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PERIPHERAL

A Prospective, Multicenter Study of a Novel Mesh-Covered Carotid Stent

The CGuard CARENET Trial (Carotid Embolic Protection Using MicroNet)

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ABSTRACT

OBJECTIVES This study sought to evaluate the feasibility of the CGuard Carotid Embolic Protective Stent system—a novel thin strut nitinol stent combined with a polyethylene terephthalate mesh covering designed to prevent embolic events from the target lesion in the treatment of carotid artery lesions in consecutive patients suitable for carotid artery stenting.

BACKGROUND The risk of cerebral embolization persists throughout the carotid artery stenting procedure and remains during the stent healing period.

METHODS A total of 30 consecutive patients (age 71.6 ± 7.6 years, 63% male) meeting the conventional carotid artery stenting inclusion criteria were enrolled in 4 centers in Germany and Poland.

RESULTS The primary combined endpoint was the procedure success of the CGuard system and the number and volume of new lesions on the ipsilateral side assessed by diffusion-weighted magnetic resonance imaging at 48 h post-procedure and at 30 days. The secondary endpoint was 30-day major adverse cardiac or cerebrovascular events (death, stroke, or myocardial infarction). Protection devices were used in all procedures. Procedure success was 100%, with 0% procedural complications. The 30-day major adverse cardiac or cerebrovascular events rate was 0%. New ipsilateral ischemic lesions at 48 h occurred in 37.0% of patients and the average lesion volume was 0.039 ± 0.08 cm^3. The 30-day diffusion-weighted magnetic resonance imaging showed complete resolution of all but 1 periprocedural lesion and only 1 new minor (0.116 cm^3) lesion in relation to the 48-h scan.

CONCLUSIONS The use of the CGuard system in patients undergoing carotid artery stenting is feasible. In addition, the benefit of using CGuard may extend throughout the stent healing period. (J Am Coll Cardiol Intv 2015;8:1229–34)

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ABBREVIATIONS AND ACRONYMS

CAS = carotid artery stenting

DW-MRI = diffusion-weighted magnetic resonance imaging

MACCE = major adverse cardiac or cerebrovascular event(s)

TIMI = Thrombolysis In Myocardial Infarction

Carotid artery stenting (CAS) is associated with a stroke risk mainly due to dislodgement of debris from the target lesion during the procedure. The CGuard Embolic Protection Stent (InspireMD Inc., Boston, Maryland) is a novel thin strut nitinol stent combined with a polyethylene terephthalate mesh covering designed to trap and exclude thrombus and friable atheromatous debris to prevent acute and late embolic events from the target lesion. The CARENET (Carotid Embolic Protection Using MicroNet) trial was the first multicenter study of CGuard following the CE Mark of this device in March 2014. The trial was designed to evaluate the feasibility of the CGuard system in the treatment of carotid lesions and the number and volume of new lesions on the ipsilateral side assessed by diffusion-weighted magnetic resonance imaging (DW-MRI) at 48 h post-procedure and at 30 days in consecutive patients suitable for CAS in a multioperator, real-life setting.

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METHODS

STUDY DESIGN AND PATIENTS. The prospective multicenter single arm clinical trial included 30 consecutive eligible patients enrolled in 4 centers in Germany and Poland. The principal inclusion criteria were age of at least 18 years, written informed consent, de novo atherosclerotic target lesion. Symptomatic patients had to have transient ischemic attack, stroke, or amaurosis fugax within the last 6 months on the ipsilateral side with carotid stenosis ≥50% as diagnosed by angiography using NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria. Asymptomatic subjects had to have carotid stenosis ≥80% that qualified for revascularization in the opinion of a vascular specialist and an independent neurologist. The principal exclusion criteria were stage III renal insufficiency, acute stroke within 30 days, myocardial infarct within 72 h, atrial fibrillation, or any other than carotid stenosis known reason for stroke, total occlusion of the index carotid artery, a pre-existing stent that extended into the aortic arch, severe circular calcification of the target lesion, and lesion length exceeding 30 mm.

CAS PROCEDURE. The CAS procedure was to follow the operator's routine except for the use of CGuard in place of a conventional noncovered carotid stent. In particular, the vascular access and the type of embolic protection during CAS were left to the discretion of the operator. Because CAS-related embolization is not limited to the stent deployment and post-dilation phase (1), use of an embolic protection device was recommended.

DEVICE DESCRIPTION. The CGuard System is a carotid stent wrapped with a MicroNet mesh, mounted on a self-expandable delivery system compatible with a 6-F (2.0-mm) catheter (**Figure 1**). The pore size of the mesh when the stent is fully expanded is 150 to 180 μm. Prior to carotid application, this particular mesh type was evaluated in the coronary balloon-expandable stents where it demonstrated a substantial benefit in myocardial perfusion, indicating its impact on reducing thrombotic lesion embolization (2). The CGuard System is available in an array of diameters (6 to 10 mm) and lengths (20 to 60 mm), and is CE-marked for this indication.

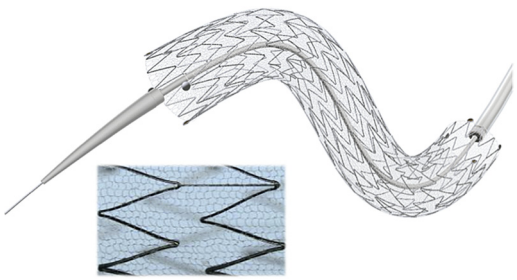
STUDY ENDPOINTS AND DEFINITIONS. The primary combined endpoint was the procedure success of the CGuard system and the number and volume of new lesions on the ipsilateral side assessed by DW-MRI at 48 h post-procedure and at 30 days. Procedure success was defined as device delivered to the target lesion, deployed in the target lesion, and delivery system retrieved. Secondary endpoints were 30-day major adverse cardiac or cerebrovascular events (MACCE) (death, stroke, or myocardial infarction), in-hospital MACCE, and any procedural complications. Per-protocol analysis also includes 12-month MACCE; ipsilateral stroke from 31 days to 1 year; peak systolic velocity and end-diastolic velocity assessment at 30 days, 6 months, and 12 months. Diameter stenosis was determined angiographically according to the NASCET criteria (3). The flow in the external carotid artery was determined according to modified TIMI (Thrombolysis In Myocardial Infarction) criteria (4).

Perfusion was defined as follows: TIMI flow grade 0 = no flow; TIMI flow grade 1 = penetration without perfusion; TIMI flow grade 2 = partial perfusion; TIMI flow grade 3 = complete perfusion.

Detailed evaluation of the patient status at baseline, 24 h after CAS, and at 30 days was by a consultant neurologist independent of the study team. Angiographic and DW-MRI analysis were performed by external core labs, independent of the study sponsor or investigators.

DW-MRI ANALYSIS. MR images available for analysis included T1, T2, fluid attenuated inversion recovery, DW-MRI, and apparent diffusion coefficient sequences. The images were evaluated by a core lab neuroradiologist without the knowledge of the patient's age, sex, or symptoms. Images were analyzed

FIGURE 1 CGuard System



The CGuard System is a carotid stent wrapped with MicroNet mesh, mounted on a self-expandable delivery system. The CGuard System is CE-marked and is available in an array of diameters (6 to 10 mm) and lengths (20 to 60 mm).

TABLE 1 Baseline and Procedural Characteristics (N = 30)

Age, yrs	71.6 ± 7.6
Male	63.4
Hypertension	83.3 (25)
Hyperlipidemia	90 (27)
Diabetes mellitus	23.3 (7)
Cigarette smoking, current	13.4 (4)
Previous myocardial infarction	26.7 (8)
Previous TIA	13.3 (4)
NIH stroke scale	1.37 ± 2.6
Femoral access	100 (30)
Target vessel	
Left ICA	33.3 (10)
Right ICA	66.6 (20)
Protection used	
Distal filter protection	96.6 (29)
Proximal balloon protection	3.4 (1)
Pre-dilation	70.9 (22)
Post-dilation	77.4 (24)
Post-dilation pressure, atm	13.6 ± 4.5
Procedure success	100 (30)
Stent deployed	100 (30)
Stent diameter, mm	8.23 ± 0.8
Stent length, mm	34.8 ± 5.0
Second stent used	3.33 (1)

Values are mean ± SD, %, or % (n).
ICA = internal carotid artery; NIH = National Institutes of Health; TIA = transient ischemic attack.

for evidence of acute ischemia as indicated by significant restricted diffusion (increased signal) with corresponding decreased apparent diffusion coefficient and no or minimal T2/fluid attenuated inversion recovery signal.

Volume analysis of acute ischemic lesions was measured on a separate workstation (Olea Medical, La Ciotat, France) using a region-growing image segmentation technique.

RESULTS

PATIENT CHARACTERISTICS AND PROCEDURAL DETAILS. Consistent with the study protocol, 30 consecutive, all-comer patients were enrolled at 4 sites in Europe. Full baseline and procedural characteristics are summarized in Table 1. Mean age was 71.6 years and 63% of patients were male. Among the major risk factors, 23% patients had diabetes and 27% had previous MI. Ten patients (33.3%) had symptomatic carotid artery stenosis. Distal filter protection devices were used in 29 patients (Emboshield [Abbott Vascular, Temecula, California] in 8 patients; EPI filter wire [Boston Scientific, Marlborough, Massachusetts] in 11 patients; and Spider FX [eV3, Plymouth, Minnesota] in 10 patients) and proximal balloon protection (MoMa [Medtronic, Minneapolis, Minnesota]) in 1 patient. Pre-dilation was performed in 70.9% of the cases and post-dilation in 77.4%. The CGuard System was delivered and deployed in all cases (procedural success 100%).

ANGIOGRAPHIC RESULTS. The index lesion was located in the left internal carotid artery in 33.3% and in the right in 66.6% of patients. The average length and reference vessel diameter were 16.94 ± 4.7 mm and 6.18 ± 0.68 mm, respectively. Mean percentage of diameter stenosis was 79.9 ± 5.0, which decreased to 16.9 ± 6.5 post-intervention. The complete angiographic data is shown in Table 2.

CLINICAL OUTCOMES AT 30 DAYS. Clinical follow-up at 30 days was available in all 30 patients. MACCE was 0%.

DW-MRI OUTCOMES AT 48 H AND 30 DAYS. DW-MRI imaging analysis was available for 28 patients at baseline (the analysis of 2 patients was not feasible due to multiple dental work artifacts and a large recent cerebral artery ischemia on the baseline scan precluding analysis of any potential new lesions in the context of CAS); for 27 patients at 48 h (1 MRI was not done in the study window) and for 26 patients at 30 days (2 patients without any lesions on the baseline and 48-h scans and who were free of symptoms did not agree to the 30-day scan).

At baseline, 2 patients showed minor DW-MRI lesions (total of 12 lesions, average volume of 0.06 ± 0.27 cm^3). At 48 h after the stent procedure, DW-MRI analysis revealed that 10 of 27 patients (37.0%) had new acute ischemic lesions on the ipsilateral side with a total of 83 lesions, driven mostly by a single patient in whom proximal protection was used, with

TABLE 2 Angiographic Results

	Baseline	Final
Lesion location in left/right ICA	33 left/67 right	–
Lesion length, mm	16.94 ± 4.7	–
RVD, mm	6.18 ± 0.68	–
MLD, mm	1.25 ± 0.34	4.82 ± 0.60
Percentage of in-stent diameter stenosis	79.9 ± 5.0	16.9 ± 6.5
TIMI flow grade 3 in the ECA	100.0	100.0

Values are % or mean ± SD. Dashes indicate that data are not available.

ECA = external carotid artery; ICA = internal carotid artery; MLD = minimal lumen diameter; RVD = reference vessel diameter; TIMI = Thrombolysis In Myocardial Infarction.

54 new lesions. The average lesion volume was 0.039 ± 0.08 cm^3. Six patients (22.2%) had new contralateral lesions. The total number of contralateral lesions was 34, with average lesion volume was 0.03 ± 0.08 cm^3 (range 0.028 to 0.325 cm^3). Twelve study subjects (46.2%) showed new bilateral lesions 48 h after CAS. The average lesion volume was 0.05 ± 0.09 cm^3.

All but 1 new ipsilateral lesion at 48 h had resolved by 30 days. DW-MRI at 30 days showed only 1 new ipsilateral lesion (4.0%, 0.116 cm^3) without any new lesions on the contralateral side. Key DW-MRI data are presented in Table 3.

DISCUSSION

The principal findings from the present study are the following:

1. Procedure success rate was 100% with no compromise of blood flow in the external carotid artery.
2. The new ipsilateral DW-MRI lesions present at 48 h in 37% of study patients were minor and all but 1 lesion resolved completely by 30 days, and the majority of the patients (63.0%) did not have any new procedure-related acute ischemic lesions at 48 h.
3. The 30-day MACCE rate was 0% in symptomatic as well as asymptomatic patients undergoing CAS with a novel mesh-covered carotid stent.

TABLE 3 New Ipsilateral Lesions by DW-MRI Analysis*

	48 H n = 27	30 Days n = 26
Subjects with new AIL	10	1
Incidence of new lesions, %	37.0	4.0
Total number of new AIL	83†	1
Average number of new AIL per patient‡	3.19 ± 10.33	0.04 ± 0.20
Average lesion volume, cm^3	0.039 ± 0.08	0.08 ± 0.00
Maximum lesion volume, cm^3	0.445	0.116
Permanent AIL at 30 days	–	1

Values are counts or mean ± SD. *At baseline, 1 patient had significant MRI artifacts from a dental implant that disabled cerebral analysis. DW-MRI in another subject demonstrated middle cerebral artery ischemia whose extent was prohibitive for an analysis of any further lesions in relation to CAS (core lab exclusion). At 48 h, 1 patient did not have an MRI, but did have one at baseline and 30 days. Two additional patients did not agree to the 30-day MRI scan. †One patient had 54 new lesions on the 48-h scan. ‡For 48-h imaging in relation to the pre-CAS (baseline) scan; new lesions at 30 days are in relation to the scan at 48 h after CAS.

AIL = acute ischemic lesions; CAS = carotid artery stenting; DW-MRI = diffusion-weighted magnetic resonance imaging; MRI = magnetic resonance imaging.

CAS has emerged as an alternative to carotid endarterectomy (5-10). CAS is associated with risk of embolization at every step of the procedure, including cannulation of the target artery, placement of the guiding catheter/sheath, wiring of the lesion, pre-dilation, stent placement and release, and stent post-dilation (1). Although current data support the use of embolic protection devices for CAS (11), embolic protection devices do not cover all the emboli-generating CAS phases. With conventional carotid stents, the most emboli-generating CAS phases are stent deployment and post-dilation (1). In a substudy of the SPACE (Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy) trial, the event rate was higher in the group of patients who received an open cell versus a closed cell stent (12). Also Schnaudigel et al. (13) found a significantly higher incidence of new ipsilateral DW-MRI lesions in patients who received an open versus a closed carotid stent. Therefore, tailored CAS algorithms have been proposed that include conventional carotid stent type selection based on the lesion morphology and target vessel anatomy (14) or maximized use of proximal neuroprotection (15). Plaque protrusion through the stent struts may provide a mechanism for embolization not only during CAS (when this risk may be minimized by embolic protection) but also following the CAS procedure. Indeed, De Donato et al. (16) performed optical coherence tomography after carotid stenting and found plaque prolapse related to the design of implanted stents in up to 68.6% of patients (for open cell stents).

In line with these findings, in an earlier DW-MRI study, we could demonstrate that cerebral embolization after CAS is an ongoing process beyond the time of the procedure in a significant number of patients (17). In another study using conventional carotid stents, up to two-thirds of CAS-associated adverse neurological events occurred after the procedure, within the stent healing period of about 30 days (18). This explains why temporary brain protection systems are ineffective in abolishing CAS-associated adverse neurological events. Detailed analysis of

data, generated using an open-cell stent suggest that prevention of plaque and thrombotic material protrusion through the struts may result in reduced CAS-associated embolization (10,18,19).

CGuard is a nitinol self-expanding stent covered by MicroNet mesh with a pore size ranging from 150 to 180 μm, which prohibit cerebral embolization but allow for unimpeded flow to the external carotid artery in case of bifurcation stenting. This embolic protection stent system, aimed to reduce the risk of early and late cerebral embolization, was tested in the present CARENET study in an all-comer patient population with carotid stenosis referred for revascularization. Our multicenter study demonstrates that CGuard is compatible with all embolic protection device types used in an all-comer patient population. The stent could be successfully implanted in all patients with a MACCE rate of 0% and TIMI flow grade 3 to the external carotid artery.

DW-MRI is a sensitive tool in identifying cerebral emboli during CAS (20). In the present study, 37.0% of patients had new ischemic lesions with an average volume of lesions per patient of 0.039 cm^3. This compares very favorably with data from the PROFI (Prevention of Cerebral Embolization by Proximal Balloon Occlusion Compared to Filter Protection During Carotid Artery Stenting) trial (15) as well as the MRI substudy of the ICSS (International Carotid Stenting Study) (8), where the incidences of new ipsilateral lesions were 66.2% (average of both proximal and distal filter groups) and 68.0% (ipsilateral and bilateral lesions combined), respectively, and average lesion volume 0.375 cm^3.

Studies of DW-MRI after emboli-protected CAS have consistently reported a paucity of overt neurological complications in the presence of focal ischemic brain injury (11,21,22). In a previous study (20), we found that patients with post-CAS brain ischemia who sustained a major stroke had both a markedly higher number of ischemic foci and a larger area covered by an ischemic focus than did patients without neurological symptoms. These findings of an association between the cerebral embolic load and adverse neurologic events were recently supported by Kastrup et al. (11) and are consistent with recent data from the ICSS study (23). The present study has found not only a low incidence and cerebral lesion number on DW-MRI using the CGuard system, but also a small size of the limited embolic lesions that did occur.

Little is known about the extent by which focal cerebral ischemia affects cognitive function. In a recent study (24), a deterioration of cognitive function after emboli-protected CAS was observed at discharge in 18 of 22 patients with cerebral ischemia on post-CAS DW-MRI. A decline in cognitive function has also been found in elderly patients with silent brain infarcts (25). The best CAS procedure is the one with optimal angiographic result paralleled by minimal embolization both during procedure and afterward, during stent healing. Thus, minimization of new ischemic lesions during and after CAS using the CGuard system is anticipated to translate into clinical benefit for the patients treated with a mesh-covered embolic protection stent.

STUDY LIMITATIONS. One limitation of the present study is its protocol-determined moderate size. Therefore, the extremely low MACCE rate in this first multicenter trial may require further confirmation in large-size clinical studies or registries that will be adequately powered for clinical endpoints. Another limitation is that selection of the embolic protection device was left to the operator's discretion and was not standardized. Nevertheless, this first study fully describes the feasibility of a novel mesh-covered carotid stent implantation in an all-comer CAS population in a multicenter setting. Importantly, the 0% MACCE rate at 30 days is fully consistent with the DW-MRI-determined low incidence of new ischemic lesions and the extremely low periprocedural lesion volume that is unprecedented by DW-MRI data in studies that employed previous generations of carotid stents with embolic filter protection.

STUDY IMPLICATIONS. This first completed multicenter study of a mesh-covered carotid stent indicates that the use of CGuard system may translate into minimized brain embolization during the CAS procedure as well as during the stent healing period; both may lead to a paradigm shift in CAS.

CONCLUSIONS

The use of the CGuard system in patients undergoing CAS is feasible in a multicenter setting. In addition, the benefit of using CGuard may extend to the stent healing period.

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PERSPECTIVES

WHAT IS KNOWN? CAS is associated with a stroke risk mainly due to dislodgement of debris from the target lesion during the procedure and during the healing period.

WHAT IS NEW? We demonstrate the feasibility and safety of the CGuard Embolic Protection Stent to minimized cerebral embolization during CAS.

WHAT IS NEXT? The data have to be confirmed in a larger trial with clinical endpoints.

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KEY WORDS carotid artery stenting, diffusion-weighted magnetic resonance imaging, embolic protection, mesh stent