New Brain Lesions After Carotid Stenting Versus Carotid Endarterectomy
A Systematic Review of the Literature

Sonja Schnaudigel, MD; Klaus Gröschel, MD; Sara M. Pilgram, MD; Andreas Kastrup, MD

Background and Purpose—Against the background of a relatively low rate of clinical events during carotid angioplasty and stenting (CAS) or carotid endarterectomy (CEA), diffusion-weighted imaging (DWI) is increasingly being used to compare the incidence of new ischemic lesions after both procedures. In addition, DWI may also provide a means of defining the role of different CAS techniques on this adverse outcome. Therefore, we performed a PubMed search and systematically analyzed all peer-reviewed studies published between January 1990 and June 2007 reporting on the occurrence of new DWI lesions after CAS or CEA.

Summary of Review—In 32 studies comprising 1363 CAS and 754 CEA procedures, the incidence of any new DWI lesion was significantly higher after CAS (37%) than after CEA (10%) (P<0.01). Similar results were obtained in a meta-analysis focusing on those studies directly comparing the incidence of new DWI lesions after either CEA or CAS (OR, 6.1; 95% CI, 4.19 to 8.87; P<0.01). The use of cerebral protection devices (33% vs 45% without; P<0.01) and closed-cell designed stents during CAS (31% vs 51% with open-cell stents; P<0.01), as well as selective versus routine shunt usage during CEA (6% vs 16%; P<0.01) significantly reduced the incidence of new ipsilateral DWI lesions.

Conclusions—New DWI lesions occur more frequently after CAS than after CEA. However, technical advances mainly in the field of endovascular therapy potentially reduce the incidence of these adverse ischemic events. In this scenario, DWI appears to be an ideal tool to compare and further improve both techniques. (Stroke. 2008;39:1911-1919.)

Key Words: carotid  diffusion-weighted imaging stent  embolism  endarterectomy

Atherosclerotic stenosis of the extracranial carotid artery is a major cause of disabling stroke or death; therefore, it constitutes a huge medical, social, and economic problem. Carotid endarterectomy (CEA) was first performed in 1954 to prevent imminent stroke, and its effectiveness in preventing stroke has subsequently been proven in several prospective randomized clinical trials comparing CEA to best medical treatment in patients with both symptomatic and asymptomatic carotid stenosis.1–4 Therefore, it is currently considered to be the standard of care for the primary and secondary prevention of stroke related to carotid artery stenosis.5 In the past few years, however, carotid angioplasty and stenting (CAS) is increasingly used in place of CEA. Although some recent large case-series, industry-sponsored registries, and randomized trials have indicated that CAS can be performed with acceptable complications rates,6–8 a high incidence of emboli shed to the brain has generated great concern regarding the safety of this technique, especially when considering the established low risk and durability of CEA. In fact, higher embolization rates during CAS compared to surgery have been reported using either transcranial Doppler sonography to monitor microembolic events or applying diffusion-weighted imaging (DWI) to detect new embolic brain lesions after the intervention.9–11

However, CAS is a rapidly evolving technique and advances in the technique such as the use of embolic protection devices could significantly reduce the rate of adverse events. In addition, it is increasingly being realized that the design of the stent—closed-cell versus open-cell—might also influence the results.12 Because of the relatively small number of clinical events after CEA and CAS (≈6% to 7% within 30 days according to a recent multi-center trial13), large patient groups are essential for a reliable comparison of the 2 techniques, thereby possibly overlooking rapid technological advances that take place in the meantime. Therefore, DWI is increasingly being used as a surrogate marker for stroke.10 This technique not only may provide a means to detect and compare the incidence of clinically silent emboli during both procedures but also presents an ideal tool to define the role of different CAS techniques on outcome.

Therefore, the goals of this study were: (1) to systematically search for all reports dealing with DWI to detect embolic lesions after either CAS or CEA; (2) to compare the incidence of new DWI lesions between these 2 procedures;
and (3) to analyze the potential influence of procedural variables on the incidence of new DWI lesions after CAS or CEA.

Materials and Methods

Search Strategy

Two independent observers (S.S. and K.G.) performed an electronic literature search with Entrez PubMed NIH. A combination of key words including carotid, artery, stenosis, angioplasty, stent, stenting, cerebral protection, (thromb)endarterectomy, ischemic lesion, cerebral embolism, peri-procedural, MRI, and diffusion-weighted imaging was used to extract all relevant abstracts. Studies were included if published between January 1990 (first publication of diffusion-weighted MR imaging for the detection of cerebral ischemia) and June 2007 inclusive. The abstract of each article was carefully studied to detect appropriate publications; if there was any suggestion of the data we looked for, then the full text was retrieved. Furthermore, all reference sections of these articles were checked for further leads.

Eligibility Studies

Studies were included if the following criteria were fulfilled: (1) they were written in English; (2) DWI had been performed in all patients before (within 1 to 2 days) CEA or CAS and within 72 hours after the procedure; and (3) the follow-up imaging was systematic and not just in case of complications. Articles were excluded if only angioplasty without stent placement had been performed. Editorials, letters, case reports, and reviews were also excluded. In case of multiple publications from the same study population, we used the most recent publication.

Data Extraction

For all studies the following data were extracted independently by 2 observers (S.S. and K.G.) by use of a predefined electronic data sheet: (1) year of publication, number of patients or treated arteries; (2) patient characteristics: age, sex, medical risk factors, angiographic risk factors (such as contralateral stenosis/occlusion, degree of stenosis, or presence of ulceration), symptomatic or asymptomatic carotid artery disease; (3) procedural characteristics of CAS (including type of stent, use of protection devices) and of CEA (type of anesthesia and surgery, usage of shunts); (4) peri-procedural complication rates within 30 days: any cerebral or retinal event lasting >24 hours or death of any cause; (5) number of patients/procedures with any new DWI lesion after CAS and CEA; and (6) number of patients/procedures with any new DWI lesion within or outside the territory of the treated artery after CEA or CAS (these data were only included if a clear description of lesion location was given). If patients with lesions both inside and outside the territory were reviewed, then they were added to both types of new DWI lesions.

Statistical Analysis

For comparisons of categorical data 2-tailed \( \chi^2 \) statistics with Yates correction were used. A value of \( P<0.05 \) was considered to indicate a statistically significant difference. A meta-analysis in a subgroup of 6 studies directly comparing CEA and CAS was performed applying Peto odds ratio. All statistical analyses were performed using SPSS (Version 13; SPSS Inc).

Results

Studies

Our electronic literature search with Entrez PubMed NIH resulted in 42 abstracts for which full text articles were retrieved. Thirty-two studies fulfilled all inclusion criteria and were therefore used for further analysis: 17 CAS studies, and 9 CEA studies. The reasons for exclusion of the remaining 9 articles were as follows: (1) DWI was not performed systematically in all patients before and after CEA or CAS; (2) they were written in Spanish, or (3) they reported on patients already used in other publications from the same institution.

The main characteristics of the studies included in this analysis are summarized in Tables 1 and 2. The total number of patients in the CEA studies was 754, and that in the CAS studies totaled 1363, yielding a group of 2117 patients undergoing review. Of those, six studies directly comparing CEA (356 procedures) and CAS (264 procedures) could additionally be included in the meta-analysis.

Clinical and MRI Results

The percentage of symptomatic stenoses treated was comparable between the 2 groups: 59% for CAS and 61% for CEA patients (\( P=0.33 \)). Patient age could not be statistically analyzed because in the majority of studies it was given as mean, median, or range only.

The combined stroke and death rate within 30 days was 2.12% in patients treated with CAS compared with 3.45% in patients treated with CEA (\( P=0.085 \)). Even in those studies included in the subgroup for the meta-analysis, the rate for any new cerebral or retinal event or death of any cause was not significantly different between the 2 treatment groups, albeit still indicating a trend toward a higher neurological complication rate after CAS (OR, 2.03; 95% CI, 0.88 to 4.66; \( P=0.096 \); Figure 1). In contrast to these nonsignificantly different clinical complication rates, the incidence of any new DWI lesion (including the combined incidence of patients with new lesions both ipsilateral and contralateral to the treated artery) was significantly higher after CAS (37%) than after CEA (10%) (\( P<0.01 \)). Similar results were obtained in a meta-analysis focusing on those single center studies that directly compared the incidence of new DWI lesions after either CEA or CAS (OR, 6.1; 95% CI, 4.19 to 8.87; \( P<0.01 \); Figure 2).

Differential information about new DWI lesions within or outside the treated artery territory was given for 68% of all CAS and 71% of all CEA procedures. The incidence of new ischemic lesions outside (0.01% in CEA vs 14.5% in CAS; \( P<0.01 \)) and within the territory of the treated carotid artery (10.4% in CEA vs 35% in CAS; \( P<0.01 \)) was also significantly greater after the endovascular procedure.

Considering an effect of the status of stenosis, ie, asymptomatic versus symptomatic carotid stenosis, further details about the incidence of any new DWI lesions with respect to previous symptoms could be retrieved for 55.1% of all CEA and 46.3% of all CAS procedures. In CAS patients, new DWI lesions were found in 32.7% of initially symptomatic and 30.8% of asymptomatic patients (\( P=0.72 \)). After CEA the incidence of new DWI lesions was 14.3% in symptomatic and 8.6% in asymptomatic patients, respectively (\( P=0.13 \)).

Procedural Variables

Additional analyses were performed to identify the potential influence of procedural variables on the incidence of new DWI lesions after CAS and CEA. Only those studies in which
the incidence of new DWI lesions was differentiated into “inside” and “outside” of the treated artery territory could be included in this analysis. The assessed variables were: (1) the use of distal filter protection devices as opposed to no use of protection devices in CAS (excluding 1 study with the use of “balloon occlusion” devices29); (2) the type of stent used for CAS, differentiating between “open-cell” (Precise [Cordis, Miami Lakes, Fla] and Acculink [Guidant, Santa Clara, Calif]) and “closed-cell” (Carotid Wallstent [Boston Scientific Corp, Natick, Mass]) design for studies in which only either type of stent was used (560 procedures [41%] analyzed); and (3) the usage of shunts during CEA.

Among those 51% of all CAS procedures included in this analysis, the incidence of new ipsilateral DWI lesions was significantly higher in patients treated without cerebral protection (45%) than in those patients in whom cerebral protection devices had been used during CAS (33%; P<0.01; Figure 3). As expected, the use of cerebral protection devices during CAS had no effect on the incidence of new DWI lesions outside the vascular territory of the treated artery (14% with protection vs 13% without protection; P=0.6). The incidence of new ipsilateral DWI lesions after CAS was significantly higher in patients treated with open-cell designed stents than in patients treated with closed-cell designed stents (51% vs 31%; P<0.01; Figure 3).

Five hundred ten procedures of the CEA group were included and procedures with obligate shunting (45%) were compared to those with selective shunting (55%). A significantly higher incidence of new ipsilateral DWI lesions was found in procedures with obligate as opposed to selective shunt usage (16% vs 6%; P<0.01; Figure 3).

### Discussion

On the basis of a systematic review of the literature and a total of 2117 patients, we demonstrate that the incidence of any new DWI lesions is significantly higher after endovascular than after surgical treatment of a carotid stenosis. Moreover, our data indicate that the use of a cerebral protection device and a closed-cell stent in CAS as well as selective shunting during CEA significantly reduce the occurrence of new ipsilateral DWI lesions after carotid interventions.

CAS is currently being evaluated as a treatment alternative to CEA. Whereas initial single-center case series and registries have reported acceptable periprocedural complication

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Procedures, N</th>
<th>Age, yr</th>
<th>Symptomatic Stenoses, N</th>
<th>Any New Stroke, N</th>
<th>Within Treated Artery Territory</th>
<th>Outside Treated Artery Territory</th>
<th>Any New DWI Lesions</th>
<th>Details About Anesthesia, Surgical Procedure, and Shunt Usage</th>
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<td>GA; selective shunting</td>
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<tr>
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<td>38</td>
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<td>7</td>
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<tr>
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<td>66.7 (±7); range, 46–83</td>
<td>32</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
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<td>1</td>
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<td>0</td>
<td>0</td>
<td>GA; 1 shunt</td>
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<td>68</td>
<td>33</td>
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<td>6</td>
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<td>No-touch CEA; shunting in all</td>
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<td>33</td>
<td>67 (±8)</td>
<td>22</td>
<td>1</td>
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<td>GA; shunting in all</td>
</tr>
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<td>Poppert41</td>
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<td>69; range, 45–84 (whole group)</td>
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<tr>
<td>Iihara44</td>
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<td>68.1 (±6.9); range, 43–82</td>
<td>92</td>
<td>3</td>
<td>NG</td>
<td>NG</td>
<td>13</td>
<td>GA; selective shunting</td>
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<td>70.1 (±7)</td>
<td>32</td>
<td>1</td>
<td>NG</td>
<td>NG</td>
<td>3</td>
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</tr>
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<td>GA; shunting in all; standard CEA</td>
</tr>
<tr>
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<td>20</td>
<td>Median, 64</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>GA; selective shunting</td>
</tr>
</tbody>
</table>

*Age given as mean (±SD) unless otherwise stated.

GA indicates general anesthesia; LA, local anesthesia; NG, not given.

- Table 1. Carotid Endarterectomy

rates after CAS even in surgical high-risk patients. Recent randomized trials directly comparing CAS with CEA have produced conflicting results. The initially promising results of the SAPPHIRE study could not be reproduced in SPACE. A noninferiority of CAS as opposed to CEA could not be proven in this biggest randomized trial to date yielding complication rates of 6.34% in CEA and 6.84% in CAS, respectively ($P < 0.09$). Even higher complication rates after CAS were found in the recently published EVA-3S trial, which lead to a premature termination of the study.

### Table 2. Carotid Artery Stenting

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Procedures, N</th>
<th>Age, * yr</th>
<th>Symptomatic Stenoses, N</th>
<th>New Stroke, N</th>
<th>New DWI Lesions, N</th>
<th>Within Treated Artery Territory</th>
<th>Outside Treated Artery Territory</th>
<th>Use of Distal Filter Protection Devices</th>
<th>Type of Stent Used</th>
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<tr>
<td>Lövblad</td>
<td>2000</td>
<td>19</td>
<td>Range, 43–83</td>
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<td>NG</td>
<td>NG</td>
<td>4</td>
<td>Without</td>
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<tr>
<td>Jaeger</td>
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<td>20</td>
<td>66.5; range, 58–77</td>
<td>13</td>
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<td>3</td>
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<td>5</td>
<td>16 with, 4 without</td>
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<td>Schluter</td>
<td>2003</td>
<td>44</td>
<td>67; range, 44–66</td>
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<td>8</td>
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<td>10</td>
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<td>Both</td>
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<tr>
<td>Gauvrit</td>
<td>2004</td>
<td>22</td>
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<td>0</td>
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<td>2</td>
<td>9</td>
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<td>Both</td>
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<td>22</td>
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<td>n.g.</td>
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<td>16</td>
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<td>Hammer</td>
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<td>13</td>
<td>21</td>
<td>With</td>
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<td>22</td>
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<td>du Mesnil de Rochemont</td>
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<td>Maleux</td>
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<td>8</td>
<td>n.g.</td>
<td>n.g.</td>
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<td>95 with, 12 without</td>
<td>NG</td>
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<td>Pinero</td>
<td>2006</td>
<td>162</td>
<td>68.5; range, 33–86</td>
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<td>NG</td>
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<td>Balloon occlusion in postdilatation phase in 74, 18 with filter protection</td>
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<td>10</td>
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<td>3</td>
<td>1</td>
<td>4</td>
<td>With</td>
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<tr>
<td>Rapp</td>
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<td>71; range, 59–83</td>
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<td>Lacroix</td>
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<td>61</td>
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<td>10</td>
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<td>Tedesco</td>
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<td>10</td>
<td>19</td>
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*Age given as mean (±SD) unless otherwise stated.
ECA indicates external carotid artery; ICA, internal carotid artery.
Therefore, an uncritical, widespread use of CAS does not seem to be justified at this time and continuous efforts are needed to optimize this technique. The major risk for both CEA and CAS appears to be the possibility of periprocedural embolic strokes attributable to release of debris during surgical or endovascular manipulation and subsequent distal embolization into the cerebral vasculature.

For those studies included in this review there was a trend toward higher clinically evident periprocedural neurological complication rates in patients treated with CAS compared to those treated with CEA. Although this finding alludes to an increased procedural risk associated with CAS, it is also well perceivable that more adverse events were detected because of a critical scrutiny for this new technique.

In general, it is noteworthy that the 30-day stroke and death rates (2.12% for CEA and 3.45% for CAS) were much lower than the 30-day complication rates observed in a recent large multicenter trial, which likely reflects the lack of a standardized postprocedural neurological assessment in several of these studies and the inclusion of asymptomatic patients.

Patients submitted to CAS had a significantly higher incidence of new DWI lesions (on average 37%) than patients treated with CEA (on average 10%). This significantly higher incidence points to an increased risk of periprocedural embolism during CAS as opposed to CEA. Although it is beyond doubt that this finding is largely related to the manipulation of catheters, guidewires, and sheaths in the supra-aortic vasculature, it may also be the consequence of a diagnostic angiography, which is usually performed before CAS. Bendzus et al, for instance, detected new DWI lesions in 23 of 100 patients undergoing consecutive diagnostic cerebral angiographies.

When comparing CAS with CEA, it has to be stressed that major technological advances in the field of CAS have occurred in the past few years. Most importantly, there has been a widespread introduction of cerebral protection devices aimed at reducing the passage of embolic material into the cerebral vasculature. Although no randomized study has been conducted as yet to investigate the clinical efficacy of distal protection devices, several case series and stent registries clearly support this concept.

### Table 1: Meta-analysis of the incidence of any new DWI lesion in 6 studies directly comparing CAS with CEA.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>CAS [n/N]</th>
<th>CEA [n/N]</th>
<th>Peto odds ratio</th>
<th>Weight [%]</th>
<th>Odds ratio (with 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poppert</td>
<td>2004</td>
<td>2/41</td>
<td>2/88</td>
<td></td>
<td>15.25%</td>
<td>2.36 (0.28-19.89)</td>
</tr>
<tr>
<td>Flach</td>
<td>2005</td>
<td>1/21</td>
<td>2/23</td>
<td></td>
<td>12.86%</td>
<td>0.55 (0.05-5.56)</td>
</tr>
<tr>
<td>Roh</td>
<td>2005</td>
<td>2/22</td>
<td>1/26</td>
<td></td>
<td>12.85%</td>
<td>2.40 (0.24-24.47)</td>
</tr>
<tr>
<td>Iihara</td>
<td>2006</td>
<td>7/92</td>
<td>3/139</td>
<td></td>
<td>41.48%</td>
<td>3.71 (1.02-13.49)</td>
</tr>
<tr>
<td>Lacroix</td>
<td>2007</td>
<td>2/61</td>
<td>2/60</td>
<td></td>
<td>17.56%</td>
<td>0.98 (0.14-7.16)</td>
</tr>
<tr>
<td>Combined Effect:</td>
<td></td>
<td>14/237</td>
<td>10/336</td>
<td></td>
<td>100%</td>
<td>2.03 (0.88-4.66)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: \( \chi^2 = 2.62; \) df = 4; \( p = 0.62 \)
Test for overall effect: \( z = 1.66; \) \( p = 0.096 \)

![Figure 1](http://stroke.ahajournals.org/)

Figure 1. Meta-analysis of the incidence of any new stroke or death within 30 days in those 6 studies directly comparing CAS and CEA. Please note that one of the studies was excluded from the analysis because no neurological events occurred.
In line with this finding, the use of cerebral protection devices appears to significantly reduce the number of new ipsilateral DWI lesions after CAS. However, ≈33% of patients had new DWI lesions within the vascular territory of the treated carotid artery even after protected CAS, which documents that dislodgement of a large number of embolic particles to the brain is not prevented by the use of filter-type protection devices.

Aside from the use of cerebral protection devices, our data clearly indicate that the use of closed-cell stents is associated with a significantly lower incidence of new ipsilateral DWI lesions than the use of open-cell designed stents. This finding could be related to the greater potential of closed-cell stents at preventing continuous embolization attributable to further small particles breaking off the fractured plaque into the blood system and subsequently into the brain. In support of this notion, the use of stents with a closed-cell design was associated with lower periprocedural complication rates in a recent analysis of a dual-center CAS database of 701 consecutive CAS patients. Regarding the potential of an ongoing embolization even after the procedure from a damaged plaque as a result of the manipulation, another retrospective analysis of 3179 consecutive CAS patients could demonstrate a significantly greater rate of postprocedural neurological complications in patients treated with open-cell stents. Only 1 of the studies undergoing review included serial MRI measurements postprocedurally, and the authors found an increase in new DWI lesions depending on the time of scanning. Because of the different types of stents used in their study, no statement as to whether there is an association with the type of stent used can be made.

For CEA patients, a general use of intra-arterial shunts for the maintenance of cerebral perfusion during carotid artery clamping has been found to be associated with a significantly higher incidence of new ipsilateral DWI lesions as opposed to patients who selectively underwent shunting. To date, both the efficacy of shunting to reduce negative outcome after CEA and the form of intraoperative monitoring for the decision toward or against shunting are still an ongoing issue, and DWI imaging could possibly provide a means of monitoring the effects of shunting.

The main limitation of the studies undergoing review is the lack of a patient randomization to either CEA or CAS. With respect to the clinical outcome, which has been found to be fairly low in both groups as compared to large randomized trials, it may be argued that potentially less affected patients capable of serial MRI measurements were involved in the studies and may have resulted in a selection bias. Differences in patient follow-up and the profession of the investigator (neurologists, neuroradiologists, vascular surgeons) in addition to the self-reported manner of complication rates, which have been found to be less reliable, may also account for the low event rate. Regarding the completeness of the available data, differential information about lesion location either inside or outside the treated artery territory was only available for ≈70% of all procedures both in the CAS and the CEA group and could be used for further analysis. It is likely that the degree of stenosis significantly influences the incidence of new DWI lesions after both CEA and CAS. However, the degree of stenosis had been determined with different techniques (such as conventional angiography, MRA, CTA, duplex sonography) and classification schemes (ECST/NASCET or not mentioned) so that this variable could not be extracted reliably from the studies and therefore was not used for further analyses. Finally, different postprocedural time points of DWI scanning may partly explain the large range (9% to 70.3% for CAS and 0% to 27.27% for CEA) of the reported incidence of new DWI lesions.

To date, the impact of new DWI lesions after carotid interventions beyond that on manifest neurological complications remains elusive. Especially with regard to subtle neuropsychological alterations, the findings of a significantly greater amount of new DWI lesions after CAS is opposed to a comparable effect of carotid surgery or angioplasty on neuropsychological functions as reported in a substudy of CAVATAS.9 Because only angioplasty was performed in their study, the results may not be directly applicable to CAS patients and therefore have led to further studies testing neuropsychological functions after CAS. An evaluation of a possible relationship between cognitive changes and new DWI lesions has been performed in 1 of the studies undergoing review. In a group of 10 patients, 4 showed new DWI...
lesions after CAS. It remains unclear whether cognitive performance had changed in those 4 patients, but the authors report an overall improvement across the whole group in some of the cognitive domains tested. None of the CEA studies reported herein included neuropsychological testing. However, over the past decades, conflicting effects of CEA on cognition have been found and reviewed.67,68 So far, only 1 study has attempted at correlating cognitive changes with new DWI lesions, although not using preoperative and postoperative DWI.50 For a differentiation between the possible benefit of a restored cerebral perfusion that might result in an amelioration of cognitive performance as opposed to the potential harms of microembolic lesions that could lead to cognitive impairment, DWI might contribute to a further elucidation of the effects of carotid interventions on cognitive functions.

Conclusion

In summary, CAS as opposed to CEA was found to be associated with a significantly greater incidence of any new DWI lesion as well as new DWI lesions both inside and outside the treated artery territory. This greater amount of ischemic burden may be reflected by a higher percentage of neurological events in the CAS group, although not reaching statistical significance between the 2 groups. The use of closed-cell design stents and a general deployment of distal embolic protection devices in CAS, as well as a restriction to selective shunting only during CEA, can further reduce adverse events after carotid interventions. DWI has been found to be a valuable tool for the detection of differences between the 2 procedures and should be part of future studies, even in small patient groups, to allow for a comparison between the 2 methods and thereby optimize the technique and patient selection.

Sources of Funding

None.

Disclosure

Conflict of Interest: A.K. has received speaker honoraria from Boehringer Ingelheim. S.S., K.G., S.P. have no conflicts of interest to disclose.

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New Brain Lesions After Carotid Stenting Versus Carotid Endarterectomy: A Systematic Review of the Literature
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Stroke. 2008;39:1911-1919; originally published online April 3, 2008;
doi: 10.1161/STROKEAHA.107.500603

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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