Carotid artery stenting (CAS) has emerged as a less invasive potential alternative to carotid endarterectomy (CEA) in patients with symptomatic and asymptomatic high-grade carotid artery stenosis.1–4 A meta-analysis of randomized clinical trials comparing CAS and CEA revealed a higher risk of stroke or death after CAS than CEA at 30 days. At 1 year, however, the risk of stroke or death was comparable between both treatment modalities.5 Most of these trials had inadequate requirements in terms of endovascular expertise and the use of embolic protection devices (EPD).6 The Carotid Revascularization Endarterectomy versus Stenting Trial7 is the only randomized controlled trial of CAS patients with EPD compared with CEA. In this trial, death was not different; the rate of myocardial infarction was lower but the minor stroke rate was higher in the CAS group.

Subgroup analyses indicate that elderly patients may benefit from CEA, whereas younger patients and symptomatic patients with a contralateral carotid artery occlusion seem to perform better with CAS.8,9 Appropriate patient selection seems to be crucial to optimize patient’s outcome. We sought to identify those patients with a high risk of cerebral embolization during CAS by diffusion-weighted magnetic resonance imaging (DW-MRI), which is a sensitive tool in identifying cerebral emboli during CAS.9–11 The aim of the present study was to evaluate the risk factors for ipsilateral and contralateral new ischemic lesions, as assessed by DW-MRI, during CAS with cerebral embolic protection in a large cohort of consecutive patients.

**Methods**

**Study Population**

From February 2001 to December 2010, 837 consecutive patients underwent CAS with EPD. In 728 patients (86.9%) a pre- and postinterventional cerebral DW-MRI was performed. Patients were eligible for CAS if they had a symptomatic carotid artery stenosis ≥60% or an asymptomatic stenosis of ≥70%.
WHAT IS KNOWN

• New cerebral ischemic lesions during carotid artery stenting are found by diffusion-weighted MRI in ≤70% of patients. Factors predictive for these lesions have not been identified.

WHAT THE STUDY ADDS

• Age, hypertension, lesion length, lesion eccentricity, and aortic arch type III were significantly associated with new ischemic lesions, and age, >50% stenosis of the contralateral internal carotid artery, and a complex aortic arch type were identified as risk factors for the occurrence of new cerebral ischemic lesions in both hemispheres.
• The clinical implication of these findings, and whether prevention of events improves outcomes, deserves further investigation.

Asymptomatic stenosis ≥80%. As potential risk factors the following characteristics for cerebral embolization after CAS were examined: patient characteristics including age, sex, symptomatic/asymptomatic, diabetes mellitus, hypertension, dyslipidemia, uni- or bilateral carotid artery stenosis, and aortic arch type. Lesion characteristics including percent stenosis, lesion length, lesion eccentricity, ulcerated lesions, thrombi containing lesions, calcified lesions. Procedural characteristics including duration of CAS procedure and type of EPD. Patients were either on aspirin 100 mg and clopidogrel 75 mg before CAS or received a loading dose of aspirin 500 mg IV and clopidogrel 600 mg PO on the same day before the procedure. Dual antiplatelet therapy was continued for 4 weeks.

DW-MRI

Cerebral DW-MRI scans were obtained on the day of the procedure and 12 to 24 hours after CAS using a 1.5-T Magnetom Sonata (Siemens, Erlangen, Germany). An independent radiologist (A.W.) analyzed the DW-MRI for new ischemic lesions.

Echo-planar imaging with the following parameters was used: repetition time 3000 ms, echo time 84 ms, 19 slices with a slice thickness of 6 mm, field of view 230 mm, diffusions values b=0, 500, 1000 s/mm², fat-saturation, time of acquisition 71 seconds. Additionally, apparent diffusion coefficient maps were obtained. A new lesion was defined as any detectable focal hyperintense area on DW images, corresponding to a restricted diffusion and confirmed by apparent diffusion coefficient mapping to rule out a shine-through artifact.

Definitions

Patients were considered symptomatic if they had an ipsilateral neurological ischemic event within 6 months before the procedure. Diameter stenosis was determined by ultrasound, using the peak systolic velocity ratio, the ratio of the peak systolic velocity in the internal carotid artery (ICA) to the peak systolic velocity in the distal common carotid artery, with a value of <2.0 for <50% stenosis, a value of >4.0 for 70% stenosis, a peak systolic velocity ratio >4.0 and <5.0 as 70% to 90% stenosis and a value of >5.0 for 90% stenosis to less than near occlusion.

Lesion Eccentricity was defined as eccentricity index >0.7. The maximal (A) and the minimal wall thickness (B) were measured. The eccentricity index was calculated using the formula: (A−B)/A. Calcification of the target carotid artery was defined as positive if angiographically visible. Ulceration was defined as extension of contrast material beyond the vascular lumen into the surrounding plaque.

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics</th>
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<tbody>
<tr>
<td>Mean age</td>
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<tr>
<td>&lt;60 y</td>
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<tr>
<td>61–70 y</td>
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<tr>
<td>71–80 y</td>
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<tr>
<td>&gt;80 y</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Asymptomatic stenosis</td>
</tr>
<tr>
<td>Symptomatic stenosis</td>
</tr>
<tr>
<td>TIA</td>
</tr>
<tr>
<td>Amaurosis fugax</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Risk factors</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Hypertension</td>
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<tr>
<td>Dyslipidemia</td>
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<td>Aortic arch type</td>
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<td>Aortic arch type I</td>
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<td>Aortic arch type II</td>
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<tr>
<td>Aortic arch type III</td>
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</tbody>
</table>

TIA indicates transient ischemic attack.

Thrombi containing lesions were defined by angiography as noncalcified filling defect outlined by contrast media. Cerebral ischemic lesions were defined as ipsilateral, if present in the hemisphere supplied by the treated carotid artery, otherwise as contralateral.

The type of the aortic arch was defined as described previously12:

Type I, if the vertical distance from the origin of the innominate artery to the top of the arch is <1 diameter of the left common carotid artery.

Type II, if vertical distance from the origin of the innominate artery to the top of the arch is between 1 and 2 left common carotid artery diameters.

Type III, if the vertical distance from the origin of the innominate artery to the top of the arch is >2 left common carotid artery diameters.

Major adverse cerebral and cardiovascular event was defined as stroke, myocardial infarction, and death. Stroke was defined as a new neurological deficit lasting >24 hours. Minor stroke was defined as a neurological deficit, which dissolves completely within 30 days or did not lead to impairment in daily activities as judged by an independent neurologist. Major stroke was defined as a persistent neurological deficit leading to impairment in daily activities as judged by the neurologist.

Myocardial infarction was defined as a creatine kinase level that was 3-fold the upper limit of the normal range or higher, in addition to either chest pain or symptoms consistent with ischemia or ECG evidence of ischemia.

Statistical Analyses

Continuous variables are reported as means±SD, categorical variables are reported as percentages. Multivariable logistic regression with backward stepwise elimination was performed to identify predictors using new cerebral ischemic lesions as outcome variables. A P<0.05 was considered statistically significant. Statistical tests were performed using SPSS version 18.0 and Graph Pad Prism 3.00.
Results
Patients’ characteristics are summarized in Table 1. Lesion and procedural characteristics are shown in Table 2.

Thirty-Day Major Adverse Cerebral and Cardiovascular Event Rate
Thirty-day major adverse cerebral and cardiovascular event rate was 1.79% (n=15). Nine patients sustained a minor stroke, 5 patients a major stroke. In 13 patients the stroke occurred within 12 hours after the CAS procedure. In 1 patient a minor stroke occurred 4 weeks after, as a minor stroke in the posterior circulation. In 10 patients the stroke was in the ipsilateral hemisphere, in 1 patient in the contralateral hemisphere, and in 2 patients in the ipsilateral retina. One patient died 2 days after the CAS procedure because of a hyperperfusion syndrome with massive intracerebral bleeding. There were no myocardial infarctions at 30 days.

DW-MRI Findings
In 728 patients (86.9%) a cerebral DW-MRI was performed before and after CAS (Figure). Reasons for not performing a DW-MRI were contraindications (pacemaker, claustrophobia) or patient’s refusal.

No patient had acute ischemic lesions in the baseline DW-MRI. Postprocedure new cerebral ischemic lesions were detected in 32.8% (n=241) of patients.

New lesions were found in 75.0% patients (n=180) exclusively in the ipsilateral hemisphere and in 25.0% patients (n=61) in the ipsilateral as well as in the contralateral hemisphere. In none of the patients lesions were seen exclusively in the contralateral hemisphere.

DW-MRI Findings in Stroke Patients
In 78.6% (11 of 14 stroke patients) a pre- and postprocedural DW-MRI was performed. In 8 patients DW-MRI was positive, with lesions in the ipsilateral hemisphere and in 3 of 8 patients also in the contralateral hemisphere. One of these patients had a contralateral stroke.

Of the 3 stroke patients with no ischemic lesions in the postprocedural DW-MRI, 2 patients had an ipsilateral retinal infarction, and the remaining patient had a cerebral ischemia induced by hypotension, which resolved completely after 48 hours.

Table 2. Lesion and Procedural Characteristics

<table>
<thead>
<tr>
<th>Lesion and Procedural Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA-stenosis, % (mean±SD)</td>
<td>86.6±7.4</td>
</tr>
<tr>
<td>Lesion length, mm (mean±SD)</td>
<td>15.5±5.6</td>
</tr>
<tr>
<td>Eccentricity, %</td>
<td>83.1</td>
</tr>
<tr>
<td>Calcified lesion, %</td>
<td>59.4</td>
</tr>
<tr>
<td>Ulcerated lesion, %</td>
<td>41.1</td>
</tr>
<tr>
<td>Thrombus containing lesion, %</td>
<td>4.4</td>
</tr>
<tr>
<td>Duration of procedure, min (mean±SD, min)</td>
<td>34.1±19.3</td>
</tr>
<tr>
<td>Embolic protection used, %</td>
<td>97.0 (n=787)</td>
</tr>
<tr>
<td>Filter, %</td>
<td>94.2 (n=741)</td>
</tr>
<tr>
<td>Occlusive protection, %</td>
<td>5.8 (n= 46)</td>
</tr>
</tbody>
</table>

ICA indicates internal carotid artery.

Table 3. Risk Factors for New Cerebral Ischemic Lesions as Evaluated by Multivariable Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per added 1 y)</td>
<td>1.02 (1.00–1.04)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.89 (1.02–3.49)</td>
<td>0.041</td>
</tr>
<tr>
<td>Lesion length (per 1 mm increase)</td>
<td>1.04 (1.01–1.07)</td>
<td>0.018</td>
</tr>
<tr>
<td>Eccentric lesion</td>
<td>1.69 (1.03–2.75)</td>
<td>0.035</td>
</tr>
<tr>
<td>Calcified lesion</td>
<td>0.68 (0.48–0.96)</td>
<td>0.028</td>
</tr>
<tr>
<td>Aortic arch type III</td>
<td>1.66 (1.02–2.69)</td>
<td>0.040</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

Risk Factors for Positive DW-MRI
Multivariable logistic regression analysis of patient, lesion, and procedural characteristics revealed the following (Table 3):

Among patient characteristics age as well as aortic arch type III were significant risk factors for new ischemic lesions after CAS (P=0.026 and P=0.040, respectively).

Among comorbidities only hypertension was significantly (P=0.041) associated with new cerebral lesions. No association was found between diabetes mellitus, sex, dyslipidemia, and new cerebral lesions.

Regarding lesion morphology, lesion length as well as eccentric lesions were positively associated with new ischemic lesions (P=0.018 and P=0.035, respectively), whereas calcified lesions were negatively correlated (P=0.028).

Risk Factors for Contralateral New Ischemic Lesions in DW-MRI
The occurrence of contralateral ischemic lesions was independent of the site of the target lesion (right ICA 34 patients versus left ICA 27 patients; P=0.27).

Multivariable logistic regression analysis identified age and contralateral ICA-stenosis >50% as significant risk factors for new ischemic lesions in the contralateral hemisphere (Table 4). No association was found between contralateral ischemic lesions and aortic arch type I (P=0.87).

Aortic arch type II, however, was a significant predictor for contralateral cerebral lesions (P=0.007), and aortic arch type III showed a trend toward a higher incidence of contralateral lesions, which did not reach statistical significance (P=0.091).

Risk Factors in Carotid Artery Stenting

Figure. DW-MRI findings. CAS indicates carotid artery stenting; and DW-MRI, diffusion-weighted magnetic resonance imaging.
Discussion

In this study we retrospectively analyzed risk factors for ipsi- and contralateral lesions assessed by DW-MRI in a large cohort of patients who underwent CAS with EPD.

The major findings of the present study are:

1. New ischemic lesions were found in 32.8% of patients.
2. Among several potential risk factors age, hypertension, lesion length, lesion eccentricity, and aortic arch type III were significantly associated with new ischemic lesions, whereas calcified lesions were negatively associated with new lesions.
3. In 25% of patients, lesions were found in the ipsi- as well as in the contralateral hemisphere.
4. Predictive factors for contralateral ischemic lesions were age, >50% stenosis of the contralateral ICA, and an aortic arch type II, with a trend for aortic arch type III.

Previous Studies on Transcranial Doppler

Transcranial Doppler (TCD) has the advantage to relate the amount of microembolic signals to different steps of the procedure. In previous studies TCD monitoring of the middle cerebral artery was used to assess procedure-related cerebral events during CAS. Adverse outcome was associated with microemboli during poststenot dilation, particulate macroembolism and air embolism because of balloon rupture. In another small study microembolic counts detected by TCD embolism and air embolism because of balloon inflation. In contrast, calcified lesions were negatively associated with new lesions. We, however, excluded patients from CAS if severe circular calcification was present. Others determined the composition of atherosclerotic plaques of the carotid artery by virtual histological intravascular ultrasound and also found no correlation between calcified lesions and the degree of cerebral embolization, whereas plaque burden, necrotic core, fibro-fatty, and fibrous volumes showed a positive correlation. In another study fibro-lipid plaques as compared with calcified plaques assessed by ultrasound and multislice computer tomography were associated with significantly higher numbers of new ischemic lesions.

Incidence of New Cerebral Ischemic Lesions During CAS

DW-MRI is a sensitive tool to identify ischemic lesions during CAS. New cerebral ischemic lesions after CAS with embolic protection have been found in up to 70% of patients. About 30% of these lesions occur in the cerebral hemisphere contralateral to the target lesion. Although in a small randomized trial of CAS the incidence of new MRI lesions was not significantly different in patients with and without cerebral protection, a meta-analysis comprising 1300 patients revealed a significantly lower incidence (33%) in protected patients as compared with unprotected patients (45%). This is well in accordance to the finding of the present study (32.8%), in which 97% of the patients underwent CAS with embolic protection.

Risk Factors for New Cerebral Ischemic Lesions

Clinical, procedural, and morphological parameters predictive for cerebral embolization during CAS have been studied previously. In a retrospective analysis of a subset of patients who received a DW-MRI, Gröschel et al identified a risk score to predict ipsilateral ischemic lesions after protected stenting in a smaller group of patients including age, lesion ulceration, and lesion length >1 cm. The type of the aortic arch was not considered for the analysis, and patient selection may have caused a bias.

In another study in 147 patients undergoing CAS for symptomatic carotid artery stenosis, age ≥68 years in combination with an intima-media thickness >1.5 mm predicted ischemic lesions with an odds ratio of 18. None of the patients, however, had cerebral protection, and lesion characteristics as well as the type of the aortic arch were not included in the analysis.

In the present study age, hypertension, lesion length, lesion eccentricity, and aortic arch type III were significantly associated with new ischemic lesions.

Incidence of and Risk Factors for New Contralateral Cerebral Ischemic Lesions

New ischemic lesions outside the territory of the treated carotid artery have also been described earlier by our group and by others in 29% to 40% of patients. In the present study lesions in the contralateral hemisphere were found in 25% of patients with new ischemic lesions, and were only present in those patients who had also lesions in the ipsilateral hemisphere. Because contralateral lesions mainly arise from the aortic arch and supra-aortic vessels during manipulation of endoluminal devices, they cannot be prevented by EPD and may have risk factors that are different from those associated with ipsilateral lesions. Indeed, lesion morphology, which was a predictor for ipsilateral lesions, was not a predictor for contralateral lesions in the present study. In contrast, factors reflecting the complexity of the target vessel access, such as advanced age and complicated aortic arch, were associated with lesions in the contralateral hemisphere.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contralateral ICA stenosis &gt;50%</td>
<td>2.45 (1.22–4.93)</td>
<td>0.012</td>
</tr>
<tr>
<td>Age (per added 1 y)</td>
<td>0.97 (0.97–0.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic arch type I</td>
<td>1.13 (0.26–4.84)</td>
<td>0.87</td>
</tr>
<tr>
<td>Aortic arch type II</td>
<td>2.95 (1.35–6.47)</td>
<td>0.007</td>
</tr>
<tr>
<td>Aortic arch type III</td>
<td>2.06 (0.89–4.78)</td>
<td>0.091</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and ICA, internal carotid artery.
hemisphere. As shown by Kim et al\textsuperscript{27} the incidence of contralateral lesions can be reduced by improving catheterization techniques of the carotid artery.

Another predictor for a contralateral event was a contralateral carotid artery lesion stenosis. Most probably a contralateral stenosis reflects a more advanced or more active atherosclerotic disease.

Clinical Implications
Cerebral embolization is the main reason for a periprocedural stroke during CAS. But not every ischemic lesion is associated with a stroke. In the present study, for instance, only 5\% of patients with a positive DW-MRI had a clinically apparent stroke within 30 days. Whether a stroke occurs depends not only on the number and size of ischemic lesions, but also on its location within the brain. Preventing cerebral embolization during CAS means preventing the main reason for stroke.

Identifying a subgroup of patients with a particularly high risk for cerebral embolization during CAS, which was the focus of the present study, should characterize a group of patients at high risk for stroke.

Whether neurologically unapparent cerebral embolization, as identified by DW-MRI after CAS has any clinical implications remains unclear. Whereas a small study suggests a negative impact on cognitive function,\textsuperscript{28} in most studies, no correlation was found with any clinical sequelae.

To the best of our knowledge the present study is the first to analyze predictors for ipsilateral and contralateral ischemic lesions in a large cohort of patients undergoing embolic protected CAS. Beyond age, which has been shown to be a predictor of periprocedural cerebral embolic lesions elsewhere,\textsuperscript{3,5} characteristics of lesions and patients have been identified, which may serve as a basis for individual treatment decisions.

Elderly patients with complex aortic arches and long lesions may be at particular risk for cerebral embolic lesions, which, at least in part, cannot be prevented by embolic protection systems.

Limitations
This is a retrospective analysis from a single center. The end point of the study is a surrogate parameter instead of a clinical event. The aortic arch type could only be analyzed in 40\% of the patients. As embolic protection mostly filters were used. Proximal protection systems may be more effective, as has recently been shown by our group in a randomized trial.\textsuperscript{16} In addition, age and lesion morphology might be less-important predictors for cerebral embolic lesions with proximal protection.\textsuperscript{29} Nevertheless, filters are the mostly used protection devices in CAS.

Conclusions
In the present study, risk factors for procedural-related cerebral embolic lesions of patients undergoing CAS with cerebral protection were age, lesion length, lesion eccentricity, and aortic arch type III. Age, hypertension, significant contralateral carotid stenosis, and complex aortic arch were predictive for bilateral ischemic lesions. The present findings are an important step toward the understanding of the best revascularization alternatives for patients with carotid artery disease. However, the clinical implications of ischemic lesions are not yet fully understood.

Disclosures
None.

References


Risk Factors for Cerebral Embolization After Carotid Artery Stenting With Embolic Protection: A Diffusion-Weighted Magnetic Resonance Imaging Study in 837 Consecutive Patients
Klaudija Bijuklic, Andreas Wandler, Yurii Varnakov, Thilo Tuebler and Joachim Schofer

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What is known

New cerebral ischemic lesions during carotid artery stenting are found by diffusion weighted magnetic resonance imaging (DW-MRI) in up to 70% of patients.

Factors predictive for those lesions have not been identified.

What the study adds

Age, hypertension, lesion length, lesion eccentricity, and aortic arch type III were significantly associated with new ischemic lesions, and age, > 50% stenosis of the contralateral internal carotid artery, and a complex aortic arch type were identified as risk factors for the occurrence of new cerebral ischemic lesions in both hemispheres.

The clinical implication of these findings, and whether prevention of events improves outcomes, deserves further investigation.