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

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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 mm³ [95% CI, 159-353]) vs in the control group (527 mm³ [95% CI, 364-830]) (difference, 234 mm³ [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.

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T
ransectherapeuticavalveimplantation(TAVI)usingthe
balloon-expandableSAPIENvalvehasbeenshown
tobe superior to standard medical therapy in inoperable
patients. 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. However, although the clinical
outcomes of TAVI have improved considerably during the last
decade, stroke, which is associated with a 3-fold increase
in mortality following SAVR or TAVI, remains an important
concern. Adding to this concern is the observation that is-
chemic lesions, as determined by diffusion-weighted mag-
netic resonance imaging (DWMRI), are found in as many as 80%
of TAVI patients.

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

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 eli-
gible 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 brachio-
cephalic trunk, and the left common carotid artery. Exclusion
criteria were an anatomy unsuitable for a safe TAVI, preexist-
ing 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 filtra-
tion rate [GFR]<30 mL/min/1.73 m² 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 enve-
lopes. 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 en-
sure blinding of the core laboratory.

Study Procedures

TAVI Treatment
Patients were randomized in a 1:1 ratio to undergo transfemo-
oral 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. Briefly, the proximal filter was deployed in the
brachiocephalic trunk, covering all areas of the brain sup-
plied by the right vertebral and carotid arteries; the distal fil-
ter 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.

Meaning
Among patients with severe aortic stenosis undergoing
TAVI, the use of a cerebral protection device reduced the frequency of ischemic brain lesions in potentially protected
regions.
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. 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 (Interia 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. 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 postprocedure DWI MRI 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 postprocedure DWI MRI–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 DWI MRI lesions after TAVI was reported as 5.9 (6.8) by Astarci et al and in a separate study as 4.2 (6.5) by Fairbairn et al. However, Astarci et al used 3T-MRI infrequently, and all MRIs in the study by Fairbairn et al 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 DWI–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 1 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 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 χ2 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 samples
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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Filter Group (n = 50)</th>
<th>Control Group (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>80.0 (5.1)</td>
<td>79.3 (4.1)</td>
</tr>
<tr>
<td>Female sex</td>
<td>29 (58)</td>
<td>28 (56)</td>
</tr>
<tr>
<td>New York Heart Association class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>5 (10)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>II</td>
<td>13 (26)</td>
<td>13 (26)</td>
</tr>
<tr>
<td>III</td>
<td>23 (46)</td>
<td>29 (58)</td>
</tr>
<tr>
<td>IV</td>
<td>9 (18)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>STS PROM estimate, mean (SD), %</td>
<td>5.6 (3.2)</td>
<td>5.2 (2.7)</td>
</tr>
<tr>
<td>STS PROM by risk level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4%</td>
<td>19 (38)</td>
<td>20 (40)</td>
</tr>
<tr>
<td>4%-10%</td>
<td>24 (48)</td>
<td>26 (52)</td>
</tr>
<tr>
<td>&gt;10%</td>
<td>7 (14)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Logistic EuroSCORE, mean (SD), %</td>
<td>16.4 (10.0)</td>
<td>14.5 (8.7)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>20 (40)</td>
<td>25 (50)</td>
</tr>
<tr>
<td>Controlled by insulin</td>
<td>5 (10)</td>
<td>15 (30)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 2, GFR 60-89</td>
<td>20 (40)</td>
<td>28 (56)</td>
</tr>
<tr>
<td>Stage 3, GFR 30-59</td>
<td>23 (46)</td>
<td>11 (22)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>44 (88)</td>
<td>47 (94)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2 (4)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Prior stroke or transient ischemic attack</td>
<td>1 (2)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Cardiac risk factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>26 (52)</td>
<td>25 (50)</td>
</tr>
<tr>
<td>Prior coronary artery bypass surgery</td>
<td>8 (16)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Prior percutaneous coronary intervention</td>
<td>5 (10)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Preexisting pacemaker or defibrillator</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>6 (12)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>46 (92)</td>
<td>46 (92)</td>
</tr>
<tr>
<td>Prior atrial fibrillation or flutter</td>
<td>17 (34)</td>
<td>17 (34)</td>
</tr>
<tr>
<td>MRI No. of lesions at baseline, median (IQR) [range], mm³</td>
<td>0 (0-1) [0-5]</td>
<td>0 (0-1) [0-5]</td>
</tr>
<tr>
<td>MRI lesion volume at baseline, (95% CI), [range], mm³</td>
<td>0 (0-36) [0-7604]</td>
<td>0 (0-0) [0-615]</td>
</tr>
</tbody>
</table>

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

* Data are reported as No. (%) unless otherwise stated.

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

‡ 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).

§ GFR was calculated as mL/min/1.73 m². There were no patients with stage 4 (GFR 15-29) or stage 5 (GFR<15 or dialysis) chronic kidney disease in 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, because of wire perforation of the left ventricle that could not solely be solved by pericardiotomy 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 mm³ (95% CI, 159-353) vs 527 mm³ (95% CI, 364-830), difference 234 mm³ (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 4.00 (IQR 2.00-5.00), P = .003. Likewise, at 7 days, new lesion volume in the potentially protected areas was lower in the filter group, 101 mm³ (95% CI, 60-174) vs 292 mm³ (95% CI, 181-515), difference 160 mm³ (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 mm³ (95% CI, 349-711) compared with 800 mm³ (95% CI, 594-1409), difference 314 mm³ (95% CI, 66-580), P = .02, 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 compared with the control group and hence, the findings of the modified intention-to-treat analysis eTable 7 in Supplement 2).
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 in the control group, the number of DW-MRI-positive brain 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 ever, 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 DW-MRI in a nonrandomized fashion.6-11 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 DW-MRI-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...
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

<table>
<thead>
<tr>
<th></th>
<th>Potentially Protected Areas</th>
<th>Partially Protected Areas</th>
<th>Entire Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 Days</td>
<td>7 Days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Filter (n = 49)</td>
<td>Control (n = 45)</td>
<td>Difference</td>
</tr>
<tr>
<td></td>
<td>(IQR)</td>
<td>(IQR)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>No. of new lesions, median</td>
<td>4.00 (3.00-7.25)</td>
<td>10.00 (6.75-17.00)</td>
<td>5.00 (2.00-8.00)</td>
</tr>
<tr>
<td></td>
<td>(IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of new lesions, median (95% CI), mm$^3$</td>
<td>242 (159-353)</td>
<td>527 (364-830)</td>
<td>234 (91-406)</td>
</tr>
<tr>
<td></td>
<td>(IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of new lesions, median (IQR)</td>
<td>2.00 (1.00-3.25)</td>
<td>2.00 (1.00-3.00)</td>
<td>1.00 (0.00-3.00)</td>
</tr>
<tr>
<td>Volume of new lesions, median (95% CI), mm$^3$</td>
<td>113 (72-164)</td>
<td>247 (147-399)</td>
<td>98 (18-194)</td>
</tr>
<tr>
<td></td>
<td>8.00 (5.00-12.00)</td>
<td>16.00 (9.75-24.25)</td>
<td>6.00 (3.00-10.00)</td>
</tr>
<tr>
<td>Volume of new lesions, median (95% CI), mm$^3$</td>
<td>466 (349-711)</td>
<td>800 (594-1407)</td>
<td>311 (66-580)</td>
</tr>
<tr>
<td></td>
<td>205 (115-338)</td>
<td>472 (385-909)</td>
<td>240 (51-393)</td>
</tr>
<tr>
<td></td>
<td>101 (60-174)</td>
<td>292 (181-515)</td>
<td>160 (57-281)</td>
</tr>
<tr>
<td></td>
<td>(IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>(1.00-5.25)</td>
<td>(2.00-3.00)</td>
<td>1.00 (0.00-2.00)</td>
</tr>
<tr>
<td></td>
<td>(IQR)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| * Differences calculated as independent samples Hodges-Lehmann median difference estimates.
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 Européenne [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.
Cerebral Protection Device Effects on Brain Lesions After TAVI

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patients who cannot undergo surgery.

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