◆ CLINICAL INVESTIGATION ◆

Covered Versus Bare Self-Expanding Stents for Endovascular Treatment of Carotid Artery Stenosis: A Stopped Randomized Trial

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Purpose: To investigate whether filter-protected carotid artery stenting (CAS) using a covered self-expanding stent reduces the risk of cerebral embolization.
Methods: Fourteen asymptomatic patients (13 men; median age 77 years, IQR 73–83) were enrolled in a randomized pilot trial comparing the rates of cerebral microembolism during and after filter-protected CAS using either a self-expanding covered (n=8) or a bare (n=6) carotid stent. Transcranial Doppler (TCD) monitoring was done during and for 90 minutes after the procedure. Diffusion-weighted magnetic resonance imaging (DW-MRI) was performed before and 24 hours after CAS. Patients were followed for 6 months for neurological events and occurrence of restenosis.
Results: A significant reduction in ipsilateral microembolic signals by TCD was observed with the covered (median 1, IQR 0–4) versus the bare stent (median 6, IQR 3–8; p=0.043). Comparison of the preprocedural and 24-hour postprocedural DW-MRI images showed no new ipsilateral lesions but 1 new lesion in the contralateral hemisphere in the covered stent group, resulting in an overall 7% (95% CI 0%–20%) rate of new ischemic lesions. No neurological complications occurred up to 6 months. Restenosis (>70%) occurred in 3 (38%) of 8 patients with the covered versus none of the bare stents (p=0.21). The trial was stopped when the third restenosis of a covered stent was detected.
Conclusion: Self-expanding covered stents potentially reduce the risk of cerebral microembolism during and after carotid stenting. However, the problem of in-stent restenosis has to be resolved before these devices can be considered for further investigation.
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Key words: carotid artery, stenosis, stent, microembolism, covered stent, self-expanding stent

Elective carotid artery stenting (CAS) has emerged as a promising therapeutic alternative to endarterectomy,[1–9] particularly in medical high-risk patients.[1] The reported rates of neurological complications of CAS substantially decreased during the past years,[10] and the routine use of cerebral protection devices and low-profile catheter systems have further

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increased procedural safety.[1,9,10] Recent data suggest comparable complication rates of CAS and endarterectomy.[1,11–13]

Despite the low rates of neurological complications with CAS, cerebral microembolism remains a major concern. Intracranial embolic signals were detected in >80% of CAS procedures by continuous transcranial Doppler (TCD) monitoring,[14,15] and 22% to 36% of the patients exhibited new ischemic lesions by diffusion-weighted magnetic resonance imaging (DW-MRI) after CAS.[16–18]

We hypothesized that the use of a covered self-expanding stent may reduce the risk of cerebral microemboli during and after CAS, as a covered stent may mechanically stabilize any potential thrombogenic and embolic material of the carotid plaque.[19] Therefore, the aim of the present randomized pilot trial was to investigate the rate of cerebral microemboli measured by TCD and DW-MRI after filter-protected CAS using self-expanding covered or bare carotid stents.

METHODS

Study Design

The study was designed as a randomized pilot trial comparing filter-protected CAS using self-expanding covered or bare carotid stents in patients with asymptomatic high-grade (NASCET >80%) carotid artery stenosis. The study was approved by the institutional review board and ethics committee, and all patients provided written informed consent. Trial design, analysis, and presentation of the data were performed in agreement with the CONSORT statement.[20]

Inclusion and Exclusion Criteria

All consecutive asymptomatic patients who were scheduled for elective CAS at our institution were screened. Only asymptomatic patients were included to obtain a homogenous patient sample with respect to the risk for cerebral microembolism. The covered stent was available in a diameter of 5 mm and a length of 20 mm. Therefore, morphological inclusion criteria were a maximum 5-mm reference vessel diameter of the ipsilateral internal carotid artery (ICA), a 10-mm maximum lesion length, and a location of the stenosis that allowed selective stenting of the ICA without the need to cover the carotid bifurcation. Furthermore, suitable anatomy for TCD monitoring of the ipsilateral middle cerebral artery (MCA) was an inclusion criterion.

Contraindications to MRI (such as cardiac pacemakers, metal implants, etc.) were exclusion criteria. Furthermore, patients with restenosis after endarterectomy or prior stenting were also excluded.

Study Protocol

Eligible patients who were admitted for elective CAS were identified at the inpatient ward of the Angiology Department. In a 12-month inclusion period, 118 CAS candidates were screened. After verification of the inclusion and exclusion criteria, patient informed consent was obtained, and a neurological examination was performed by an independent neurologist. Baseline investigations included routine laboratory assessment of traditional cardiovascular risk factors, medical history, physical examination, duplex ultrasound investigation of both carotid arteries, and preintervention TCD monitoring to assess the acoustic window for monitoring of the ipsilateral MCA. Eligible patients then underwent a baseline DW-MRI investigation.

Neurological Evaluation

A complete neurological history and clinical exam were performed by an independent neurologist at baseline and after CAS. In cases of suspected neurological events, an instant clinical neurological check, including cranial computed tomography, was performed. Neurological events were categorized as transitory ischemic attacks (TIA), minor stroke, and major stroke according to a modified Rankin Stroke Scale.[21]

Imaging Studies

High-resolution color-coded duplex ultrasound, which had been validated earlier at our institution,[22,23] was used for baseline and follow-up investigations. A Sequoia 512 plat-

form (Siemens/Acuson, Mountain View, CA, USA) with a 5- to 8-MHz linear probe (model 8L5) was used for the duplex investigations. Good agreement of duplex ultrasound compared to intra-arterial digital subtraction angiography has been recently demonstrated at our institution.[23]

DW-MRI images were obtained 24 hours before and 24 hours after the index procedure (Philips 1.5T Intera; Philips, Best, The Netherlands) following a standard protocol[17,18] using diffusion gradients in 3 orthogonal directions, with a maximum b of 1000 s/mm^2.

Continuous TCD was performed during the intervention starting immediately at insertion of the arterial sheath and was continued until 90 minutes after arterial closure. A 2-MHz pulse wave TCD device (DWL Elektronische Systeme Multidop X-TCD7; Sipplingen, Germany) was used according to current guidelines.[24] Injection of dye invariably leads to showers of microembolic signals caused by microbubbles, which are considered less hazardous than solid particles[25]; phases of contrast injection were therefore excluded from the analysis, as described previously.[26] TCD monitoring during the CAS procedure was continuously recorded, and markers were set on the digital record to identify the following predefined procedural phases: (1) baseline angiography, (2) introduction of the long sheath to the CCA, (3) filter placement, (4) predilation, (5) stent implantation, (6) postdilation, (7) filter retrieval, (8) final angiography, and (9) 90 minutes post intervention. Two independent observers who were blinded with respect to all patient data, including the type of implanted stent, analyzed the TCD and DW-MRI data offline.

Randomization Process

Random assignment to either protected CAS with a covered stent or protected CAS with a bare stent was performed with computer-generated random digits by 1:1 blockwise randomization in blocks of 4. Sealed numbered envelopes were available in the institution's catheterization laboratory. No stratification criteria were applied.

Carotid Artery Stenting

All patients received clopidogrel (75 mg/d) indefinitely, ASA (100 mg) daily for 4 weeks postintervention, and simvastatin (40 mg/d) indefinitely. A 300-mg loading dose of clopidogrel was administered the day before CAS in patients without pre-existing clopidogrel therapy.

All stenting procedures were done by an experienced interventionist.[10] Briefly, using retrograde transfemoral access and 6-F sheaths, an overview aortic angiogram was established. Thereafter, ipsilateral selective biplanar carotid and intracranial angiograms were obtained, engaging the CCAs with a 5-F right coronary diagnostic catheter. A stiff 0.035-inch guidewire (Amplatz extra stiff; Cook Inc., Bloomington, IN, USA) was then placed in the external carotid artery (ECA) to introduce a long, flexible 6-F sheath to the CCA. Heparin (5000 units) was given intra-arterially. The stenosis was then crossed with a protection device (Filter Wire EZ; Boston Scientific, Natick, MA, USA) under the roadmap technique, and the patient was randomized to receive either a covered stent (Symbiot Covered Stent System; Boston Scientific) or a bare carotid stent (Monorail Carotid Wallstent; Boston Scientific). Atropine (0.5–1.0 mg) was given intravenously immediately before predilation, which was performed with a 3.0-mm rapid-exchange balloon for 5 seconds at a maximum 12 atmospheres. Postdilation after stenting was performed using 5.0- or 5.5-mm monorail balloons ($<$5 seconds at a maximum pressure of 12 atmospheres). After postdilation, a control angiogram was performed to ensure correct placement of the stent, complete apposition of the stent to the vessel wall, and persistent flow through the distal filter device; the angiograms were also reviewed to exclude vessel dissection, spasms, or thrombotic filter occlusions. After verification of a good result, the filter was retrieved, and final biplanar carotid and intracranial angiograms were obtained in the same projections and magnifications as the baseline images.

Surveillance Protocol and Study Endpoints

All patients were re-evaluated at 24 hours, 30 days, and 6 months after CAS. Follow-up

TABLE
Demographic Data and Clinical Characteristics of 14 Patients Undergoing Elective CAS for a High-Grade ICA Stenosis Using Either a Covered or a Bare Metal Stent

	Covered Stent (n=8)	Bare Stent (n=6)	p
Age, y	77 (73–82)	78 (73–83)	0.49
Male sex	7 (88%)	6 (100%)	1.00
Body mass index, kg/m^2	25.6 (23.4–26.9)	25.2 (24.2–28.8)	0.95
Hypertension	4 (50%)	4 (67%)	0.63
Hyperlipidemia	5 (63%)	3 (50%)	1.00
Smoking	1 (13%)	0	1.00
Diabetes	3 (38%)	2 (33%)	1.00
Peripheral artery disease	5 (63%)	3 (50%)	1.00
History of stroke	1 (13%)	0	1.00
History of myocardial infarction	2 (25%)	3 (33%)	1.00
Atrial fibrillation	3 (38%)	1 (17%)	0.58
Chronic renal insufficiency	3 (38%)	2 (33%)	1.00
Degree of stenosis, %	80 (80–95)	85 (80–90)	0.64
Ulceration present	3 (38%)	2 (33%)	1.00

Data are given as counts (%) or median (IQR).

investigations included a clinical history, a neurological examination, and bilateral carotid artery duplex ultrasound.

Primary study endpoints were (1) the rates of cerebral microemboli measured by TCD monitoring during the intervention and up to 90 minutes post intervention and (2) the occurrence of new ischemic lesions as indicated by serial DW-MRI investigations at baseline and 24 hours post CAS. Secondary objectives were (3) the occurrence of neurological events at hospital discharge, 30 days, and 6 months, and (4) the occurrence of in-stent restenosis (>50%) up to 6 months post intervention as measured by duplex ultrasound.

Statistical Analysis

For this pilot study, a sample size of 10 patients per group was estimated as necessary to demonstrate a significant difference in the TCD microembolic signals, which are reported in >80% of the patients undergoing protected CAS.[14,15] A ≥70% reduction of procedure-related microemboli was expected in the covered stent group. A 2-sided $p<0.05$ was considered as statistically significant, and beta was defined as 0.80.

Metric data are presented as the median and interquartile range (from the 25th to the 75th percentile). Discrete data are given as counts and percentages. Mann-Whitney U tests and Fisher exact tests were used for between-group comparisons. Calculations were performed with Stata (release 8.0; StataCorp LP, College Station, TX, USA) and SPSS (version 12.0; SPSS, Chicago, IL, USA).

RESULTS

Demographic data and clinical characteristics of the 14 asymptomatic patients (13 men; median age 77 years, IQR 73–83) randomized to receive a covered (n=8) or a bare carotid stent (n=6) were comparable (Table). All stenting procedures were technically successful. In 1 patient in the covered stent group, 2 overlapping stents had to be implanted because of an initially incomplete coverage of the target lesion. The further course of this patient was uneventful.

The median duration of fluoroscopy was 13 minutes (IQR 8–23). All patients ambulated within 6 hours; median hospitalization was 3 days (IQR 3–4). No peri- or postinterventional neurological complications occurred in any patient, and no other adverse events were recorded up to hospital discharge in any patient.

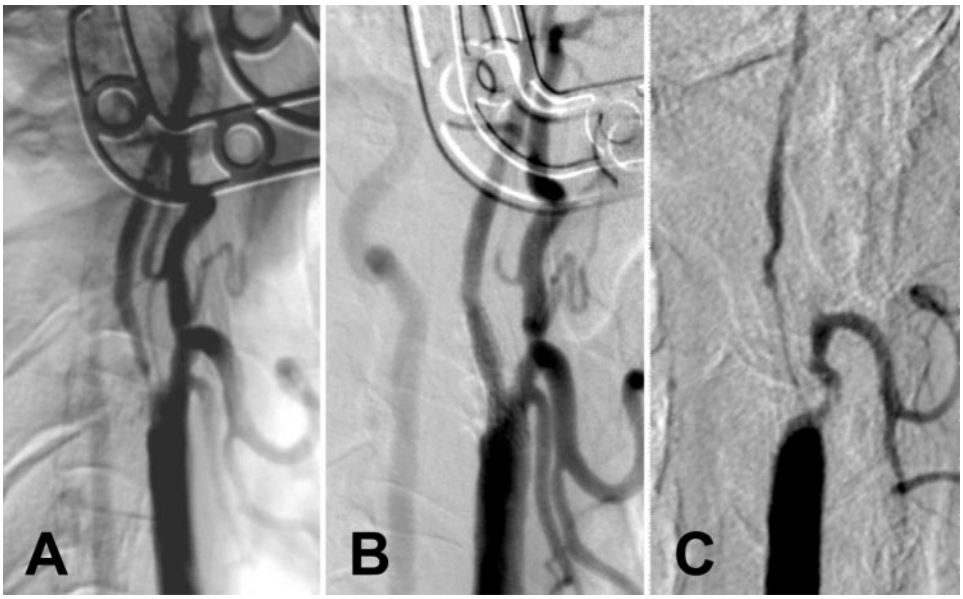

Figure 1 ◆ (**A**) Baseline angiographic image of a patient undergoing covered stent implantation for treatment of a high-grade internal carotid artery stenosis. (**B**) Final angiogram after implantation of the covered stent. (**C**) Follow-up angiogram after 6 months showing a near-occlusion (string sign) of the covered stent.

Cerebral Microembolism

Overall, the median number of recorded microembolic signals was very small (3 signals/patient, IQR 1–7). All signals were recorded during the stenting procedure, none during the 90-minute postintervention period. We observed a significant reduction of ipsilateral signals by TCD in the covered (median 1 signal/patient, IQR 0–4) versus the bare stent group (median 6 signals/patient, IQR 3–8; $p=0.043$). This seemed to be caused mainly by a reduced number of embolic signals during the procedural steps of stent implantation and postdilation [median 0 signals (IQR 0–1) in the covered versus median 2 signals (IQR 1 to 3) in the bare stent group, respectively; $p=0.18$].

Comparison of the pre- and 24-hour post DW-MRI images showed no new ipsilateral hyperintensity in any patient; only 1 new lesion was seen in the contralateral hemisphere in a patient receiving a covered stent, resulting in an overall frequency of 7% (95% CI 0%–20%) of new ischemic DW-MRI lesions.

Follow-up

Clinically, no ipsilateral or contralateral neurological complications occurred during the first 24 hours, 30 days, or 6 months in any patient. However, restenoses (all $>70\%$ lumen diameter reduction) were detected by duplex ultrasound in 3 (38%) of 8 patients in the covered stent group (95% CI 13%–63%) (Figs. 1 and 2), but none was seen in the bare stent group ($p=0.21$). One of these restenotic lesions was re-dilated and stented using a Wallstent 5 months after the index procedure (Fig. 2). The patient with 2 overlapping covered stents showed no restenosis.

The trial was stopped at the discretion of the investigators when the third in-stent restenosis in the covered stent group was detected.

DISCUSSION

We observed a very low rate of intracranial microemboli during and after carotid stenting by TCD monitoring and DW-MRI in this small patient series. Despite the overall low number of cerebral microemboli using the latest-gen-

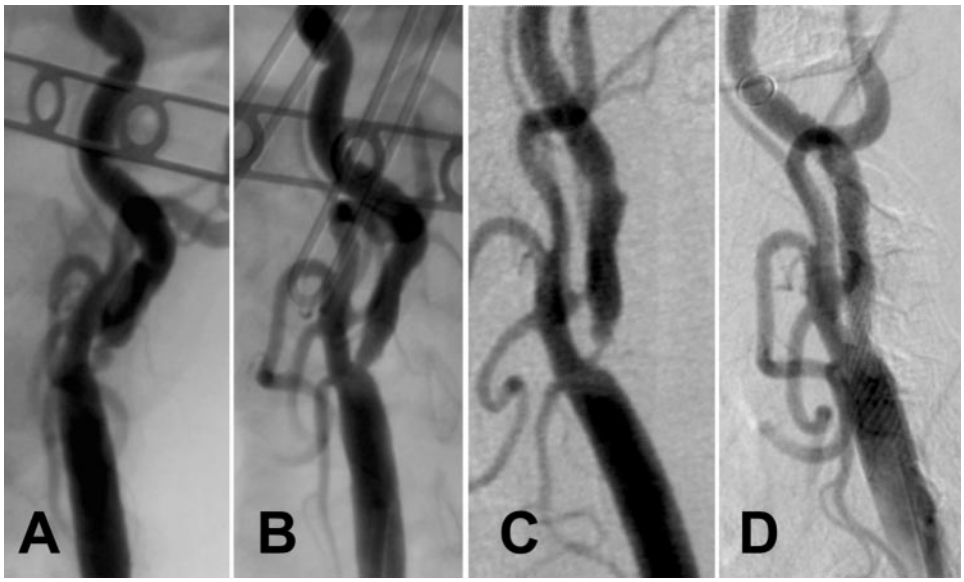

Figure 2 ◆ (**A**) Baseline angiography displaying a high-grade internal carotid artery stenosis. (**B**) Final angiogram after implantation of the covered stent, showing a 30% residual stenosis due to heavy circumferential calcification of the stenosis. (**C**) Follow-up angiogram after 5 months showing a near-occlusion of the covered stent. (**D**) Angiogram after repeat balloon angioplasty and stenting (Wallstent) of the in-stent restenosis.

eration filter devices in combination with bare stents, covered stents may have the potential to further reduce the risk of microemboli and improve procedural safety. Unfortunately, the current trial had to be stopped due to an alarming incidence of restenosis, necessitating efforts to resolve the problem of excessive neointimal hyperplasia of the covered stent.

As yet, covered stents in the carotid circulation were mainly used for repair of true or false aneurysms or carotid dissections.[27–29] However, it had been speculated earlier that covered stents may achieve an immediate mechanical stabilization of the carotid plaque,[19] thereby reducing the risk for dislodging debris and causing distal embolization. Experimentally, covered stents proved to be efficient in ex vivo flow models,[30,31] and an initial clinical experience in atherosclerotic carotid stenosis also seemed promising.[32] Unfortunately, former designs of covered stent-grafts were rigid, with relatively large crossing profiles, making routine application in the carotid arteries unacceptable. Recently, flexible, low-profile, rapid-exchange self-expanding covered stents designed for coronary vein grafts have been released, with promising technical properties and a nominal diameter of up to 5 mm. These devices allow selective stenting of ICA stenosis using a monorail technique and cerebral protection,[32] which made the current trial possible.

Remarkably, TCD as well as DW-MRI showed substantially lower frequencies of microembolic signals than described previously for protected CAS procedures. In the literature, average numbers of TCD signals were reported between 70 to 100 signals per intervention,[14,15] and 22% to 36% of the patients exhibited new ischemic lesions by DW-MRI.[16–18] In contrast, in the present trial, the number of microembolic TCD signals was consistently $<$10 in both treatment groups, and DW-MRI showed no ipsilateral ischemic lesion in any patient.

Three issues may account for this discrepancy. First, we enrolled only asymptomatic patients with clinically stable carotid plaques. These patients undoubtedly have a lower risk for neurological complications.[2] Second, latest-generation devices were used in the present study; flexible sheaths, low-profile catheters, and improved filter basket design with

optimal vessel wall alignment may have contributed to this beneficial outcome. Third, the finding may have been a problem of sample size. Nevertheless, we calculated a 95% confidence interval of 0% to 20% for the 7% point estimate of new DW-MRI lesions, suggesting that even with this small patient sample the rate of new DW-MRI lesions can be considered substantially lower than reported previously.

Limitations

We are aware of several limitations of this pilot trial. Most importantly, the number of patients was very small, and the conclusions derived have to be considered preliminary. However, a significant beneficial effect was observed even in this small sample, as anticipated by the sample size calculation. Moreover, our current findings are in line with previous preclinical and clinical observations.[30–32]

Conclusion

The concept of self-expanding covered stents may have the potential to reduce the risk of cerebral microembolism during and after carotid stenting. However, the problem of in-stent restenosis has to be resolved before these devices can be considered for further carotid trials in humans.

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