Impact of Asymptomatic Cerebral Lesions in Diffusion-Weighted Magnetic Resonance Imaging After Carotid Artery Stenting

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Objectives  This study sought to analyze the impact of new asymptomatic cerebral ischemic lesions, found in diffusion-weighted magnetic resonance imaging (DW-MRI) after carotid artery stenting (CAS) in relation to other risk factors for major adverse cerebral and cardiovascular events (MACCE) defined as death, stroke, and myocardial infarction.

Background  After CAS, new cerebral lesions have been reported in up to 70% of patients. The impact of asymptomatic lesions on prognosis after CAS has not been studied.

Methods  Eight hundred thirty-seven consecutive patients underwent CAS with cerebral embolic protection. In 728 patients (86.9%), a pre- and post-procedural DW-MRI was available; these patients were included in the analyses. Multivariate Cox regression analysis and Kaplan-Meier estimates were performed to identify independent risk factors for MACCE at follow-up. Clinical, procedural, and lesion characteristics and DW-MRI findings were included in the analyses.

Results  Post-procedure new cerebral ischemic lesions were detected in 32.8% (n = 241) of patients. Fifteen patients (1.79%) had a periprocedural MACCE and were therefore excluded from the analysis. At a mean follow-up of 766.8 ± 513.4 days (range 30 to 2,577 days), MACCE occurred in 45 patients (6.2%). Cox regression analysis and Kaplan-Meier estimates both identified diabetes as the only significant independent risk factor of MACCE. Asymptomatic cerebral lesions after CAS were not associated with MACCE.

Conclusions  Beyond 30 days, diabetes is the only risk factor of MACCE at follow-up. Asymptomatic cerebral embolic events after CAS had no prognostic impact.  (J Am Coll Cardiol Intv 2013; 6:394–8) © 2013 by the American College of Cardiology Foundation
Diffusion-weighted magnetic resonance imaging (DW-MRI) has been shown to be a sensitive tool in identifying new ischemic cerebral lesions that are caused by emboli during carotid artery stenting (CAS) (1–3). New lesions have been reported in up to 70% of patients despite the use of cerebral embolic protection devices (4–6). In most patients, those lesions are not associated with acute neurological symptoms. The impact of acutely asymptomatic cerebral ischemic lesions on prognosis is unknown.

We therefore studied the relevance of new asymptomatic cerebral ischemic lesions in relation to other risk factors for major adverse cerebral and cardiovascular events (MACCE) (death, stroke, myocardial infarction) in a large cohort of consecutive patients. Our hypothesis was that a positive DW-MRI identifies a subgroup of patients with a more advanced atherosclerotic disease and a higher risk of cerebral and cardiovascular events at follow-up after a successfully performed CAS.

**Methods**

**Study population.** In this retrospective study, 837 consecutive patients underwent CAS with cerebral embolic protection between February 2001 and December 2010. Of these patients, 728 had pre- and post-procedural DW-MRI available and were included in the analyses.

Patients were eligible for CAS if they had a symptomatic carotid artery stenosis ≥60% or an asymptomatic carotid artery stenosis ≥80%.

The following clinical, lesion, and procedural characteristics were recorded: age, sex, symptom status, diabetes mellitus, hypertension, hyperlipidemia, uni- or bilateral carotid artery stenosis, and aortic arch type. Lesion characteristics included percent stenosis, lesion length, lesion eccentricity, ulcerated lesions, thrombi-containing lesions, and calcification. Procedural characteristics included duration of the CAS procedure and the use and type of embolic protection.

**Diffusion-weighted magnetic resonance imaging.** Cerebral DW-MRI scans were obtained on the day of the procedure and 12 to 24 h after CAS using a 1.5-T Sonata Magnetom scanner (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: TR 3,000 ms, TE 84 ms, 19 slices with a slice thickness of 6 mm, field of view 230 mm, diffusion values b = 0, 500, 1,000 s/mm², fat saturation, time of acquisition 71 s. Additionally, apparent diffusion coefficient maps were obtained. A new lesion was defined as a focal hyperintense area detected by the fluid-attenuated inversion recovery sequence, corresponding to a restricted diffusion signal in the diffusion-weighted imaging sequence, confirmed by apparent diffusion coefficient mapping to rule out a shine-through artifact.

**Procedure.** Patients were on dual antiplatelet therapy (aspirin 100 mg and clopidogrel 75 mg/day) before the intervention and for 4 weeks after. CAS with embolic protection was performed as described previously (7). Patients underwent neurological examination by an independent neurologist before CAS and before discharge. Patients were monitored for at least 24 h. The first follow-up visit with neurological evaluation and duplex ultrasound of the target vessel was scheduled at 30 days.

**Definitions.** Patients were considered symptomatic if they had an ipsilateral neurological ischemic event within 6 months before the procedure.

Diameter stenosis was determined angiographically according to the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria (8).

The degree of stenosis was calculated from the ratio of the linear luminal diameter of the narrowest segment of the diseased portion of the artery to the diameter of the artery beyond any post-stenotic dilation.

Lesion calcification was defined as positive if angiographically visible.

Ulceration was defined as the extension of contrast material beyond the vascular lumen into the surrounding plaque.

Lesion eccentricity was defined as an eccentricity index >0.7. The maximal (A) and the minimal wall thickness (B) were measured. The eccentricity index was calculated using the following formula: (A − B)/A.

Thrombi-containing lesions were defined by angiography as noncalcified filling defect outlined by contrast medium.

The type of the aortic arch was defined as described previously (9):

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 (CCA).

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

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

MACCE was defined as stroke, myocardial infarction, and death.

Stroke was defined as a new neurological deficit lasting longer than 24 h.

Minor stroke corresponded to Rankin Scale grade 2 to 3 (minor or moderate handicap; some or significant restrictions in lifestyle), and major stroke corresponded to Rankin...
Scale grade 4 to 5 (moderately severe or severe handicap; precludes independent existence).

**Statistical analyses.** Continuous variables are reported as mean ± SD; discrete variables are reported as percentages.

Multivariate stepwise Cox regression analysis was performed to identify independent predictors of adverse outcomes at follow-up.

Univariate analyses with patient, procedural, and lesion characteristics were performed. Factors entered into the multivariate model included those with a p value < 0.10 from the univariate analyses and new ischemic lesions in DW-MRI. A p value < 0.05 was considered statistically significant. Survival curves were estimated by the Kaplan-Meier method and compared by the log-rank test. Statistical tests were performed using SPSS version 18.0 (IBM, Armonk, New York) and GraphPad Prism version 3.00 (GraphPad Software, La Jolla, California).

**Results**

**Patient and lesion characteristics.** Between February 2001 and December 2010, 728 consecutive patients had pre- and post-procedural DW-MRI and underwent carotid artery stenting with embolic protection.

Patient’s characteristics are summarized in Table 1. The mean age was 68.6 ± 9.6 years, male 69.1%; 11.3% of the patients were ≥ 80 years of age. A symptomatic stenosis was present in 26.6% of the patients.

Lesion and procedural characteristics are shown in Table 2. Mean percent stenosis of the target vessel was 86.2 ± 7.5%, mean lesion length was 15.4 ± 5.3 mm, 82.8% of lesions were eccentric, and 58.8% were calcified.

Embolus protection was used in 94.4% of patients.

**DW-MRI findings.** Of 837 consecutive patients, a cerebral DW-MRI was performed in 728 patients (86.9%) before and after CAS. Reasons for not performing a DW-MRI were contraindications for MRI (pacemaker, claustrophobia) or patient’s refusal. No patient had acute ischemic lesions in the pre-procedural DW-MRI. Post-procedure new cerebral ischemic lesions were detected in 32.8% (n = 241) of patients.

**Thirty-day follow-up.** At 30 days, all patients had a clinical follow-up visit. The 30-day MACCE rate was 1.79% (n = 654) of the patients and was performed either by a patient visit or by telephone interview. The mean duration of follow-up was 766.8 ± 513.4 days (range 30 to 2,577 days).

The MACCE rate was 6.2% (n = 45). During follow-up, 34 patients died. Causes of death were cardiovascular in 10 patients, fatal stroke in 5 patients, and unknown in 19 patients. Ten patients sustained a stroke (5 minor and 5 major strokes), and 3 patients had a myocardial infarction.

The overall 2-year MACCE-free survival rate was 92.9%.

**Risk factors for MACCE.** Age, sex, symptom status, diabetes mellitus, hypertension, hyperlipidemia, uni- or bilateral carotid artery stenosis, aortic arch type, lesion characteristics (including percent stenosis, lesion length, lesion eccentricity, ulcerated lesions, thrombi-containing lesions, calcification), and procedural characteristics (including duration of CAS procedure, embolic protection, and the post-procedural result of the DW-MRI) were entered into univariate analyses.

In multivariate Cox regression analysis, diabetes mellitus and the post-procedural result of the DW-MRI were included.

Diabetes mellitus was the only independent risk factor of MACCE during follow-up (hazard ratio: 3.3, 95% confidence interval: 1.7 to 6.6, p = 0.001). All the other clinical,

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<th>Table 1. Patient Characteristics</th>
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<td><strong>Asymptomatic stenosis</strong></td>
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<td><strong>Symptomatic stenosis</strong></td>
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<td><strong>Risk factors</strong></td>
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<td><strong>Diabetes mellitus</strong></td>
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Values are mean ± SD, n (%), or %.

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<th>Table 2. Lesion and Procedural Characteristics</th>
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<td><strong>Internal carotid artery stenosis,</strong> %</td>
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<td><strong>Lesion length,</strong> mm</td>
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<td><strong>Eccentricity</strong></td>
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<td><strong>Embolic protection used</strong></td>
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<td><strong>Occlusive protection</strong></td>
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Values are mean ± SD or %.
procedural, and lesion characteristics were not significantly associated with MACCE. A positive DW-MRI after CAS had no impact on long-term prognosis (hazard ratio: 1.2, 95% confidence interval: 0.6 to 2.5, \( p = 0.65 \)).

In support of the multivariate analysis, the Kaplan-Meier analysis demonstrated that patients with diabetes had a significantly higher incidence of MACCE after CAS (log-rank test 18.67, \( p < 0.0001 \)) (Fig. 1).

**Discussion**

The major findings of the present study are:

1. Post-procedural asymptomatic cerebral lesions as assessed by DW-MRI were found in 32.8% of patients.
2. The MACCE rate beyond 30 days at a mean follow-up of 2.1 years was 7.2%.
3. Cox regression analyses and Kaplan-Meier estimates revealed diabetes as the only predictor for MACCE after CAS.
4. Asymptomatic cerebral lesions in DW-MRI after CAS were not associated with MACCE during follow-up.

The incidence of new ischemic lesions found in the present study is well in accordance with what has been described in the literature (4–6,10–13). Only 14 of 241 patients (5.8%) with positive DW-MRI after CAS had a periprocedural minor or major stroke; the remaining patients were neurologically asymptomatic, as assessed by an independent neurologist.

Whereas the periprocedural MACCE rate in the present study is lower, the MACCE rate beyond 30 days is well in the range of what has been reported in randomized trials of high- and intermediate-risk symptomatic and asymptomatic patients (14–18).

Risk factors for periprocedural MACCE have been identified in earlier studies, such as symptom status, comorbidities, and unfavorable anatomical and lesion characteristics (19–21). By contrast, risk factors for MACCE after the periprocedural period are not well studied. Cremonesi et al. (21) found a significant difference in long-term survival of symptomatic versus asymptomatic patients \( \geq 79 \) years of age. Others have identified low high-density lipoprotein cholesterol in combination with elevated inflammatory markers as risk factors for adverse long-term outcome after CAS (22). Diabetes was not identified as a risk factor.

By contrast, in the present study of a large cohort of consecutive patients, Cox regression analysis, as well as Kaplan-Meier estimates, revealed diabetes mellitus as the only independent risk factor.

To the best of our knowledge, this is the first study analyzing the impact of asymptomatic cerebral ischemic lesions after CAS on prognosis in terms of MACCE (death, stroke, and myocardial infarction).

In the present study, a positive DW-MRI after CAS is not an indicator for an increased risk of major adverse events at follow-up. The same is true for other well-known risk factors such as age, dyslipidemia, and hypertension. The only indicator is diabetes, which indicates a more advanced atherosclerotic disease and a higher risk of cerebral and cardiovascular events (23).

The meaning of asymptomatic cerebral emboli during CAS remains to be elucidated.

It has to be considered, for instance, that we did not perform neuropsychological testing. Neuropsychological
changes in the absence of stroke have been described after cardiopulmonary bypass procedures and were strongly associated with microembolic events (10,11). Others have found that multiple emboli during carotid endarterectomy can cause deteriorations in cognitive functions (12). Further studies on the potential long-term effect of asymptomatic cerebral embolic events should include a battery of neuro-psychometric tests.

**Clinical implications.** Diabetes mellitus is a key risk factor of MACCE in patients undergoing CAS. These patients need intensive treatment and careful surveillance.

**Study limitations.** Although this is a large cohort of patients with DW-MRI after CAS, it is a retrospective analysis. Cerebral ischemic lesions were only qualitatively assessed, not quantified. A DW-MRI was performed in most (86.6%), but not in all patients. Follow-up ranged from 30 to 2,577 days, thus some patients had only a short follow-up.

With a longer follow-up, other risk factors for MACCE might have been identified.

The cause of death could not be identified in all patients. Diabetic patients were not differentiated by insulin dependency.

**Conclusions**

Beyond 30 days, diabetes is the only risk factor of MACCE at follow-up after CAS. Asymptomatic embolic events after CAS, as assessed by DW-MRI, have no prognostic impact.

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**REFERENCES**


**Key Words:** carotid artery stenting ▪ cerebral ischemic lesions ▪ diffusion-weighted magnetic resonance imaging ▪ follow-up ▪ MACCE.