cerebral DW MRI reflecting foci of restricted diffusion were found in 19 of 22 patients (86%) of group 1 and in 8 of 10 patients (80%) of group 2 (P = 0.947). These foci were typically multiple and dispersed in both hemispheres (Figure 2) in a radiographic pattern, suggesting an embolic origin of these lesions. New foci of restricted diffusion were found more frequently in both TAVI groups compared with group 3 (P = 0.016; Table 3). Interestingly, however, the volumes of the new foci of restricted diffusion were significantly smaller in TAVI patients compared with patients undergoing open cardiac surgery (Table 3), of whom 1 patient developed a clinically apparent stroke postoperatively.

**Follow-Up**

During the 3-month follow-up period, a single patient with a preexisting patent foramen ovale developed a transient ischemic attack 2 weeks after discharge, which was considered to be unrelated to the TAVI procedure itself. DW MRI at the time of the event failed to show any diffusion abnormalities. On 3-month DW MRI, there were no new foci of restricted diffusion in any patient, and there was no residual signal change associated with the majority (80%) of the foci of restricted diffusion detected in the periprocedural period. Clinical examination at 3 months did not show a new neurological deficit, a new disability, or any progressive deficits in cognitive function. Accordingly, the NIHSS rating as well as MMSE score remained unchanged compared with the baseline examination, and the mRS score was 0 for all TAVI patients (Table 2, Figure 1).

For the historical control group of patients undergoing surgical aortic valve replacement, the mRS score was also 0 for all patients except for the 1 patient with postoperative stroke who was graded a score of 1, indicating no significant impairment.

**Identification of Potential Risk Factors for Periprocedural DW Imaging Lesions**

Univariate analysis (Table 4) suggested hyperlipidemia, renal dysfunction, lower aortic atheroma thickness, porcelain aorta, increased left atrial appendage velocity, and reduced aortic valve area at baseline to be potentially associated with the amount of new foci of restricted diffusion on postinterventional MRI, but these could not be confirmed as independent predictors by multivariate analysis.

**Discussion**

The present descriptive study is the first to provide insights into the risk of silent and clinically apparent cerebral ische-
mia in patients undergoing TAVI with the use of clinical examination as well as comprehensive serial DW MRI. New foci of restricted cerebral diffusion were detected in 84% of patients after TAVI and were found to be more frequent than after conventional cardiac surgery. These foci were typically multiple and dispersed in both hemispheres, a pattern typical for embolic lesions, but were associated neither with apparent neurological deficits nor with measurable impairment of neurocognitive function during 3-month follow-up. Interestingly, the majority of the acute foci of restricted diffusion had resolved without residual signal change on 3-month MRI.

Hyperintense signals on DW MRI reflecting restricted cerebral diffusion are well established as a surrogate parameter for cerebral embolization and have been investigated extensively after catheter-based or surgical vascular interventions. The pattern of the lesions observed in our study (multiple, small lesions dispersed in both hemispheres) supports the hypothesis of embolic lesions, and, in fact, the TAVI procedure appears to be particularly prone to embolization. However, such hyperintense signals on DW MRI have also been associated with hypotension, seizure, migraine, or hypoglycemia. In our study, the absence of neurological and neurocognitive impairment contrasts with the high incidence of these foci of restricted diffusion. Because TAVI involves temporary tachycardic heart arrest, these lesions may also reflect the hemodynamic perturbations on cerebral perfusions exerted by rapid right ventricular pacing, which would explain the high rate of spontaneous resolution of the lesions on follow-up MRI. Nevertheless, severe aortic valve stenosis itself predisposes to embolic stroke because of spontaneous...

### Table 4. Univariate Analysis of Potential Risk Factors for Ischemic Brain Lesions in Patients After TAVI

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No Lesions (n=5)</th>
<th>Single Lesion (n=8)</th>
<th>Multiple (≥2) Lesions (n=19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>83.2 (75.8–90.6)</td>
<td>79.9 (75.8–84.0)</td>
<td>79.3 (76.5–82.0)</td>
<td>0.387</td>
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<tr>
<td>Female gender, n (%)</td>
<td>3 (60)</td>
<td>4 (50)</td>
<td>11 (58)</td>
<td>0.916</td>
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<tr>
<td>Logistic EuroSCORE, %</td>
<td>26.6 (5.6–47.6)</td>
<td>24.5 (12.8–36.3)</td>
<td>18.5 (13.3–23.8)</td>
<td>0.333</td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
<td>5 (100)</td>
<td>7 (88)</td>
<td>18 (95)</td>
<td>0.638</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>5 (100)</td>
<td>4 (50)</td>
<td>15 (79)</td>
<td>0.106</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>1 (20)</td>
<td>3 (38)</td>
<td>6 (32)</td>
<td>0.802</td>
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<tr>
<td>Smoking, n (%)</td>
<td>0 (0)</td>
<td>2 (25)</td>
<td>5 (26)</td>
<td>0.435</td>
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<tr>
<td>Obesity, n (%)</td>
<td>2 (40)</td>
<td>2 (25)</td>
<td>5 (26)</td>
<td>0.811</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>3 (60)</td>
<td>5 (63)</td>
<td>11 (58)</td>
<td>0.975</td>
</tr>
<tr>
<td>Prior cardiac surgery, n (%)</td>
<td>0 (0)</td>
<td>2 (25)</td>
<td>2 (11)</td>
<td>0.382</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>46.2 (24.9–67.5)</td>
<td>56.0 (47.6–64.3)</td>
<td>50.5 (43.4–57.7)</td>
<td>0.466</td>
</tr>
<tr>
<td>Renal dysfunction, n (%)</td>
<td>0 (0)</td>
<td>5 (63)</td>
<td>3 (16)</td>
<td>0.014</td>
</tr>
<tr>
<td>Prior cerebral ischemic event, n (%)</td>
<td>1 (20)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>0.337</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>1 (20)</td>
<td>2 (25)</td>
<td>4 (21)</td>
<td>0.969</td>
</tr>
<tr>
<td>Spontaneous echo contrast, n (%)</td>
<td>1 (20)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>0.337</td>
</tr>
<tr>
<td>Patent foramen ovale, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>0.702</td>
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<td>Aortic atheroma thickness, mm</td>
<td>3.2 (2.2–4.2)</td>
<td>3.1 (2.4–3.8)</td>
<td>2.4 (2.2–2.7)</td>
<td>0.015</td>
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<td>Aortic arch atheroma, n (%)</td>
<td>4 (80)</td>
<td>4 (50)</td>
<td>8 (42)</td>
<td>0.321</td>
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<tr>
<td>Porcelain aorta, n (%)</td>
<td>0 (0)</td>
<td>3 (38)</td>
<td>0 (0)</td>
<td>0.007</td>
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<td>Carotid artery stenosis, %</td>
<td>34 (8–76)</td>
<td>30 (11–48)</td>
<td>22 (13–31)</td>
<td>0.489</td>
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<td>Left atrial appendage velocity, cm/s</td>
<td>40.6 (7.2–74.9)</td>
<td>63.1 (54.7–71.6)</td>
<td>53.3 (44.8–61.9)</td>
<td>0.097</td>
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<td>General anesthesia, n (%)</td>
<td>0 (0)</td>
<td>1 (13)</td>
<td>6 (32)</td>
<td>0.240</td>
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<tr>
<td>Conscious sedation, n (%)</td>
<td>5 (100)</td>
<td>7 (87)</td>
<td>13 (68)</td>
<td>0.240</td>
</tr>
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<td>Procedure time, min</td>
<td>146.2 (109.4–183.0)</td>
<td>129.8 (97.5–162.0)</td>
<td>126.0 (108.6–143.4)</td>
<td>0.542</td>
</tr>
<tr>
<td>Fluoroscopy time, min</td>
<td>14.0 (8.2–19.8)</td>
<td>17.5 (11.6–23.3)</td>
<td>15.4 (13.3–17.5)</td>
<td>0.463</td>
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<td>Contrast volume, ml</td>
<td>226.0 (103.7–348.3)</td>
<td>263.6 (147.9–379.3)</td>
<td>239.4 (190.0–288.7)</td>
<td>0.816</td>
</tr>
<tr>
<td>Administered heparin, IU</td>
<td>6375.0 (3827.8–8922.2)</td>
<td>9000.0 (7229.1–10 770.9)</td>
<td>9111.1 (7176.5–11 045.7)</td>
<td>0.333</td>
</tr>
<tr>
<td>Aortic valve area at baseline, cm²</td>
<td>0.52 (0.36–0.67)</td>
<td>0.76 (0.58–0.93)</td>
<td>0.59 (0.48–0.70)</td>
<td>0.131</td>
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<tr>
<td>Mean transaortic gradient at baseline, mm Hg</td>
<td>65.5 (36.4–94.6)</td>
<td>49.8 (31.3–68.3)</td>
<td>52.6 (45.6–59.7)</td>
<td>0.319</td>
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<tr>
<td>Prosthesis type</td>
<td></td>
<td></td>
<td></td>
<td>0.850</td>
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<tr>
<td>Balloon-expandable</td>
<td>3 (60)</td>
<td>6 (75)</td>
<td>13 (68)</td>
<td></td>
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<tr>
<td>Self-expandable</td>
<td>2 (40)</td>
<td>2 (25)</td>
<td>6 (32)</td>
<td></td>
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<tr>
<td>Prosthesis size, cm</td>
<td>25.4 (21.3–29.5)</td>
<td>26.4 (24.8–28.0)</td>
<td>25.4 (24.6–26.1)</td>
<td>0.480</td>
</tr>
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</table>
dislodgement and subsequent embolization of calcific micro-debris from the degenerative leaflets.\textsuperscript{33} Catheter manipulation of the calcified, stenotic valve increases this risk, and it has been shown previously that cerebral embolism as detected by DW MRI occurs even after valve passage with relatively soft diagnostic catheters.\textsuperscript{6} Omran et al\textsuperscript{6} reported a total of 30 acute diffusion abnormalities in a pattern consistent with acute embolic events on postprocedural DW MRI in 22 of 101 patients (22\%) who underwent retrograde catheterization of the stenotic aortic valve for diagnostic hemodynamic evaluation. Three (3\%) of these patients developed clinically apparent neurological deficits, including right hemiparesis persistent at 3-month follow-up. In comparison, none of 51 patients in whom the stenotic valve was not crossed showed diffusion abnormalities or neurological deficits. The high incidence of new foci of restricted diffusion in the present study may therefore not be surprising because TAVI exerts a significantly greater trauma to the calcified valve including initial valvuloplasty, valve passage with semirigid, large-bore delivery catheters containing the crimped stent valve, and crushing of the native leaflets to the aortic wall by the metallic stent frame.

Additionally, patients with aortic valve stenosis who are currently considered for TAVI are usually elderly patients in whom the presence of aortic atheroma is very common. All of our patients had aortic atheroma of various degrees, and in half of them atheroma involved the aortic arch, with the presence of atheroma in the aortic arch being a known independent risk factor for recurrent strokes.\textsuperscript{34} The risk of cerebral embolism is associated with the complexity of aortic atheroma and may be increased during invasive cardiovascular procedures when aortic plaques are scraped by catheters with subsequent embolization of debris to the brain.\textsuperscript{35,36} It has been shown that scraping of aortic plaques occurs in >50\% of percutaneous cardiac interventions and is more frequent with large than with small catheters.\textsuperscript{36,37} Therefore, dislodgement of debris from ascending or arch atheroma during passage of the large-bore valve delivery catheters has the potential to add substantially to the high risk of cerebral embolization. Although dislodgement of aortic plaques is inherent to transfemoral TAVI, the transapical approach may potentially reduce this risk by obviating passage of the aortic arch with the large-bore delivery system and may thus be recommended in patients with large mobile arch atheroma.

Preinterventionally, we assessed other potential sources of embolism in our patients. However, because of the high incidence of foci of restricted diffusion suggestive of cerebral embolizations, we were not able to identify independent predictors of TAVI-associated embolism in our somewhat small patient cohort. Besides patient-related factors, procedure-related factors such as air embolism and thrombus formation in the catheter or on its surface may also contribute to peri-procedural cerebral embolization.\textsuperscript{19} To minimize these risks, catheters were frequently and carefully flushed with saline, guidewires were thoroughly cleaned, and activated clotting time was kept at >250 s.

In our study, new foci of restricted diffusion suggestive of embolization were observed in 48\% of patients undergoing surgical aortic valve replacement, which is in agreement with previous reports,\textsuperscript{38,39} but more frequently after TAVI (84\%; \textit{P}=0.011 versus surgery). This could imply concerns about the safety of this novel less invasive treatment option. It should, however, be noted that TAVI patients were significantly older and sicker than surgical patients, which may explain the higher frequency of embolic lesions in the TAVI group. These differences obviously limit the results of our study. However, patients currently referred for TAVI undergo this procedure because they are not considered surgical candidates. It is therefore very difficult to obtain an appropriate control group of elderly patients undergoing surgical aortic valve replacement. It was an interesting observation from our study that brain lesions after TAVI were significantly smaller in volume than lesions after surgery and were not associated with acute neurological events, whereas 1 of 21 control patients (5\%) developed a stroke after surgery.

The high incidence of new cerebral lesions after TAVI warrants longer-term evaluation of neurocognitive function. In our short-term follow-up period of 3 months, no impairment of neurocognitive function was observed clinically, and the majority of lesions (80\%) had resolved on 3-month MRI. However, the issue of peri-procedural brain embolization and its potential effects on neurocognitive function may portend greater clinical implications once the indication for TAVI is broadened to include younger patients with long life expectancy. Future research in the field of TAVI should thus be directed at developing strategies to reduce the risk of embolization (eg, less traumatic, smaller-bore catheter systems, improved identification of patients at risk for embolization, potential use of cerebral protection devices). The performance of preinterventional and postinterventional DW MRI should be used to monitor the effects of these developments on the frequency of procedure-related ischemic brain lesions.

**Strengths and Limitations**

Our study is the first to provide important insights into the risk of peri-procedural cerebral ischemia in patients undergoing TAVI with the use of comprehensive serial DW MRI evaluation, clinical examination, and neurological testing. Nevertheless, our analysis should be viewed in the light of its limitations.

First, this is a descriptive, mechanistic study without any prespecified power or sample size for any of the outcomes and is not a randomized trial of transfemoral, transcatheter aortic valve implantation versus surgical aortic valve replacement. Specifically, a historical rather than a randomized control group of patients undergoing surgical aortic valve replacement was used to put the high incidence of foci of restricted diffusion into perspective. This historical control group naturally differs from the 2 groups of TAVI patients in terms of baseline characteristics and operative risk because TAVI patients currently are elderly, high-risk patients who are denied open heart surgery. Hence, it is not possible to find a closely balanced control group undergoing surgical aortic valve replacement at present. This may become possible when indications for TAVI are broadened to include younger, lower-risk patients.

Second, our single-center study is limited by the relatively small number of patients affecting the precision and statistical
power of our analysis and therefore needs to be confirmed in a larger patient population. However, TAVI is an emerging technique, which was introduced to the clinical arena in 2002; thus, the current number of patients treated in an individual institution is relatively low. Nevertheless, we believe that the patient population of our study provides a realistic sample of patients referred for TAVI today.

Third, we used a somewhat simple methodology for analysis of neurocognitive function. Therefore, subtle changes in neurocognitive function may not have been detected in the present analysis but may be identified with more extensive neuropsychological testing. However, complex tests may not be applicable to the frail elderly patients because of the long testing time and may possibly require a larger number of patients to detect statistically significant changes. Nevertheless, this issue will be of great clinical importance once younger patients will be eligible for TAVI.

Fourth, we did not use transcranial Doppler during TAVI, which has the potential of intraprocedural detection of microembolism and determination of that part of the procedure in which it predominantly occurs.

Conclusion
Our data indicate that TAVI, which is increasingly used in the treatment of elderly high-risk patients with severe aortic stenosis, is associated with a high incidence of clinically silent foci of restricted diffusion on DW MRI that may reflect periprocedural cerebral embolization. These events were, however, not associated with apparent neurological deficits or measurable impairment in neurocognitive function during short-term follow-up and resolved spontaneously without scar formation on 3-month DW MRI. Further work needs to be done to determine the clinical significance of these findings in a larger patient population.

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Disclosures
Drs Thielmann, Sack, and Eggebrecht are clinical proctors for Duisburg-Essen. Drs Thielmann, Sack, and Eggebrecht for Edwards Lifesciences Inc and have received honoraria payments. Drs Thielmann, Sack, and Eggebrecht are clinical proctors for Duisburg-Essen.

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Ischemic stroke is among the most devastating complications in cardiac surgery and interventional cardiology, associated with a high rate of morbidity and mortality. A 2% to 10% stroke incidence has been reported after transfemoral aortic valve implantation (TAVI), which is an emerging treatment option for elderly high-risk patients with severe aortic stenosis. The rate of clinically silent cerebral embolism during TAVI may be higher but is yet unknown. We prospectively examined 32 patients who underwent TAVI with the use of the 2 currently commercially available bioprostheses with serial cerebral diffusion-weighted magnetic resonance imaging and compared the results with a historical control group of 21 patients undergoing surgical aortic valve replacement. After the procedure, a total of 115 new foci of restricted diffusion suggestive of embolization were detected by diffusion-weighted magnetic resonance imaging in 27 of 32 patients (84%) and were significantly more frequent than after conventional open surgery (10 of 21 patients [48%]; P = 0.011). Interestingly, volumes of cerebral diffusion-weighted imaging lesions were significantly smaller in the elderly TAVI patients, and there were no periprocedural neurological deficits despite the high lesion load compared with 1 stroke in the younger, lower-risk surgical control group. After 3 months, 80% of diffusion-weighted imaging lesions had resolved without residual signal change on follow-up magnetic resonance imaging. Nevertheless, the high incidence of new foci of restricted diffusion may portend greater clinical importance once younger patients undergo TAVI; thus, future research needs to be directed at strategies to reduce the risk of embolization including development of less traumatic, smaller-bore delivery catheters as well as protection devices.
Silent and Apparent Cerebral Ischemia After Percutaneous Transfemoral Aortic Valve Implantation: A Diffusion-Weighted Magnetic Resonance Imaging Study
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