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ORIGINAL RESEARCH

Effects of Age and Symptom Status on Silent Ischemic Lesions after Carotid Stenting with and without the Use of Distal Filter Devices

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BACKGROUND AND PURPOSE: The routine use of distal filter devices during carotid angioplasty and stent placement (CAS) is controversial. The aim of this study was to analyze their effects on the incidence of new diffusion-weighted imaging (DWI) lesions as surrogate markers for stroke in important subgroups.

MATERIALS AND METHODS: DWI was performed immediately before and after CAS in 68 patients with and 175 without protection, and patients were further subdivided according to their age or symptom status.

RESULTS: The proportion of patients with new ipsilateral DWI lesion(s) was significantly lower after protected versus unprotected CAS (52% versus 68%), as well as in symptomatic patients (56% versus 74%) or those at or younger than 75 years of age (46% versus 67%; all $P < .05$). Similarly, the total number of lesions was significantly lower after protected versus unprotected CAS (median, 1; interquartile range [IQR], 0–2; versus median, 1; IQR 0–4.75) and in symptomatic patients (median, 1; IQR, 0–3; versus median, 2; IQR, 0–6) or those at or younger than 75 years of age (median, 0; IQR, 0–2; versus median, 1; IQR, 0–4; all $P < .05$). In contrast, for asymptomatic patients (48% versus 52%; $P = .8$; median, 0; IQR, 0–2; versus median, 1; IQR, 0–2.5; $P = .6$) or those older than 75 years of age (73% versus 69%; $P = .7$; median, 1; IQR, 0–4; versus median, 1.5; IQR, 0–5.75; $P = .6$), the proportion of patients with new lesion(s) and the total number of these lesions were not significantly different between protected and unprotected CAS.

CONCLUSIONS: The use of distal filter devices generally reduces the incidence of new DWI lesions; however, this beneficial effect might not necessarily pertain to older and asymptomatic patients.

Carotid endarterectomy (CEA) is currently the accepted standard of treatment for patients with symptomatic and some selected patients with a severe asymptomatic internal carotid artery stenosis.[1,2] In the past few years, however, carotid angioplasty and stent placement (CAS) has emerged as an alternative endovascular treatment strategy for these disorders. Although initial single-center case series and registries have reported acceptable periprocedural complication rates after CAS even in surgical high-risk patients,[3-6] recent randomized trials directly comparing CAS with CEA have produced conflicting results.[7-9] Compared with surgery, CAS potentially has the major disadvantage of producing more emboli to the brain,[10] which has led to the development and widespread application of cerebral protection devices aimed at preventing the passage of embolic material into the cerebral vasculature. Although the concept of cerebral protection is generally appealing and has been corroborated by a meta-analysis of single-center studies and large registries,[6,11] the use of either balloon occlusion techniques or filter systems increases the duration, the technical complexity, as well as the costs of the intervention and is, thus, no panacea for CAS. Indeed, the periprocedural complication rates were comparable between those patients treated with and without cerebral protection in the recently published stent-protected angioplasty versus carotid endarterectomy in symptomatic patients (SPACE) trial.[7] Moreover, the 30-day incidence of death and stroke was unacceptably high in the Endarterectomy Versus Angioplasty in Patients with Severe Symptomatic Carotid Stenosis Trial despite the use of cerebral protection devices during CAS.[8] Although these results partially reflect a lack of experience of the interventional physicians in these trials,[12] it is also conceivable that only certain subgroups of patients actually profit from the use of these devices. In fact, it could be speculated that the potential impact of protection devices on outcome is pronounced in those patients who have been shown to have a high risk of embolic complications during unprotected CAS, such as older patients, and is negligible or even harmful in low-risk patients.[6,13] Because of the relatively small number of clinical events after CAS, it has become a major challenge to identify correlates of clinically silent events to define the role of cerebral protection devices on outcome overall, as well as in important subgroups. The use of diffusion-weighted imaging (DWI) to detect clinically silent emboli during CAS as surrogate markers for stroke could pave the way out of this dilemma.[14-16] In support of this notion, we demonstrated recently an overall positive effect of cerebral protection devices on the number of new DWI lesions after CAS, which were closely related to the clinical outcome.[15] Using this prospective and updated CAS series, the aim of this study was to analyze the effects of cerebral protection devices on the incidence of new DWI lesions in 2 important sub-

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groups, namely, younger and older patients, as well as those with a symptomatic or asymptomatic carotid stenosis.

Methods

Study Population

From April 1999 to December 2006, a total of 415 patients with high-grade carotid stenosis (≥70% in symptomatic patients and ≥90% in asymptomatic patients assessed with sonography according to the European guidelines to estimate the stenosis) were treated with CAS following a prospective protocol. The severity of carotid stenosis was evaluated by measuring the peak systolic velocity (PSV) with angle correction at the narrowest point of stenosis. A stenosis was classified at or more than 70% if the PSV was more than 200 cm/s and at or more than 90% if it was more than 300 cm/s, respectively. A carotid stenosis was considered symptomatic if the patient had experienced an ipsilateral ocular or cerebral (transient or permanent) ischemic event within the past 180 days. Within this series, 243 patients (181 men and 62 women; mean age, 68 ± 8.5 years; range, 46–89 years) without contraindications for MR imaging (eg, pacemaker, unstable medical condition, or severe agitation) consented to preinterventional and postinterventional DWI of the brain. Although the overall effects of distal filter devices on the incidence of new DWI lesions have been published recently for those patients treated until October 2005,[15] we used this updated dataset to perform 2 subgroup analyses. The patients were subdivided according to their age (≤75 years and >75 years) or symptom status (symptomatic versus asymptomatic) and the use/nonuse of distal filter devices during CAS. All of the patients were informed about the investigational nature of CAS and gave their written consent. Our CAS protocol and the additional performance of MR imaging studies have been approved by our institutional ethics review board.

Carotid Stent Protocol

All of the CAS procedures were performed by using a standardized protocol described recently.[15] Initially, all of the CAS procedures had been performed without cerebral protection devices. When cerebral protection devices became available, the choice of which type of device to use, if any, depended on the personal preference of the interventional neuroradiologist performing the procedure. Twenty-three patients were treated without cerebral protection devices before these had become available, 45 patients were treated without cerebral protection devices after these had become available, and in 175 patients, filter-type embolic protection devices were used during the CAS procedures.

According to physician preference and commercial availability, 4 different cerebral protection devices (NeuroShield, MedNova, Galway, Ireland; AngioGuard, Cordis J&J, Minneapolis, Minn; EmboShield, Abbott, Chicago, Ill; and FilterWire, Boston Scientific, Natick, Mass) were used in this study: a common characteristic of all of these devices is a self-expanding, basket-type filter, which is deployed distal to the lesion to maintain cerebral blood flow and to capture debris deliberated during CAS. All of the patients were treated with 2 different self-expandable stents (Smart/Precise, Cordis and Wallstent, Boston Scientific).

MR Imaging

In all of the patients MR imaging scans were obtained immediately before and within 48 hours after the intervention. MR imaging was performed by echo-planar imaging (EPI) using a 1.5T MR imaging system (Magnetom Vision or Sonata; Siemens, Erlangen, Germany) according to a standardized protocol. In all of the patients, multisection diffusion-weighted, single-shot EPI images with the following parameters were acquired: TR at 0.8 ms, TE at 123 ms, acquisition time at 4 seconds, and b at 1100s/mm^2. Diffusion sensitivity was in the section selection direction and, hence, perpendicular to the imaging plane. The number of measurements was 5, the first run was omitted, and the remaining 4 were added to create an average image with improved signal intensity to noise ratio. The high contrast of this and similar imaging protocols has been shown recently to allow a clear delineation of acute lesions with good reader reproducibility.[17,18] The conventional MR imaging sequences included T2-weighted fluid-attenuated inversion recovery turbo spin-echo images (TR, 9000 ms; inversion time, 2200 ms; TE, 119 ms). In all of the subjects an MR angiography was performed before CAS using either a time-of-flight technique or a heavily T1-weighted, contrast bolus-enhanced 3D-gradient-echo sequence (TR, 3.2 ms; TE, 1.2 ms; flip angle, 30°; FOV, 300; section thickness, 60–70 mm; 36 partitions).

Image Analysis

MR image analysis was performed jointly by a neuroradiologist (U.E.) and a neurologist (A.K.). Both MR imaging readers had extensive experience with the interpretation of DWI scans. With the exception of those patients who had developed a stroke during CAS and had also been examined physically by A.K., both readers were blinded to the clinical data. In addition, AK was blinded to the use of cerebral protection devices. For each patient abnormal DWI lesions were identified by visual inspection. New DWI lesions were determined by section-to-section comparison of the DWI images between both scanning sessions. In case of dissent, a second neuroradiologist (T.N.) reviewed the images, and a decision was made by consent. Enlargement of a previous DWI lesion was not considered as a new ischemic lesion. All of the new DWI lesions were described by their number, location in the brain (inside or outside the vascular territory of the target lesion), and their maximal diameter (given in millimeters and classified as <10 mm, 10–20 mm, or >20 mm). Large confluent lesions, as well as territorial infarctions, were noted separately. The preinterventional MR angiographies were used to decide whether the new DWI lesions were inside or outside the vascular territory of the treated artery. This was done by determining the distribution of the lesions within the different vascular territories (anterior or posterior circulation; ipsilateral or contralateral to the treated artery) and visualizing collateral blood flow patterns within the circle of Willis. With respect to the number, size, and location of the DWI lesions, interobserver agreements were assessed with κ statistics.

Data Collection and Clinical Evaluation

Careful history taking and precise neurologic examination were carried out in each patient by 3 stroke neurologists before CAS (A.K., K.G., and F.S.), and additional neurologic examinations were performed by 1 of 2 board certified neurologists (A.K. or F.S.) the day after CAS and at day 30.

The following cerebrovascular risk factors were recorded using history or direct measurements: hypertension (initially blood pressure ≥160/90 mm Hg measured on repeated occasions; throughout the study period this threshold was changed to ≥140/90 mm Hg), diabetes mellitus (HbA1c >6.5% or fasting blood glucose >120 mg/dL), hyperlipidemia (fasting serum cholesterol levels >220 mg/dL or current statin medication), smoking (current or within the previous year), previous transient ischemic attacks and strokes, coronary artery

Table 1: Baseline characteristics of study population

Variable	Data
Mean age ± SD, y	68 ± 9
≥75 y, *n* (%)	190 (78)
>75 y, *n* (%)	53 (22)
Male gender, *n* (%)	181 (74)
Symptomatic stenosis, *n* (%)	134 (55)
Hypertension, *n* (%)	184 (76)
Hyperlipidemia, *n* (%)	139 (57)
Current tobacco use, *n* (%)	79 (33)
Diabetes, *n* (%)	67 (28)
Coronary artery disease, *n* (%)	54 (22)
Degree of stenosis, mean ± SD, %	88 ± 8
Contralateral ICA occlusion, *n* (%)	42 (17)

Note:—ICA indicates internal carotid artery.

disease (angina, myocardial infarction, percutaneous transluminal angioplasty, or surgery), and the presence of contralateral carotid disease (assessed with sonography). Moreover, the current medication (type and dose) of each patient was recorded on a predefined electronic data sheet.

Definitions of Postinterventional Complication Rates

The definitions of postinterventional neurologic complication rates that occurred within the first 24 hours after CAS and within 30 days were based on a previous study by Mathur et al[13] and were defined as described below.

Minor Stroke. This included any new neurologic deficit (either ocular or cerebral) that persisted for more than 24 hours and that either resolved completely within 30 days or increased the National Institutes of Health Stroke Scale at or less than 3 points.

Major Stroke. This included any new neurologic deficit that persisted after 30 days or increased the National Institutes of Health Stroke Scale by more than 3 points.

Statistical Analysis

Continuous values were expressed as mean ± SD and nominal variables as counts and percentages. Median values and the interquartile range were computed as appropriate. For comparisons of categoric data 2-tailed χ^2 statistics with Yates correction and univariate Fisher exact test were used. The Fisher exact test was used when the predicted contingency table cell values were less than 5. Analyses of continuous variables between the cohorts were performed with an unpaired Student *t* test. Because the imaging data were not distributed normally, differences between subgroups were tested using the Mann-Whitney *U* statistic. A value of $P < .05$ was considered to indicate a statistically significant difference. All of the statistical analyses were performed with SPSS (version 12; SPSS, Chicago, Ill).

Results

The demographic and clinical characteristics of the entire study population are summarized in Table 1. With respect to the baseline characteristics, there were no significant differences between the subgroups of patients treated with and without cerebral protection devices who were at or younger than 75 years of age, older than 75 years of age, or who had been treated for an asymptomatic/symptomatic carotid stenosis.

The total number of mainly small (diameter of <10 mm in 97%) and asymptomatic new DWI lesions within the vascular territory of the treated artery was 241 in patients treated without and 474 in those patients treated with cerebral protection, respectively. A total of 14 patients (21%) treated without and 32 patients (18%) treated with cerebral protection had had new DWI lesions outside of the vascular territory of the target lesion ($P = .7$). There was overall agreement between both reviewers as to the number ($\kappa = 0.94$ for interobserver agreement; 95% confidence interval [CI], 0.91–0.97), size ($\kappa = 0.92$ for interobserver agreement; 95% CI, 0.86–0.99), and location ($\kappa = 0.82$ for interobserver agreement; 95% CI, 0.73–0.91) of new DWI lesions. Neither the type of protection device nor the type of stent used was associated with the incidence of new DWI lesions (data not shown).

Table 2: New DWI lesions after CAS according to age or presenting event and treatment

Variable	Unprotected	Protected	*P*
Age ≤75 y			
No. of lesions	52	138	
Median (interquartile range)	1 (0–4)	0 (0–2)	<.01
No. of procedures with any new ipsilateral DWI lesion, *n*/*N* (%)	35/52 (67)	64/138 (46)	<.05
Age >75 y			
No. of lesions	16	37	
Median (interquartile range)	1.5 (0–5.75)	1 (0–4)	.6
No. of procedures with any new ipsilateral DWI lesion, *n*/*N* (%)	11/16 (69)	27/10 (73)	.7
Symptomatic patients			
No. of lesions	47	87	
Median (interquartile range)	2 (0–6)	1 (0–3)	<.05
No. of procedures with any new ipsilateral DWI lesion, *n*/*N* (%)	35/47 (74)	49/87 (56)	<.05
Asymptomatic patients			
No. of lesions	21	88	
Median (interquartile range)	1 (0–2.5)	0 (0–2)	.6
No. of procedures with any new ipsilateral DWI lesion, *n*/*N* (%)	11/21 (52)	42/88 (48)	.8

Note:—DWI indicates diffusion-weighted imaging; CAS, carotid angioplasty and stent placement.

The proportion of patients with any new ipsilateral DWI lesion(s) after protected CAS was significantly lower than after unprotected CAS for the entire group (52% versus 68%; $P < .05$), for patients at or younger than 75 years of age (46% versus 67%; $P < .05$), and for patients with a symptomatic stenosis (56% versus 74%; $P < .05$; Table 2). Similarly, the total number of new ipsilateral DWI lesions after protected CAS was significantly lower than that after unprotected CAS for the entire study population (median, 1; interquartile range [IQR], 0–2; versus median, 1; IQR, 0–4.75; $P < .01$), for patients at or younger than 75 years of age (median, 0; IQR, 0–2; versus median, 1; IQR, 0–4; $P < .01$), and for patients with a symptomatic stenosis (median, 1; IQR, 0–3; versus median, 2; IQR, 0–6; $P < .05$).

In contrast, neither the proportion of patients with any new ipsilateral DWI lesion(s) after protected CAS nor the total number of new ipsilateral DWI lesions were significantly different from after unprotected CAS in patients older than 75 years (73% versus 69%; $P = .7$; median, 1; IQR, 0–4; versus median, 1.5; IQR, 0–5.75; $P = .6$) or in those patients treated for an asymptomatic carotid stenosis (48% versus 52%; $P = .8$;

Table 3: Periprocedural complications within 30 days after CAS according to age or presenting event and treatment

Variable	Unprotected CAS	Protected CAS	P*
Age ≤75 y			
No.	52	138	
Minor stroke, *n/N* (%)	4/52 (7.7)	5/138 (3.6)	.3
Major stroke, *n/N* (%)	0/52 (0)	0/138 (0)	NA
Death, *n/N* (%)	0/52 (0)	0/138 (0)	NA
Any stroke or death, *n/N* (%)	4/52 (7.7)	5/138 (3.6)	.3
Age >75 y			
No.	16	37	
Minor stroke, *n/N* (%)	2/16 (12.5)	2/37 (5.4)	.6
Major stroke, *n/N* (%)	0/16 (0)	1/37 (2.7)	1.0
Death, *n/N* (%)†	0/16 (0)	1/37 (2.7)	1.0
Any stroke or death, *n/N* (%)	2/16 (12.5)	4/37 (10.8)	1.0
Symptomatic patients			
No.	47	87	
Minor stroke, *n/N* (%)	5/47 (10.6)	5/87 (5.7)	.3
Major stroke, *n/N* (%)	0/47 (0)	0/87 (0)	NA
Death, *n/N* (%)†	0/47 (0)	1/87 (1.1)	1.0
Any stroke or death, *n/N* (%)	5/47 (10.6)	6/87 (6.9)	0.5
Asymptomatic patients			
No.	21	88	
Minor stroke, *n/N* (%)	1/21 (4.8)	2/88 (2.2)	.5
Major stroke, *n/N* (%)	0/21 (0)	1/88 (1.1)	1.0
Death, *n/N* (%)	0/21 (0)	0/88 (0)	NA
Any stroke or death, *n/N* (%)	1/21 (4.8)	3/88 (3.4)	.6

Note:—CAS indicates carotid angioplasty and stent placement; NA, not applicable.
* *P* values are from χ^2 analysis.
† In the group of patients treated with cerebral protection devices, there was 1 nonstroke-related death secondary to pneumonia 3 weeks after the procedure.

median, 0; IQR, 0–2; versus median, 1; IQR, 0–2.5; $P = .6$; Table 2).

In patients treated without protection, the minor stroke rate was 8.8%, the major stroke rate was 0%, and the death rate was 0%, whereas in patients treated with protection devices, the minor stroke rate was 4%, the major stroke rate was 0.6%, and the death rate was 0.6%, respectively. For the entire study population, the incidence of any stroke or death within 30 days was not significantly different between patients treated without versus those treated with protection (8.8% versus 5.1%; $P = .4$). Likewise, the neurologic complication rates within 30 days were not significantly different among younger, older, symptomatic, or asymptomatic patients treated with and without protection (Table 3).

Discussion

Our study demonstrates that the application of a filter protection system during CAS significantly reduces the incidence of new DWI lesions, of which most are asymptomatic. However, this beneficial effect could not be observed in asymptomatic or older patients. Because advanced age has been associated with a significantly increased stroke risk during unprotected CAS,[19,20] the finding that older patients might not profit from the use of cerebral protection devices is of great practical importance. Although it could principally be argued that DWI lesions do not necessarily represent irreversible brain damage,[21] we could demonstrate recently a close correlation between the number of new DWI lesions and clinical outcome after CAS.[15] Our imaging data are also supported by the clinical results of the lead-in phase of the ongoing Carotid Revascularization Endarterectomy versus Stent Placement Trial, which documented increasingly high complication rates at older ages despite the obligatory use of a protection device during CAS.[22] Divided into age cohorts of less than 60 years, 60–69 years, 70–79 years, and more than 80 years, the composite 30-day stroke and death rates in that study were 1.7%, 1.3%, 5.3%, and 12.1%, respectively ($P < .001$). Similarly, the 30-day stroke and death rates tended to be higher in older than in younger subjects undergoing protected CAS in this and other single-center studies.[23]

Patients with a symptomatic carotid stenosis tended to have more new DWI lesions after unprotected CAS than asymptomatic patients (74% versus 52%; $P = .09$), indicating that these patients have an increased microembolic risk during this procedure. It is conceivable that the high prevalence of thrombotically active plaques in recently symptomatic patients is the main determinant for this finding[24] and could also serve as an explanation for the increased risk of clinical stroke during CAS in these patients.[6] The use of cerebral protection devices during CAS appears to reduce the increased microembolic risk in these patients.

To date, several investigators have used DWI to detect clinically silent embolic lesions after CAS. In these studies, new DWI lesions were observed in 29%,[25] 36%,[26] or 54% of the patients[10] after unprotected CAS and in 17.3%,[27] 19%,[28] 25%,[29] 40%,[14] 41.5%,[16] or 41%[30] after protected CAS, respectively. In contrast to these results, the proportion of patients with new DWI lesion(s) was higher in this study, even in those patients treated with distal filter devices. Because our study was composed of all of the patients treated consecutively at a single center, this finding probably reflects a learning curve.[31] Moreover, most patients were treated with an open-cell design stent (Precise, Cordis) in this study. In a recent study, patients treated with open-cell design stents had significantly higher stroke and death rates after CAS than those treated with closed-cell design stents,[32] indicating that the latter type of stents might have an intrinsically greater potential to prevent embolism of fractured plaque or other thrombogenic material to the brain. Finally, our results could also have been influenced by the use of 4 different distal filter devices, which might not be equally effective in preventing thromboembolic complications during CAS. On the other hand, in a recent large study involving more than 3000 patients, the type of embolic protection device did not influence the clinical outcome after CAS.[33] In support of this notion, we did not find any association between the incidence of new DWI lesions after CAS and the different types of filter protection devices. Nonetheless, future studies should clarify the effects of stent design, as well as the type of cerebral protection device on the incidence of new DWI lesions after CAS.

We acknowledge that our study has inherent limitations imposed by its retrospective nature and the nonrandomization of treatment allocation. The relatively small sample size of our study and the few observed neurologic complications allow no conclusions to be drawn on the clinical efficacy of the neuroprotective devices investigated. Moreover, cognitive studies or histologic analyses of the filter contents were not performed. Finally, follow-up MR imaging to document established infarction was not performed. In fact, Kidwell et al[34] demonstrated that 5 of 9 patients who had early abnormalities on DWI after a transient ischemic attack did not have evidence

of established infarction on follow-up images, indicating that we might have overestimated the incidence of truly irreversible ischemic brain damage after CAS.

In conclusion, the use of distal filter devices during CAS appears to generally reduce the incidence of predominantly silent ischemic lesions. However, this beneficial effect might not necessarily pertain to older patients or those with an asymptomatic stenosis. Therefore, randomized trials of unprotected versus protected CAS using DWI as an additional surrogate end point should be expedited.

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