JAMA | Original Investigation

# 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

Stephan Haussig, MD; Norman Mangner, MD; Michael G. Dwyer, MD; Lukas Lehmkuhl, MD; Christian Lücke, MD; Felix Woitek, MD; David M. Holzhey, MD; Friedrich W Mohr, MD; Matthias Gutberlet, MD; Robert Zivadinov, MD; Gerhard Schuler, MD; Axel Linke, MD

**IMPORTANCE** Stroke remains a major predictor of mortality after transcatheter aortic valve implantation (TAVI). Cerebral protection devices might reduce brain injury as determined by diffusion-weighted magnetic resonance imaging (DWMRI).

**OBJECTIVE** To determine the effect of a cerebral protection device on the number and volume of cerebral lesions in patients undergoing TAVI.

**DESIGN, SETTING, AND PARTICIPANTS** Investigator-initiated, single center, blinded, randomized clinical trial in higher-risk patients with severe aortic stenosis undergoing TAVI at the University of Leipzig Heart Center. Brain MRI was performed at baseline, 2 days, and 7 days after TAVI. Between April 2013 and June 2014, patients were randomly assigned to undergo TAVI with a cerebral protection device (filter group) or without a cerebral protection device (control group). The last 1-month follow-up occurred in July 2014.

**INTERVENTIONS** TAVI with or without a cerebral protection device (filter system).

**MAIN OUTCOMES AND MEASURES** The primary end point was the numerical difference in new positive postprocedure DWMRI brain lesions at 2 days after TAVI in potentially protected territories. The first hierarchical secondary outcome was the difference in volume of new lesions after TAVI in potentially protected territories.

**RESULTS** Among the 100 enrolled patients, mean (SD) age was 80.0 (5.1) years in the filter group (n = 50) and 79.1 (4.1) years in the control group (n = 50), and the mean (SD) procedural risk scores (logistic EuroScores) were 16.4% (10.0%) in the filter group and 14.5% (8.7%) in the control group. For the primary end point, the number of new lesions was lower in the filter group, 4.00 (interquartile range [IQR], 3.00-7.25) vs 10.00 (IQR, 6.75-17.00) in the control group (difference, 5.00 [IQR, 2.00-8.00]; $P < .001$). For the first hierarchical secondary end point, new lesion volume after TAVI was lower in the filter group (242 mm$^3$ [95% CI, 159-353]) vs in the control group (527 mm$^3$ [95% CI, 364-830]) (difference, 234 mm$^3$ [95% CI, 91-406]; $P = .001$). Considering adverse events, 1 patient in the control group died prior to the 30-day visit. Life-threatening hemorrhages occurred in 1 patient in the filter group and 1 in the control group. Major vascular complications occurred in 5 patients in the filter group and 6 patients in the control group. One patient in the filter group and 5 in the control group had acute kidney injury, and 3 patients in the filter group had a thoracotomy.

**CONCLUSIONS AND RELEVANCE** Among patients with severe aortic stenosis undergoing TAVI, the use of a cerebral protection device reduced the frequency of ischemic cerebral lesions in potentially protected regions. Larger studies are needed to assess the effect of cerebral protection device use on neurological and cognitive function after TAVI and to devise methods that will provide more complete coverage of the brain to prevent new lesions.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT01833052

*JAMA*. 2016;316(6):592-601. doi:10.1001/jama.2016.10302

Editorial page 587

Author Video Interview and JAMA Report Video at jama.com

Supplemental content at jama.com

**Author Affiliations:** University of Leipzig, Heart Center, Leipzig, Germany (Haussig, Mangner, Lehmkuhl, Lücke, Woitek, Holzhey, Mohr, Gutberlet, Schuler, Linke); Buffalo Neuroimaging Analysis Center, Department of Neurology, University of Buffalo, Buffalo, New York (Dwyer, Zivadinov); Leipzig Heart Institute, Leipzig, Germany (Mohr, Linke).

**Corresponding Author:** Axel Linke, MD, University of Leipzig, Heart Center, Department of Internal Medicine/Cardiology, Struempellstrasse 39, 04289 Leipzig, Germany (axel.linke@medizin.uni-leipzig.de).

Transcatheter aortic valve implantation (TAVI) using the balloon-expandable SAPIEN valve has been shown to be superior to standard medical therapy in inoperable patients.[1] Additionally, more recent data support that TAVI with the self-expanding CoreValve prosthesis is associated with lower mortality than surgical aortic valve replacement (SAVR) in high-risk patients.[2] However, although the clinical outcomes of TAVI have improved considerably during the last decade,[3,4] stroke, which is associated with a 3-fold increase in mortality following SAVR or TAVI, remains an important concern.[5-7] Adding to this concern is the observation that ischemic lesions, as determined by diffusion-weighted magnetic resonance imaging (DWMRI), are found in as many as 80% of TAVI patients.[8-11]

Numerous devices have been developed to protect the brain from injury caused by embolic debris during TAVI.[12-15] The recently published DEFLECT III trial,[15] which evaluated the TriGuard HDH embolic deflection device (Keystone Heart) during TAVI in patients with severe aortic stenosis, was designed to evaluate potential end points and benchmark event rates to inform the design considerations of a pivotal randomized study. Although the authors reported a numerical reduction in a number of DWMRI-related end points in deflector-treated patients, none of these changes reached statistical significance.[15] Hence, clear evidence of the efficacy of any embolic protection device in TAVI is still missing.

### Key Points

**Question** Does the use of a cerebral protection device during transcatheter aortic valve implantation (TAVI) reduce the amount of ischemic brain injury as determined by magnetic resonance imaging?

**Findings** In this randomized clinical trial that included 100 patients (n = 50 in each treatment group) with severe aortic stenosis undergoing TAVI, the use of a cerebral embolic protection device during the procedure significantly reduced the number of cerebral lesions in the potentially protected brain regions to 4 (interquartile range [IQR], 3.00-7.25) in the filter group vs 10 (IQR, 6.75-17.00) in the control group.

**Meaning** Among patients with severe aortic stenosis undergoing TAVI, the use of a cerebral protection device reduced the frequency of ischemic cerebral lesions in potentially protected regions.

## Methods

### Study Design

The Claret Embolic Protection and TAVI (CLEAN-TAVI) trial was a single-center, blinded, RCT performed at the Heart Center at the University of Leipzig, Germany (study protocol in Supplement 1). All patients provided written informed consent.

### Patient Selection

Symptomatic patients with severe aortic stenosis were eligible for inclusion in the study if they were considered at increased risk for SAVR as determined by the heart team. Computed tomography scans were performed to determine the size of the aortic annulus, the access vessels, the brachiocephalic trunk, and the left common carotid artery. Exclusion criteria were an anatomy unsuitable for a safe TAVI, preexisting permanent pacemaker, stroke within the last 12 months, carotid artery stenosis of more than 70%, significant stenosis of the right subclavian artery or the brachiocephalic trunk, expected nonadherence to follow-up visits, participation in another clinical study, severe renal failure (glomerular filtration rate [GFR]<30 mL/min/1.73 $m^2$ body surface area), or pregnancy.

### Randomization and Masking

Patients were randomly assigned (1:1) to the control or filter group using concealed and black laminated identical envelopes. Physicians and nurses performing the neurological and neurocognitive tests were otherwise not involved in the study or patient treatment and were blinded to group assignment. MRIs were anonymized using the patients' study numbers and transferred to a central MRI core laboratory for analysis to ensure blinding of the core laboratory.

### Study Procedures

#### TAVI Treatment

Patients were randomized in a 1:1 ratio to undergo transfemoral TAVI using the Medtronic CoreValve (Medtronic) self-expanding prosthesis without (control group) or with (filter group) a cerebral protection device using the Claret Montage Dual Filter System (Claret Medical Inc). All of the procedures were performed under conscious sedation by the same heart team. Heparin was given until the target activated clotting time of 250 seconds was achieved. In the filter group, the cerebral protection device was deployed as described previously.[12,13] Briefly, the proximal filter was deployed in the brachiocephalic trunk, covering all areas of the brain supplied by the right vertebral and carotid arteries; the distal filter was released in the left carotid artery. The left vertebral artery, which usually originates from the left subclavian artery, remained unprotected, as did the brain areas fed by this vessel. Based on the structure of the circle of Willis, the brain was separated into 28 segments corresponding to 14 left- and 14 right-sided arteries, to provide a detailed map of the territories fed by left and right cerebral tributaries. The volume of the brain that was potentially protected was 74%, 24% was partially protected, and 2% was unprotected. A detailed description of the segmentation of the brain, the respective nutritive support, and the level of protection is provided in eTable 1 (in Supplement 2). Following predilatation in all patients, TAVI was carried out per usual practice, as described previously.[3] The access vessel was closed and the patients were transferred to the intensive care unit for further monitoring.

Follow-up assessments were performed at 2 days and 7 days after TAVI and were identical to the preprocedural tests. In addition to MRI, follow-up included serial neurological and neurocognitive assessments, New York Heart Association classification, echocardiography, and documentation of adverse events and study end points.

### Magnetic Resonance Imaging

Brain MRI assessments were performed at baseline and at 2 and 7 days. MRI scans were analyzed in blinded fashion by the MRI core laboratory (Buffalo Neuroimaging Analysis Center, Buffalo, NY). The MRI protocol included diffusion-weighted images (DWIs) acquired with a 2D-echo planar sequence, high-resolution T1-weighted images acquired with an MP-RAGE sequence, and B0 field maps acquired with a manufacturer-based dual-echo gradient echo sequence.[16-18] All examinations were acquired on a 3T scanner (Magnetom Verio) except for 11 patients who were pacemaker dependent following TAVI. For these patients, a 1.5T system (Intera by Philips) was used. MRI outcomes included calculation of number and volume of new DWIs (2 and 7 days) by subtraction of the existing baseline lesions in the whole brain and within predefined vascular territories (ie, the potentially protected and partially protected areas). None of the patients had any endovascular diagnostic tests or treatments performed between the baseline MRI and the TAVI. The details of the MRI procedures are provided in eTable 1 and the eAppendix in Supplement 2.

### Neurological and Neurocognitive Assessment

An attending physician who was at that time being trained as an internist or cardiologist or an exercise scientist (PhD) was experienced in conducting neurological assessments in research studies and was certified to administer the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale. They were blinded to group assignment.

## Study End Points

The primary end point was the numerical reduction in positive postprocedure DWMRI brain lesions relative to baseline at 2 days following TAVI in potentially protected territories. Only new lesions that were visible at 2 days, 7 days, or both but not present in the baseline scans were analyzed. Secondary end points included serial volumetric and numerical reductions in positive postprocedure DWMRI–perfused brain lesions at 2 and 7 days, as well as the results of serial neurological and neurocognitive assessments.

## Statistical Analysis

The mean (SD) number of DWMRI lesions after TAVI was reported as 5.9 (6.8) by Astarci et al[11] and in a separate study as 4.2 (6.5) by Fairbairn et al.[10] However, Astarci et al[11] used 3T-MRI infrequently, and all MRIs in the study by Fairbairn et al[10] were performed on a 1.5T scanner, which has a lower sensitivity to detect smaller lesions. Because the current study used a segmentation methodology to detect smaller lesions (eAppendix in Supplement 2) and a 3T MRI in the majority of the cases, it was anticipated that the absolute lesion number would be higher than previously reported. The primary hypothesis for clinically significant success was that the cerebral protection device would provide a 50% reduction in the number of positive DWMRI–perfused brain lesions following TAVI at 2 days relative to baseline in potentially protected territories. Given a standard deviation of 7 for the measure and assuming a drop-out rate of 16%, an estimated total of 50 patients were required in each group for the study to have a power of 90% at a 2-sided α level of 0.05. Because the device does not protect the entire brain, the primary focus was on the territory where a potential filter effect could most reliably be detected.

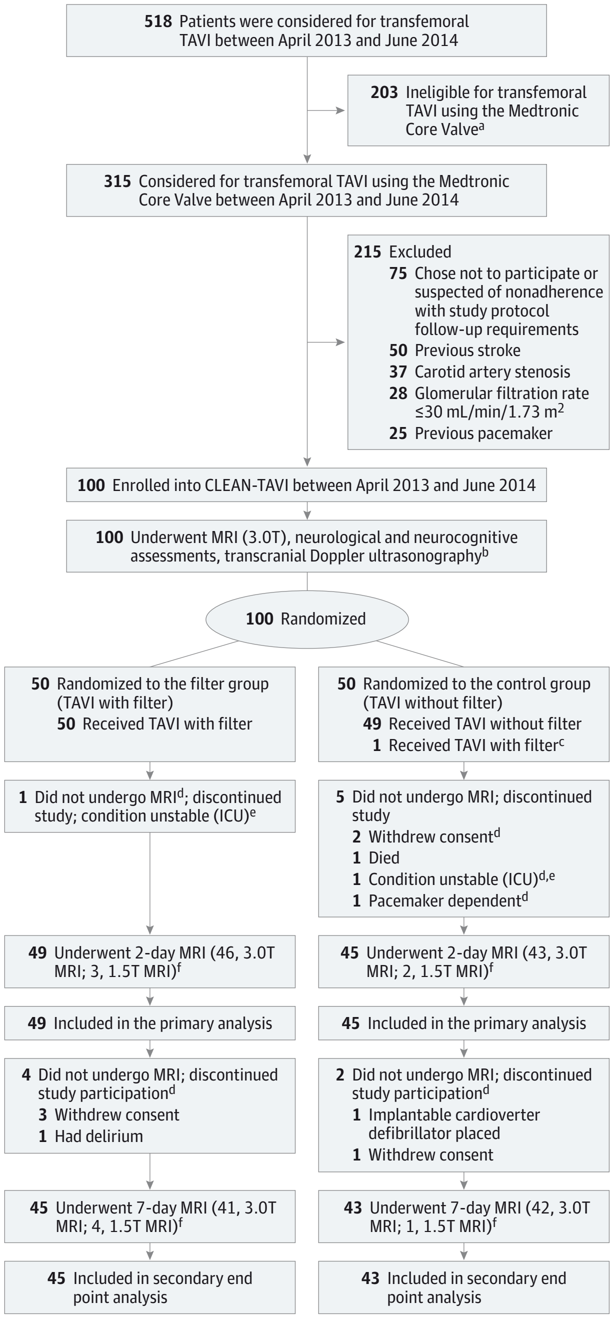
Secondary efficacy end points were evaluated and tested for statistical significance but only if the primary efficacy end point was met. To preserve overall type I error, a gatekeeping strategy was used in which secondary MRI end points were tested. These 16 end points were tested in the following order and only if the prior one on the list achieved statistical significance: (1) day 2 DWMRI median total new lesion volume within the potentially protected areas; (2) day 7 DWMRI median total new lesion number within the potentially protected areas; (3) day 7 DWMRI median total new lesion volume within the potentially protected areas; (4) day 2 DWMRI total new lesion number in all territories (entire brain); (5) day 2 DWMRI median total new lesion volume in all territories; (6) day 7 DWMRI total new lesion number in all territories; (7) day 7 DWMRI median total new lesion volume in all territories; (8) day 30 Flair MRI total new lesion number in potentially protected territories; (9) day 30 Flair MRI median total new lesion volume in potentially protected territories; (10) day 2 Montreal Cognitive Assessment and its subcomponents; (11) day 7 Montreal Cognitive Assessment and its subcomponents; (12) day 2 modified Rankin Scale; (13) day 7 modified Rankin Scale; (14) day 2 NIHSS; (15) day 7 NIHSS; and (16) periprocedural high-intensity transient signals (HITS).

The secondary end points Montreal Cognitive Assessment, modified Rankin Scale, NIHSS, high-intensity transient signals were considered exploratory and were reported descriptively.

The primary end point analysis was performed according to a modified intention-to-treat (ITT) principle, with all participants analyzed in the group to which they were randomized, and including all participants in whom the investigational study procedure was attempted and for whom MRIs were available at baseline and day 2. The same modified ITT analysis was performed for the secondary MRI end points at 2 and 7 days. In sensitivity analysis to test for the effect of the loss of values due to missing MRI data, a multiple imputation was also performed. First, the Little's Missing Completely at Random Test was performed to confirm a random distribution of missing values. Then, using the Markov chain Monte Carlo method, missing values were imputed based on the available data from the MRI assessments at 2 and 7 days, and the procedure was repeated 10 times to create 10 imputation sets.

Categorical variables were expressed as numbers, percentages, or both and were compared with use of the Fisher exact test or the $\chi^2$ test as appropriate. Continuous variables were expressed as mean (SD) values or median interquartile (IQR) ranges and compared using an appropriate parametric (Student *t*) test or nonparametric (Mann-Whitney *U*) test. All tests were 2-sided and a *P* value of less than .05 was considered statistically significant. Differences between medians were estimated using the independent

Figure 1. Treatment Flow of Patients in the CLEAN-TAVI Trial




[a] Reasons ineligible for transcatheter aortic valve implantation (TAVI): not suitable for transfemoral access (heavy calcification with resulting stenosis, high tortuosity); coronary origin less than 8 mm from the aortic annulus; or aortic annulus size too small or large.

[b] See 4.2.4 Preinterventional Procedures in Supplement 1.

[c] Patient indicated study consent would be withdrawn if TAVI was without filter protection. Therefore, a cerebral protection device was used, but the patient remained in the control group per the intention-to-treat principle.

[d] Still underwent clinical follow-up.

[e] Indicates clinical instability and inability to leave the intensive care unit (ICU) for magnetic resonance imaging (MRI) assessment.

[f] Of those who received the 2-day MRI in the filter group, 3 of 49 MRIs (6.1%) and in the control group, 2 of 45 MRIs (4.4%) were performed using the 1.5T scanner (absolute difference, 1.7%). Of those who received the 7-day MRI in the filter group, 4 of 45 MRIs (8.8%) and in the control group, 1 of 43 MRIs (2.3%) were performed using the 1.5T scanner (absolute difference, 6.5%).The 1.5T scanner was used because some patients were intermittently pacer dependent with temporary leads in place (not approved for use with 3T MRI).

samples Hodges-Lehmann estimator. Odds ratios (ORs), risk ratios (RRs), and 95% CIs were calculated using logistic-regression analysis. All analysis was performed using SPSS version 21 (IBM) or MedCalc software version 13.1.2.0 (MedCalc).

## Results

The flow of study participants is shown in **Figure 1**. Patient demographics and clinical characteristics at baseline are provided in **Table 1** and in eTable 2 (in Supplement 2). They were well balanced. However, there were more patients with insulin-dependent diabetes in the control group (15 [30%]) vs the filter group (5 [10%]), more with preexisting stage 3 kidney disease in the filter group (23 [46%]) vs the control group (11 [22%]), and more with prior coronary artery bypass surgery in the filter group (8 [16%]) vs the control group (2 [4%]). The characteristics of all patients with and without MRI follow-up in the control and filter groups are provided in eTable 3 and eTable 4 (in Supplement 2).

Table 1. Patient Characteristics at Baseline[a]

| Characteristic | Filter Group (n = 50) | Control Group (n = 50) |
|---|---|---|
| Age, mean (SD), y | 80.0 (5.1) | 79.3 (4.1) |
| Female sex | 29 (58) | 28 (56) |
| New York Heart Association class | | |
| I | 5 (10) | 5 (10) |
| II | 13 (26) | 13 (26) |
| III | 23 (46) | 29 (58) |
| IV | 9 (18) | 3 (6) |
| STS PROM estimate, mean (SD), % | 5.6 (3.2) | 5.2 (2.7) |
| STS PROM by risk level[b] | | |
| <4% | 19 (38) | 20 (40) |
| 4%-10% | 24 (48) | 26 (52) |
| >10% | 7 (14) | 4 (8) |
| Logistic EuroSCORE, mean (SD), %[c] | 16.4%(10.0) | 14.5%(8.7) |
| Diabetes mellitus | | |
| All | 20 (40) | 25 (50) |
| Controlled by insulin | 5 (10) | 15 (30) |
| Chonic kidney disease[d] | | |
| Stage 2, GFR 60-89 | 20 (40) | 28 (56) |
| Stage3, GFR 30-59 | 23 (46) | 11 (22) |
| History of hypertension | 44 (88) | 47 (94) |
| Peripheral vascular disease | 2 (4) | 4 (8) |
| Prior stroke or transient ischemic attack | 1 (2) | 3 (6) |
| Cardiac risk factor | | |
| Coronary artery disease | 26 (52) | 25 (50) |
| Prior coronary artery bypass surgery | 8 (16) | 2 (4) |
| Prior percutaneous coronary intervention | 5 (10) | 8 (16) |
| Preexisting pacemaker or defibrillator | 0 | 0 |
| Prior myocardial infarction | 6 (12) | 4 (8) |
| Congestive heart failure | 46 (92) | 46 (92) |
| Prior atrial fibrillation or atrial flutter | 17 (34) | 17 (34) |
| MRI No. of lesions at baseline, median (IQR) [range] | 0 (0-1) [0-5] | 0 (0-1) [0-5] |
| MRI lesion volume at baseline, (95% CI), [range], mm$^3$ | 0 (0-36) [0-7604] | 0 (0-0) [0-615] |

Abbreviations: GFR, glomerular filtration rate; STS PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.

[a] Data are reported as No. (%) unless otherwise stated.

[b] STS PROM predicts the risk of operative mortality (<4%, low risk; 4%-10%, intermediate risk; and >10%, high risk).

[c] Logistic EuroScore predicts risk of operative mortality with higher accuracy as compared with the standard EuroScore (<10%, low risk; ≥10%-≤20%, intermediate risk; and >20%, high risk).

[d] GFR was calculated as mL/min/1.73 m$^2$. There were no patients with stage 4 (GFR 15-29) or stage 5 (GFR<15 or dialysis) chronic kidney disease in the the filter or control groups.

## Procedural Data

Procedural data are reported in **Table 2**. Procedural data for patients included and not included in the primary end point analysis are reported in eTable 5 and eTable 6 (in Supplement 2). Radiation dose and amount of contrast dye used during the procedure did not differ between the control and treatment groups. However, fluoroscopy time and procedural time (defined as time from the first puncture until the closure of the last access site) were longer in the filter group compared with the control group. There were 2 patients in whom neither of the filters could be deployed due to significant tortuosity of the right subclavian artery or the brachiocephalic trunk. In another 2 patients, it was impossible to position the distal filter because of complex anatomy, and in 1 patient, the correctly deployed filter dislocated because of accidental pull-back of a jailed pigtail catheter. Therefore, total device success was achieved in 46 of 50 patients (92%), total or partial device success in 48 of 50 (96%), and total procedural success in 45 patients (90%).

Three patients in the filter group underwent thoracotomy, 1 because of wire perforation of the left ventricle that could not solely be solved by pericardiocentesis and 2 because of inability to release the transcatheter valve from the delivery catheter. However, none of these thoracotomies appeared to be related to the cerebral protection device. All 3 patients recovered and were alive at 30 days.

## MRI End Points

In the potentially protected regions, the median new lesion number at 2 days was lower in the filter group (4.00 [IQR, 3.00-7.25]) than in the control group (10.00 [IQR, 6.75-17.00]) (difference, 5.00 [IQR, 2.00-8.00]; $P < .001$; **Figure 2** and **Table 3**). Moreover, in the potentially protected regions, new lesion volume was lower in the filter group, 242 mm$^3$ (95% CI, 159-353) vs 527 mm$^3$ (95% CI, 364-830), difference 234 mm$^3$ (95% CI, 91-406), $P = .001$.

At 7 days, new lesion number in the potentially protected areas was lower in the filter than control groups, 3.00 (IQR 1.00-5.25) vs 7.00 (IQR 3.00-13.50), difference 3.00 (1.00-5.00), $P = .003$. Likewise, at 7 days, new lesion volume in the potentially protected areas was lower in the filter group, 101 mm$^3$ (95% CI, 60-174)) vs 292 mm$^3$ (95% CI, 181-515), difference 160 mm$^3$ (95% CI, 57-281), $P = .002$, Figure 2, Table 3).

Similar effects were seen for the entire brain. At 2 days, the median total new lesion number was lower in the filter than control groups, 8.00 (IQR 5.00-12.00) vs 16.00 (IQR 9.75-24.25), difference 6.00 (IQR 3.00-10.00), $P = .002$; and lesion volume was reduced, 466 mm$^3$ (95% CI, 349-711) compared with 800 mm$^3$ (95% CI, 594-1407), difference 311 mm$^3$ (95% CI, 66-580), $P = .02$, Figure 2, Table 3). In addition, at 7 days the median total new lesion number in the entire brain was lower in the filter group, 5.00 lesions (IQR 2.75-8.00) compared with 10.00 lesions (IQR 3.00-18.00), difference 4.00 (IQR 1.00-8.00), $P = .009$; and lesion volume was reduced, 205 mm$^3$ (95% CI, 115-338) vs 472 mm$^3$ (95% CI, 385-909), difference 240 mm$^3$ (95% CI, 51-393), $P = .009$, Figure 2, Table 3).

The comparison of the imputed data sets for the number and volume of new lesions in the potentially protected areas, partially protected areas, and the entire brain at 2 and 7 days confirmed the lower values in the filter group as compared with the control group and hence, the findings of the modified intention-to-treat analysis eTable 7 in Supplement 2).

Table 2. Procedural TAVI and Filter Deployment Data

| | Mean (95% CI)[a] | | |
|---|---|---|---|
| | Filter Group (n = 50) | Control Group (n = 50) | P Value |
| Dose-area product -cGycm$^2$ | 18 803 (15 884-21 722) | 17 772 (15 269-20 276) | .82 |
| Fluoroscopy time, min | 17.4 (14.8-19.9) | 14.4 (12.4-16.3) | .02[b] |
| Amount of contrast medium, mL | 128 (119-136) | 131 (121-141) | .59 |
| Time, min | | | |
| From insertion of sheath into radial artery to insertion of device | 21.1 (19.3-22.9) | NA | NA |
| From insertion of device to device in final position | 7.1 (5.5-8.7) | NA | NA |
| From device in final position to retraction of device | 23.9 (21.3-26.4) | NA | NA |
| Total time from insertion to retraction of device | 31.0 (27.9-34.0) | NA | NA |
| Procedural time, min | 72.1 (65.7-78.5) | 54.1 (50.0-58.1) | <.001[c] |
| Device success, No. (%)[d] | 46 (92) | NA | NA |
| Procedural success, No. (%)[e] | 45 (90) | NA | NA |
| Thoracotomy, No. (%) | 3 (6) | 0 | .24 |

Abbreviations: NA, not applicable; TAVI, transcatheter aortic valve implantation.

[a] Data are reported mean (95% CI) unless otherwise stated.

[b] Difference, 2.7 (95% CI, 0.4-4.8).

[c] Difference, 15.0 (95% CI, 10.0-20.0).

[d] Device success was defined as successful positioning and deployment of both filters in correct anatomical position.

[e] Procedural success was defined as successful positioning and deployment of both filters in correct anatomical position, correct positioning of both filters during TAVI, and successful retrieval of both filters after TAVI.

Overall, by MRI at 2 days, 98% of the patients in the filter group (48 of 49) and 98% of the patients in the control group (44 of 45) were lesion positive. At 7 days, 98% of the patients in the filter group (44 of 45) and 95% of the patients in the control group (41 of 43) were lesion positive.

## Neurological Outcomes

At 2 and 7 days in the intention-to-treat analysis, the number of patients with neurological symptoms indicative of stroke was 5 in the filter group and 5 in the control group; all were minor and nondisabling in nature (eTable 8 in Supplement 2). None of the patients had a transient ischemic attack since all patients with symptoms had positive brain imaging and were classified as stroke positive according to VARC2. At 2, 7, and 30 days, stroke frequencies were similar between both groups.

Secondary exploratory neurological outcomes were reported in eTable 8 and eTable 9 (in Supplement 2).

## Procedure Related and Other Outcomes

The clinical outcomes according to VARC-2 (the Valve Academic Research Consortium) are reported in eTable 10 (in Supplement 2). The control and filter groups did not differ with regard to the incidence of any complications. One patient in the control group died from diastolic heart failure, therefore 30-day mortality for the control group was 2%, for the filter group was 0%, and for the entire cohort was 1%. The median number of periprocedural high-intensity transient signals was 3196 (IQR, 2522-4010) in the filter group and 3674 (IQR, 2551-5217) in the control group.

TAVI resulted in improvement in aortic valve function and symptoms in both the control and filter groups (eFigure 1 and eTable 11 in Supplement 2).

# Discussion

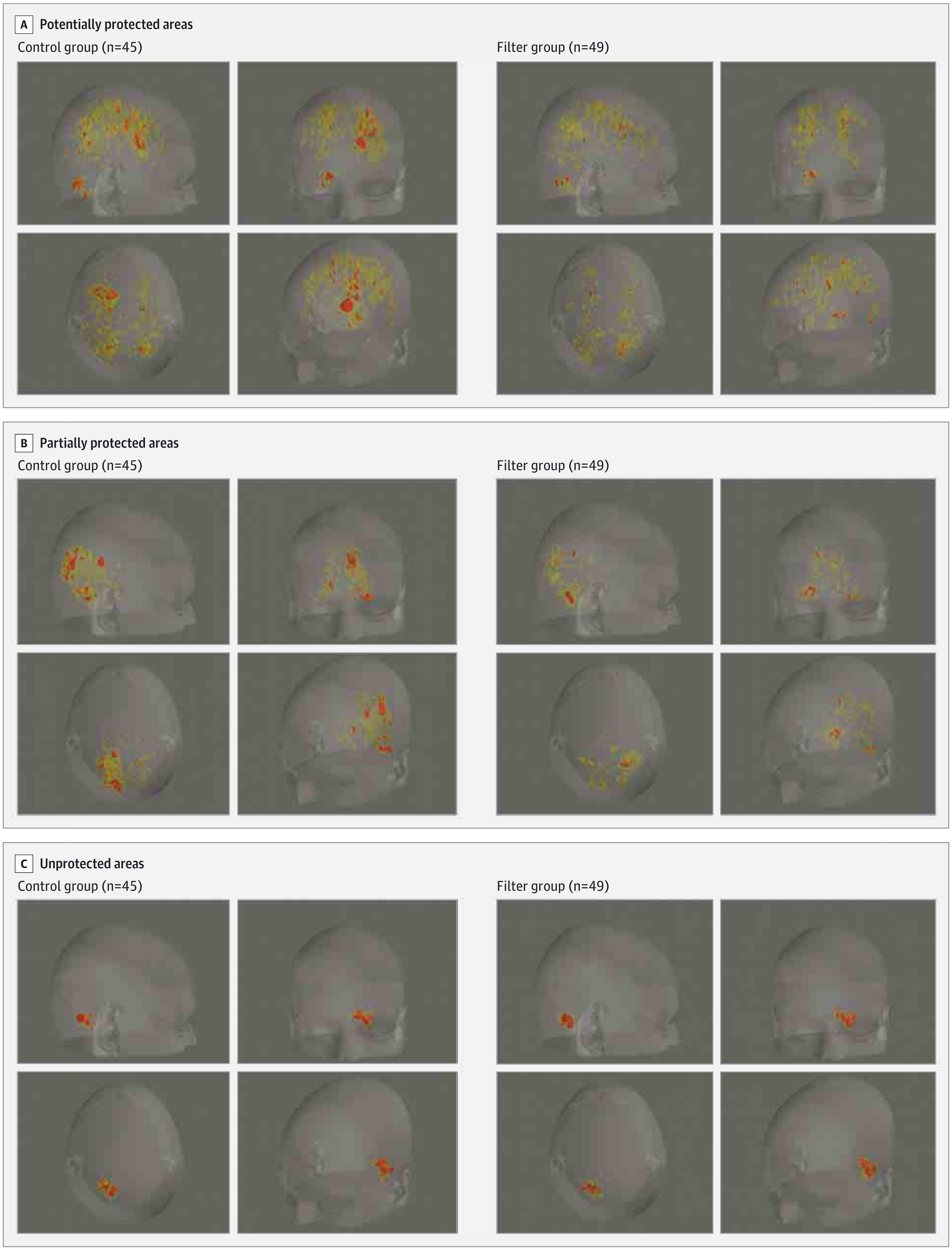
TAVI was associated with DWMRI-positive brain lesions, indicative of ischemic brain injury in almost every patient. However, use of a cerebral protection device during TAVI significantly reduced the number and volume of new lesions in the potentially protected regions and in the entire brain.

## Effect of TAVI on Brain Structure as Determined by MRI

The effect of TAVI on the brain has been studied applying DWMRI in a nonrandomized fashion.[8-11] Comparison of the values obtained in the control group of this study with previous studies is limited because previous studies used different transcatheter heart valves, lacked consistent baseline MRI (requiring the assumption that all lesions after TAVI are necessarily new lesions), used a lower MRI scanner strength field (1.5 vs 3T), and differed in time points of MRI assessments after TAVI and the definition of MRI end points.[8-11,15] The new lesion volume observed in patients in the control group was consistent with values recently reported in the DEFLECT III study.[15] However, in the control group, the number of DWMRI-positive brain lesions was higher compared with previous trials, most likely because of the following reasons: (1) the subtraction technique applied in this study enhanced the detection of smaller lesions; (2) 3T-MRI was used, which has a higher sensitivity compared with 1.5T-MRI; (3) and the first MRI after TAVI was performed at 2 days postintervention, which was earlier than in previous trials.[8-11] The latter point is of importance in the interpretation of trial results because this study provides, for the first time to our knowledge, evidence that new lesion number and volume were numerically higher at 2 days compared with 7 days after TAVI. Hence, the expected lesion number and volume will be smaller in studies in which postprocedural MRI was performed late after TAVI (eg, at 5-7 days) in comparison with studies using an early MRI (eg, at 2-3 days).

The high percentage of patients who were lesion positive in the filter group may initially appear surprising, but other studies have found similar phenomena. Although 25% of patients were completely lesion free in the DEFLECT III trial, freedom from lesions was confined to patients treated with an Edwards valve; all CoreValve-treated patients had cerebral lesions despite the use of the TriGuard device designed to

Figure 2. 3-Dimensional Reconstruction of Cumulative Lesion Burden From Diffusion-Weighted Images




All images were obtained at 2 days. Individual lesion maps were aligned with the Montreal Neurological Institute (MNI) template space and rendered in 3-dimensional format. Areas with lesions in 1 patient are shown in yellow. Areas with lesions in 2 or more patients are shown in red.

Table 3. Brain Lesion Characteristics as Determined by Magnetic Resonance Imaging

| | 2 Days | | | | 7 Days | | | |
|---|---|---|---|---|---|---|---|---|
| | Filter (n = 49) | Control (n = 45) | Difference (95% CI)[a] | *P* Value | Filter (n = 45) | Control (n = 43) | Difference (95% CI)[a] | *P* Value |
| **Potentially Protected Areas** | | | | | | | | |
| No. of new lesions, median (IQR) | 4.00 (3.00-7.25)[b] | 10.00 (6.75-17.00)[b] | 5.00 (2.00-8.00)[b] | <.001 | 3.00 (1.00-5.25) | 7.00 (3.00-13.50) | 3.00 (1.00-5.00) | .003 |
| Volume of new lesions, median (95% CI), $mm^3$ | 242 (159-353) | 527 (364-830) | 234 (91-406) | .001 | 101 (60-174) | 292 (181-515) | 160 (57-281) | .002 |
| **Partially Protected Areas** | | | | | | | | |
| No. of new lesions, median (IQR) | 2.00 (1.00-3.25) | 4.00 (2.00-7.00) | 2.00 (0.00-3.00) | .008 | 1.00 (0.00-3.00) | 3.00 (1.00-5.00) | 1.00 (0.00-2.00) | .02 |
| Volume of new lesions, median (95% CI), $mm^3$ | 113 (72-164) | 247 (147-399) | 98 (18-194) | .01 | 37 (11-70) | 129 (67-227) | 72 (3-129) | .008 |
| **Entire Brain** | | | | | | | | |
| No. of new lesions, median (IQR) | 8.00 (5.00-12.00) | 16.00 (9.75-24.25) | 6.00 (3.00-10.00) | .002 | 5.00 (2.75-8.00) | 10.00 (3.00-18.00) | 4.00 (1.00-8.00) | .009 |
| Volume of new lesions, median (95% CI), $mm^3$ | 466 (349-711) | 800 (594-1407) | 311 (66-580) | .02 | 205 (115-338) | 472 (385-909) | 240 (51-393) | .009 |

Abbreviations: DWMRI, diffusion-weighted magnetic resonance imaging; IQR, interquartile range; TAVI, transcatheter aortic valve implantation.

[a] Differences calculated as independent samples Hodges-Lehmann median difference estimates.

[b] The primary end point was numerical reduction in positive postprocedure DWMRI-perfused brain lesions relative to baseline at 2 days following TAVI in potentially protected territories. The 1.5T scanner was used in patients who were intermittently pacer dependent with a temporary lead in place and who were not approved for 3.0T MRI.

protect the entire brain from embolic injury.[15] In the ADVANCE trial, within the first months after TAVI using the CoreValve exclusively, half of the reported strokes occurred between day 2 and day 30 and the other half on the day of the procedure or the first postprocedural day, suggesting that the risk of stroke is not limited to the procedure itself.[2,19,20] This is consistent with DEFLECT III, in which 10% of patients experienced new lesions between the postprocedural MRI and the assessment at 30 days.[15] Nevertheless, the filter can only protect the brain during the TAVI procedure, which usually takes less than 1 hour and represents only 2% of the first 48 hours after which the first MRI was performed in this study. Based on the analyzed material captured and removed by the filters, eg, old and fresh thrombus, endothelium, atheromatous plaque, valve tissue, and calcium (eFigure 2 in Supplement 2), it becomes evident that causes of cerebral injury are multifactorial and that the embolic risk does not resolve immediately at the end of the TAVI procedure.[12] However, despite the delayed appearance and multifactorial etiology of neurological events after TAVI, potentially diluting the treatment effect of the filter, the difference between the filter and the control groups with regard to the primary MRI end point was notable, underlining the value of cerebral filter protection to prevent brain injury during TAVI.

## Effect of Filter Protection on Neurological Outcome

Data from RCTs suggest that the rate of neurological impairment shortly after TAVI can be greater than 5%.[1,5,6] The results of the DeNOVO study indicate that neurological events may be detected much more frequently (≤17% of patients) when the assessment is prospectively performed by skilled personnel.[7] The DeNOVO study included prospective neurologist assessments as well as MRI, which was important to confirm whether minor or transient symptoms were strokes.[7] Another finding of DeNOVO was that larger lesions were more likely to be symptomatic.[7] In the current study, applying prospective assessment by NIHSS-certified personnel, symptoms indicative of stroke were found in 5 patients in each group (10% of the entire study cohort). However, this study was not powered to assess differences in stroke rates between groups. In this study, symptoms were mild and none of the strokes were major or disabling.

Based on DWMRI findings, numerous patients had cerebral lesions consistent with infarcts in the absence of obvious functional impairments. A clear association between the total volume of cerebral lesions and the occurrence of neurological symptoms has previously been shown, but the long-term effect of subclinical brain lesions after TAVI is yet unknown.[8-11] Data from other settings suggest that the presence of subclinical brain infarcts is associated with several adverse neurological and cognitive consequences and precedes the occurrence of major stroke.[12,21,22] However, this association has not yet been shown for procedural subclinical infarcts, and further studies are necessary to address this issue.

The NIHSS and the modified Rankin Scale were used to assess neurological function before and after the intervention and revealed no obvious differences between the filter and control groups. However, a comprehensive assessment should also focus on neurocognitive function. Therefore, additional research is required to specifically define end points that reliably describe neurocognitive function before and after TAVI.

### Technical Procedural Aspects and the Cerebral Protection Device in Perspective: Comparison With Other Devices Designed to Protect the Brain

In addition to the cerebral protection device used in this study, there are other protection devices that have received the CE mark (Conformité Européene [indicates European conformity]) in Europe. However, the results of recent studies evaluating their effect on brain injury are conflicting.[14,15] Data from a recent hypothesis-generating trial (N=85 patients) indicated lower absolute volume of cerebral lesions after TAVI in patients whose brain had been protected with the deflector type Triguard (Keystone Heart) device compared with control patients, but this did not reach statistical significance.[15] In addition, the study failed to demonstrate any difference in the number of DWMRI perfused lesions between the control and the deflector-protected groups of the study. Another recent study using the Embrella device (Edwards Lifesciences) also failed to elucidate any protective effect.[14] Data from other rigorous, hypothesis-driven, RCTs like the CLEAN-TAVI study are missing. Therefore, it is currently unclear whether other types of cerebral protection devices (ie, deflectors) protect the brain and downstream organs as well as filter-based devices, which capture and remove the embolic debris.

The procedural time was 18 minutes longer in the cerebral protection device group compared with the control group because of the additional time required to obtain arterial access on the right arm for device positioning and filter deployment, as well as filter recapture and device removal. However, to understand the ease of use in the general patient population undergoing TAVI, complex anatomical cases were not excluded from this study. Despite overall good device performance, several procedures involving particularly complex anatomical situations with excessive kinking of the brachiocephalic artery or an elongated left common carotid artery were challenging and more time consuming and account for the longer procedure times. Nevertheless, over the course of the study period, a decline in deployment time was observed. It may therefore be extrapolated that with increased operator experience, in conjunction with device refinements, it may be possible to achieve procedural times almost as short as in the control group.

### Limitations

This was a single-center study, which used only 1 of the various available TAVI devices in all patients. All of the procedures were performed by the same experienced heart team to eliminate the potential bias of a procedural learning curve. Therefore, the results cannot be necessarily generalized to a broader patient population, other transcatheter heart valves, or a multicenter setting. In our proof-of-concept study, we considered a 50% reduction in new lesion number between the 2 groups a success; however, the clinical relevance of this reduction in an imaging marker of brain injury is uncertain and requires further studies. Moreover, apart from the primary MRI end point, all other findings, particularly the neurological and neurocognitive outcome measures, can only be considered hypothesis generating, especially because these were not performed by a neurologist and no routine neurological assessment was performed at 3- month follow-up. In addition, we cannot rule out the possibility that the use of 1.5T-MRI follow-up in some patients affected results, although it appears to be unlikely.

The fact that this cerebral protection device does not protect the left vertebral circulation is a limitation, but at the time of the study design, this cerebral protection device was the only device available. Knowing the shortcomings of the device, the primary focus of the study was a brain region most likely not influenced by emboli originating from the left vertebral artery circulation, in order to understand if cerebral protection could work. In the filter group, a protective effect on MRI parameters was detectable for the entire brain despite the current device limitations. Nevertheless, from a clinician's point of view, device refinement, enabling complete cerebral protection, is required.

Furthermore, because of the nature of the procedure, the interventional team could not be blinded. Therefore, it is possible that differences in the management of the control group vs the filter group during the TAVI procedure might have affected the results. Nevertheless, all procedures were conducted following standard procedural rules defined for TAVI at our institution, reducing the likelihood of any such effect.

## Conclusions

Among patients with severe aortic stenosis undergoing TAVI, the use of a cerebral protection device reduced the frequency of ischemic cerebral lesions in potentially protected regions. Larger studies are needed to assess the effect of cerebral protection device use on neurological and cognitive function after TAVI and to devise methods providing more complete coverage of the brain to prevent new lesions.

ARTICLE INFORMATION

**Author Contributions:** Drs Linke and Haussig had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
*Concept and design:* Haussig, Lehmkuhl, Luecke, Woitek, Zivadinov, Schuler, Linke.
*Acquisition, analysis, or interpretation of data:* All Authors.
*Drafting of the manuscript:* Haussig, Dwyer, Luecke, Linke.
*Critical revision of the manuscript for important intellectual content:* All Authors.
*Statistical analysis:* Haussig, Woitek, Linke.
*Obtaining funding:* Linke.
*Administrative, technical, or material support:* Mangner, Dwyer, Lehmkuhl, Luecke, Woitek, Holzhey, Gutberlet, Linke.
*Study supervision:* Haussig, Lehmkuhl, Luecke, Mohr, Zivadinov, Schuler, Linke.

**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Dwyer reports receipt of grants from Claret Medical during the conduct of the study; grants from Novartis; personal fees from EMD Serono and Novartis outside the submitted work. Dr Holzhey reports receipt of personal fees from Symetis during the conduct of the study. Dr Gutberlet reports having a research agreement with Siemens Healthcare and receipt of a moderate lecture honorarium from Bayer, Bracco, Philips, and Siemens. Dr Zivadinov reports receipt of grants and personal fees from Claret Medical during the

conduct of the study; personal compensation from Teva Pharmaceuticals, Biogen Idec, EMD Serono, Genzyme-Sanofi, Claret Medical, IMS Health, and Novartis for speaking and consultant fees; financial support for research activities from Teva Pharmaceuticals, Genzyme-Sanofi, Novartis, Claret Medical, Intekrin, and IMS Health; serving on the editorial boards of *Journal of Alzheimer's Disease*, *BMC Medicine*, *BMC Neurology*, *Vein and Lymphatics*, and *Clinical CNS Drugs*; and being the executive director and treasurer of the International Society for Neurovascular Disease outside the submitted work. Dr Linke reports receipt of speaker honoraria or serving as a consultant for Medtronic, St Jude Medical, Claret Medical, Boston Scientific, Edwards Lifesciences, Symetis, and Bard; and ownership of stock options from Claret Medical. Drs Haussig, Mangner, Lehmkuhl, Lücke, Woitek, Mohr, and Schuler report no disclosures.

**Funding/Support:** The Leipzig Heart Center received a grant from Claret Medical and Medtronic.

**Role of the Funder/Sponsor:** Claret Medical and Medtronic had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

## REFERENCES

**1**. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363(17):1597-1607.

**2**. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;370(19):1790-1798.

**3**. Linke A, Wenaweser P, Gerckens U, et al. Treatment of aortic stenosis with a self-expanding transcatheter valve. *Eur Heart J*. 2014;35(38):2672-2684.

**4**. Ludman PF, Moat N, de Belder MA, et al. Transcatheter aortic valve implantation in the United Kingdom: temporal trends, predictors of outcome, and 6-year follow-up: a report from the UK Transcatheter Aortic Valve Implantation (TAVI) Registry, 2007 to 2012. *Circulation*. 2015;131(13):1181-1190.

**5**. Miller DC, Blackstone EH, Mack MJ, et al. Transcatheter (TAVR) versus surgical (AVR) aortic valve replacement: occurrence, hazard, risk factors, and consequences of neurologic events in the PARTNER trial. *J Thorac Cardiovasc Surg*. 2012;143(4):832-843.e13.

**6**. Généreux P, Head SJ, Van Mieghem NM, et al. Clinical outcomes after transcatheter aortic valve replacement using valve academic research consortium definitions. *J Am Coll Cardiol*. 2012;59(25):2317-2326.

**7**. Messé SR, Acker MA, Kasner SE, et al. Stroke after aortic valve surgery. *Circulation*. 2014;129(22):2253-2261.

**8**. Kahlert P, Knipp SC, Schlamann M, et al. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation. *Circulation*. 2010;121(7):870-878.

**9**. Ghanem A, Müller A, Nähle CP, et al. Risk and fate of cerebral embolism after transfemoral aortic valve implantation. *J Am Coll Cardiol*. 2010;55(14):1427-1432.

**10**. Fairbairn TA, Mather AN, Bijsterveld P, et al. Diffusion-weighted MRI determined cerebral embolic infarction following transcatheter aortic valve implantation. *Heart*. 2012;98(1):18-23.

**11**. Astarci P, Glineur D, Kefer J, et al. Magnetic resonance imaging evaluation of cerebral embolization during percutaneous aortic valve implantation. *Eur J Cardiothorac Surg*. 2011;40(2):475-479.

**12**. Van Mieghem NM, Schipper MEI, Ladich E, et al. Histopathology of embolic debris captured during transcatheter aortic valve replacement. *Circulation*. 2013;127(22):2194-2201.

**13**. Naber CK, Ghanem A, Abizaid AA, et al. First-in-man use of a novel embolic protection device for patients undergoing transcatheter aortic valve implantation. *EuroIntervention*. 2012;8(1):43-50.

**14**. Rodés-Cabau J, Kahlert P, Neumann F-J, et al. Feasibility and exploratory efficacy evaluation of the Embrella Embolic Deflector system for the prevention of cerebral emboli in patients undergoing transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. 2014;7(10):1146-1155.

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

**16**. Hartkamp NS, De Cocker LJ, Helle M, et al. In vivo visualization of the PICA perfusion territory with super-selective pseudo-continuous arterial spin labeling MRI. *Neuroimage*. 2013;83:58-65.

**17**. Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Med Image Anal*. 2001;5(2):143-156.

**18**. Jezzard P, Balaban RS. Correction for geometric distortion in echo planar images from B0 field variations. *Magn Reson Med*. 1995;34(1):65-73.

**19**. Tay ELW, Gurvitch R, Wijesinghe N, et al. A high-risk period for cerebrovascular events exists after transcatheter aortic valve implantation. *JACC Cardiovasc Interv*. 2011;4(12):1290-1297.

**20**. Amat-Santos IJ, Rodés-Cabau J, Urena M, et al. Incidence, predictive factors, and prognostic value of new-onset atrial fibrillation following transcatheter aortic valve implantation. *J Am Coll Cardiol*. 2012;59(2):178-188.

**21**. van Rooij FG, Schaapsmeerders P, Maaijwee NAM, et al. Persistent cognitive impairment after transient ischemic attack. *Stroke*. 2014;45(8):2270-2274.

**22**. Goldberg I, Auriel E, Russell D, Korczyn AD. Microembolism, silent brain infarcts and dementia. *J Neurol Sci*. 2012;322(1-2):250-253.