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ORIGINAL RESEARCH

Safety and Efficacy of a Novel Micro Net Carotid Stent System

Results of the C-GUARDIANS Trial

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ABSTRACT

BACKGROUND The authors report the intention-to-treat results for the C-GUARDIANS (Safety and Efficacy of the CGuard™ Carotid Stent System in Carotid Artery Stenting) pivotal trial in carotid artery stenting patients considered high risk for carotid endarterectomy, treated with this novel stent and followed for 1 year.

OBJECTIVE The authors sought to evaluate the safety and efficacy of the MicroNet-covered stent in treating patients with significant carotid stenosis at high risk of adverse events from carotid endarterectomy.

METHODS The trial is a prospective, multicenter, single-arm trial (NCT04900844). The primary endpoint was a composite of the incidence of death, all stroke, and myocardial infarction (DSMI) through 30 days postprocedure, and ipsilateral stroke from 31 to 365 days postprocedure. Secondary endpoints included the incidence of DSMI and of each individual component through 30 days, as well as the incidence of ipsilateral strokes through 30-day and 1-year follow-up. All events were adjudicated by an independent clinical events committee.

RESULTS Between July 2021 and June 2023, 316 patients with asymptomatic ≥80% or symptomatic ≥50% carotid lesions were treated with this novel stent at 24 sites in the United States and European Union using approved embolic protection systems. The DSMI rate through 30 days was 0.95% (3/316). DSMI at 30 days and ipsilateral stroke at 1 year was 1.93% (6/296). Target lesion revascularization through 1 year was 1.0% (3/299).

CONCLUSIONS The C-GUARDIAN trial demonstrated low rates of DSMI through 30 days, and ipsilateral stroke through 1 year. No unexpected adverse device effects or unexpected serious adverse device effects were reported. These results demonstrate that carotid artery stenting with this novel stent is safe, effective and durable, and supports the potential neuroprotective properties of this unique micro mesh-covered stent. (JACC Cardiovasc Interv. 2025;■:■–■) © 2025 by the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

AE = adverse event

CAS = carotid artery stenting

CEA = carotid endarterectomy

CEC = clinical events committee

DSMI = death all stroke and myocardial infarction

DUS = duplex ultrasound

EPD = embolic protection device

FDA = Food and Drug Administration

IDE = investigational device exemption

IFU = instructions for use

ITT = intention-to-treat

MAE = major adverse event(s)

MI = myocardial infarction

MRI = magnetic resonance imaging

NIHSS = NIH Stroke Scale/Score

TLR = target lesion revascularization

Since its inception, carotid artery stenting (CAS) has undergone extensive clinical investigation in the United States and Europe.[1] Initial studies employed open-cell design stents, with or without embolic protection devices (EPDs), which were subsequently followed by closed-cell design stents and more advanced EPDs. These early investigations culminated in the initial Food and Drug Administration (FDA) approvals of stent designs and the clearance of their companion EPDs, followed by a subsequent wave of device approvals, as evidenced and in association with improved procedural outcomes.

Improvements in CAS outcomes over time have been well documented,[2] and are attributed to the combined effects of advancements in technology, better patient selection, and increased operator experience. Large postmarketing studies also played a key role in defining the results of CAS.[3] Pivotal trials were typically performed in patients at high risk for adverse events (AEs) from carotid endarterectomy (CEA). The CREST trial (Carotid Revascularization Endarterectomy versus Stenting Trial), the first large randomized controlled trial of CAS vs CEA in patients at standard risk, enrolled 2,502 patients by 2008.[4] The study demonstrated that CAS with a first-generation, open-cell stent and first-generation distal embolic protection device (filter) was overall not inferior to CEA; however, CAS was associated with a higher incidence of periprocedural minor strokes, whereas CEA showed a greater occurrence of periprocedural myocardial infarctions (MIs).[4]

Technological innovation of CAS equipment has focused on minimizing the risk of neurological complications both during the stenting procedure and in the long term. This imperative, in turn, centered on balancing device ease of use and stent navigability while minimizing the risk of intraluminal plaque prolapse, distal embolization, and stroke events. In 2014, a second-generation carotid stent, CGuard (InspireMD), received CE-mark approval in Europe. The CE-mark milestone was predicated on near-total elimination of permanent cerebral injury and the absence of major adverse cardiac and cerebrovascular events reported in the CARENET (Carotid Embolic Protection Using MicroNet) prospective trial of CGuard CAS.[5] This novel stent system consists of an open-cell, bare-metal nitinol stent encased in a single-fiber knitted mesh with pores ranging in size from 150 to 180 μm (**Figure 1**).

FIGURE 1 Novel Micro Mesh MicroNet-Covered Stent System

The stent consists of a widely open-cell nitinol frame (resulting in high conformability) encapsulated in micro mesh sleeve with pore diameter ranging from 150 to 180 μm, designed to trap and sequester plaque material from the artery lumen.[8]

Strokes can occur during any portion of the CAS procedure; however, the major incidence of documented distal embolization takes place during stent deployment and postdilatation. With first-generation carotid stents, intraluminal plaque protrusion and liberated emboli are largely responsible for cerebral defects on magnetic resonance imaging (MRI) and embolic stroke events. Furthermore, plaque protrusion and embolization are likely responsible for a significant proportion of embolic events and strokes observed in the postprocedural period. The novel dual-layer stent is designed to mechanically sequester the plaque, debris, and potential thrombotic content against the vessel wall while preventing plaque prolapse into the artery lumen, thereby reducing periprocedural stroke risk. The hypothesis is that the micro mesh (**Figure 1**) would act as a built-in intra- and postprocedural "stroke prevention" feature. Multiple studies in Europe showed an unprecedentedly low risk of AEs at 30 days and through 1 year, with average death, all stroke, and myocardial infarction (DSMI) at 30 days at ~1%, and DSMI at 30 days plus ipsilateral stroke at 1 year at ~2%, consistently.[6-10]

The compelling European data supporting the safety and effectiveness of this novel stent system was the impetus to study the stent in the United States for regulatory approval. The prospective, multicenter, primarily U.S.-based, investigational device exemption (IDE) trial of this carotid stent system was undertaken in patients with defined obstructive carotid artery disease at high risk for AEs with CEA, with a composite primary endpoint of DSMI

within 30 days and ipsilateral stroke between 31 and 365 days. Here, we report the C-GUARDIANS 30-day and 1-year outcomes.

METHODS

STUDY POPULATION & DESIGN. C-GUARDIANS is a single-arm, multicenter, prospective, pivotal IDE trial (IDE Number: G190185). Patients between 19 and 80 years of age with carotid artery disease as evidenced by asymptomatic carotid diameter stenosis ≥80% or symptomatic carotid diameter stenosis ≥50%, using NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria, treatable with CAS and considered at high risk for CEA, able to tolerate dual antiplatelet therapy for a minimum of 30 days, and with a life expectancy of at least 2 years were considered for inclusion. Symptomatic status was defined as amaurosis fugax, transient ischemic attack, or stroke ipsilateral to the side of the treated lesion within the 6 months before the procedure. All patients were required to have pre-enrollment carotid duplex ultrasound (DUS), imaging of the aortic arch and carotid anatomy with computed tomography angiography or magnetic resonance angiography and required approval by a dedicated screening committee to ensure appropriate anatomy for inclusion. All study patients had anatomical and/or comorbid characteristics that made them high risk for AEs from CEA based on standard established criteria.

Stent implantation could only be performed by physicians experienced with carotid stenting. A formal training program including stent deployment in a benchtop simulator model was conducted before subject treatment by participating investigators.

The study was conducted under Good Clinical Practices and had independent adjudication of all AEs by a clinical events committee (CEC). Ultrasound and angiograms performed throughout the study were analyzed by an independent core laboratory (Syntropic Corelab). Computed tomography angiography and magnetic resonance angiography images were reviewed by a screening committee before subject enrollment. An independent data safety monitoring board reviewed safety events reported for the study patients. This clinical trial was registered at ClinicalTrials.gov in accordance with the requirements of U.S. 42 CFR Part 11 clinical trial registration (NCT04900844).

ENDPOINTS AND DEFINITIONS. The primary endpoint was a composite of the incidence of DSMI through 30 days postprocedure, and ipsilateral stroke from day 31 to day 365 postprocedure. Technical success was defined as the number of subjects with at least 1 novel device that was successfully delivered and deployed with a final residual diameter stenosis <30%. The incidence of in-stent restenosis >70% was defined as peak systolic velocity >300 cm/s or stent occlusion based on carotid DUS through 1-year follow-up. Incidence of target lesion revascularization (TLR) through 1-year follow-up was defined as revascularization of the original treatment site, including angioplasty, stenting, or endarterectomy.

DEVICES. This carotid stent is a dual layer stent comprised of an open-cell self-expanding nitinol stent wrapped with a unique micro mesh (**Figure 1**). Detailed technical characteristics of this carotid stent have been reported previously.[5] In accordance with the protocol, the novel stent systems were used in conjunction with the FDA-approved Emboshield NAV6 (Abbott Vascular) and/or the Mo.Ma Ultra (Medtronic) embolic protection systems.

CAS PROCEDURE. The CAS procedure was performed by appropriately trained operators from different specialties (interventional cardiology, vascular surgery, interventional vascular medicine, interventional radiology, and neuroradiology/neurosurgery) according to institutional policies and the specific instructions for use (IFU) for the devices employed. Decisions regarding vascular access and the type of approved embolic protection during the CAS were determined by the operator.

Patients received aspirin (300 to 325 mg) and clopidogrel (75 mg) for a minimum of 7 days before the procedure, or loading doses of aspirin and clopidogrel (which were defined in the protocol) on the day of the procedure. Prasugrel or ticagrelor were accepted as alternatives to clopidogrel. Statin therapy was prescribed per standard of care. At the time of procedure, heparin (activated clotting time >250 seconds) or bivalirudin was administered for anticoagulation.

Carotid (target vessel) angiography was performed before stent system insertion into the vasculature to visualize the target lesion and to assess percent diameter stenosis, target vessel reference diameter, target lesion length, and appropriateness of anatomy for CAS. EPDs were deployed per manufacturer's IFU. Stent size selection was based on lesion length, with nominal stent diameter "oversized" by at least 1 mm to the common carotid artery angiographic diameter, consistent with the device IFU. Pre- and/or

post-dilatation was recommended but performed at the operator's discretion.

NIH Stroke Scale/Score (NIHSS) and Modified Rankin Scale (mRS) evaluations by trained, independent personnel were performed before the procedure, on discharge or within 96 hours postprocedure, at 30 days, 180 days, and at 1 year; the subjects will continue to be followed at 2 and 3 years with neurologic exams and carotid DUS performed.

ETHICS/STATEMENT OF COMPLIANCE. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, the International Standard Organization (ISO 14155:2020), and any regional or national regulations (ie, U.S. Code of Federal Regulations [CFR], including 21 CFR parts 50, 54, 56, 812, and 45 CFR part 46), as applicable. The study was approved by institutional review boards before activation, and all patients submitted written informed consent to participate.

STATISTICAL ANALYSIS. The study evaluated the safety and effectiveness of the CGuard/CGuard Prime stent for the treatment of carotid artery stenosis in asymptomatic and symptomatic patients and compared the outcomes to a composite performance goal of 11.6% developed from previously completed CAS IDE studies using similar patient populations for FDA approval.[11-20]

The sample size for the study was determined on a superiority test of the primary endpoint rate to the predefined performance goal agreed upon with the FDA. The primary endpoint was tested on the intention-to-treat (ITT) population. The ITT analysis population included all enrolled patients who signed informed consent, met all eligibility criteria, were approved by the screening committee, and underwent the study procedure where the study device entered the vasculature. Prespecified Kaplan-Meier estimate analyses were performed for the primary endpoint and other time-to-event endpoints. An assessment of site poolability using a Fisher exact test was performed to evaluate consistency of the primary endpoint rate across sites. All statistical analyses were performed using STATA version 18.0 (StataCorp). Statistical analysis was performed by an independent statistician.

DEFINITIONS. Major stroke was defined as symptoms and an NIHSS ≥6 persisting for 30 days after symptom onset; all strokes were adjudicated by the CEC and data safety monitoring board. Ipsilateral stroke was defined as an ischemic stroke involving the anterior circulation (the middle cerebral artery, the anterior cerebral artery, or a more proximal intracranial branch of the ipsilateral internal carotid artery) in the cerebral hemisphere corresponding to the target lesion CAS. MI was defined per the Fourth Universal Definition of Myocardial Infarction criteria and were adjudicated by the CEC.[21]

RESULTS

ENROLLMENT AND DISPOSITION. Between July 22, 2021, and June 28, 2023, 316 patients enrolled at 19 sites in the United States and 5 sites in the European Union constituted the ITT population as they met eligibility criteria for the study, were approved by the independent screening committee, and the study device entered the vasculature. Forty-four subjects were screen failures by the screening committee. The main reasons for screen failure included presence of circumferential calcium, unsuitable anatomy such as tortuosity or type III arch, and nonqualifying lesion measurements. There was 1 roll-in patient who was not included in the ITT analysis; this patient had no major adverse events (MAEs) through 1 year. Of the 316 patients in the ITT analysis, 300 were evaluable for the 1-year endpoint: 2 withdrew consent, 1 was lost to follow-up, 1 died within 30 days, 6 died within 1 year from comorbid conditions unrelated to the stent procedure, and 6 patients missed the 12-month clinical follow-up visit. Multiple attempts were made to encourage these patients to follow-up, without success.

PATIENT DEMOGRAPHICS AND LESION CHARACTERISTICS. Patient demographics and lesion characteristics are summarized in Table 1. The ITT population was predominantly male (202/316, 63.9%) with an average age of 69.0 ± 6.6 years. A total of 79 patients (25.0%) were symptomatic. The mean lesion length was 18.6 ± 7.31 mm, with moderate-to-severe calcification in 35.7% of subjects as assessed by the angiographic core lab. The mean preprocedure target lesion percent stenosis was 90.2%. The mean residual stenosis at the completion of the study procedure was 7.2%. Emboshield NAV6 alone was used in 237 patients (75%), Mo.Ma Ultra alone in 54 patients (17%), 24 patients (7.6%) had Emboshield NAV6 and Mo.Ma Ultra used together, and 1 procedure (0.3%) was performed with a non-study EPD due to the unavailability of any of the 2 study-approved EPDs at the time of procedure.

Three patients had the study device introduced into the vasculature, but not deployed, and received a non-study stent. They were followed for safety up to 30 days and exited after the 1-month follow-up

TABLE 1 Demographic, Anatomical, and Procedural Characteristics of Study Patients

Patient Demographics and Medical History	ITT (N = 316)
Sex	
Female	36.1 (114)
Male	63.9 (202)
Age, y	
Mean ± SD	69.0 ± 6.6
Min, max	47, 80
Smoking history	
Never smoked	26.6 (84)
Current smoker	26.3 (83)
Former smoker	47.2 (149)
Medical history	
Symptomatic	25 (79/316)
Asymptomatic	75 (237/316)
Diabetes mellitus	41.8 (132/316)
Angina	21.2 (67/316)
Cardiac arrhythmia	10.1 (32/316)
Atrial fibrillation	4.4 (14/316)
Congestive heart failure	7.0 (22/316)
Chronic obstructive pulmonary disease	24.1 (76/316)
Coronary artery disease	53.2 (168/316)
Previous PCI	33.9 (107/316)
Hypercholesterolemia/dyslipidemia	89.9 (284/316)
Hypertension	93.0 (294/316)
Peripheral vascular disease	30.1 (95/316)
Myocardial infarction	24.7 (78/316)
Stroke	22.2 (70/316)
Transient ischemic attack	13.0 (41/316)
Amaurosis fugax	13.3 (42/316)
Previous carotid intervention at the target vessel	5.1 (16/316)
Lesion and Procedural Characteristics (per Core Lab)	**ITT (N = 316)**
Target lesion side	
Left	51.0 (159/312)
Right	49.0 (153/312)
Calcification	
None/Mild	64.3 (200/311)
Moderate	20.6 (64/311)
Severe	15.1 (47/311)
Lesion length, mm	
Mean ± SD	18.6 ± 7.3
Median (Q1-Q3)	20 (15-25)
Stenosis, %	
Mean ± SD	90.2 ± 9.7
Median	93.0
Balloon predilation performed	
No	7.0 (22/316)
Yes	93.0 (294/316)
Balloon postdilation performed	
No	3.2 (10/316)
Yes	96.8 (306/316)
Embolic protection device	100.0 (316/316)
Emboshield NAV6 only	75.0 (237/316)
Mo.Ma Ultra only	17.1 (54/316)
Emboshield NAV6 + Mo.Ma Ultra	7.6 (24/316)
Non-study EPD	0.3 (1/316)
Postprocedure stenosis	
Mean ± SD	7.2 ± 11.9
Median (Q1-Q3)	0 (0-10)
Study stents implanted	319
Non-study stents implanted	3
More than 1 study stent implanted	6

Values are % (n), % (n/N), or n, otherwise as indicated.
ITT = intention to treat; PCI = percutaneous coronary intervention.

visit, per protocol. None experienced an AE before study exit. Six patients (1.9%) received 2 study stents to achieve good coverage of the entire lesion length.

OUTCOMES. All 316 patients were available for the ITT DSMI analysis. At 30 days, 0.95% of patients (3/316; 95% CI: 0.20%-2.75%) had at least 1 MAE through 30 days postindex procedure. Of those MAEs, 2 were due to a minor stroke, and 1 was due to a major stroke on day 10 that resulted in death. The patient (a 62-year-old man) with the major stroke stopped dual antiplatelet therapy after discharge from the hospital, a major protocol deviation. A 60-year-old male subject experienced a postoperative lower homonymous quadrantanopia with persistence of symptoms at the 1-month visit. Neurologic assessments performed at the 6- and 12-month visits demonstrated a NIHSS of 0. The CEC adjudicated the event as a minor ischemic stroke of unknown location. A 66-year-old male subject experienced postprocedural mild blurring of vision in the ipsilateral eye with persistence of symptoms at the 1-month visit. The CEC adjudicated the event as a minor retinal ipsilateral stroke.

At the 1-year follow-up, 300 patients were available for analysis in the ITT population. Three patients had an ipsilateral stroke between 31 and 365 days postindex procedure. Of those, 2 were major and 1 was minor. Of the 2 major strokes, 1 occurred in a 68-year-old male patient with prostate cancer who stopped all antiplatelet therapy for 2 weeks before prostatectomy, and the other occurred in a 75-year-old male patient not on anticoagulation therapy with atrial fibrillation; this patient had a patent vessel without any significant stenosis on DUS. There were no MIs through 30 days postprocedure.

Prespecified Kaplan-Meier estimate analyses were performed for the primary endpoint and other time-to-event endpoints. Following the index procedure, 98.06% (310/316) of treated patients were free of DSMI at 30 days and ipsilateral stroke between 31 and 365 days in the ITT population. The Kaplan-Meier estimate for the primary endpoint rate was 1.93% in the ITT population (**Figure 2**). Assessment of the primary endpoint by site demonstrated comparable event rates, with no evidence of heterogeneity across sites (Fisher exact test; $P = 0.4865$).

Technical success was achieved in 98.4% (311/316; 95% CI: 97.02%-99.78%) of the ITT patient population; 2 failures to achieve technical success were due to final residual diameter stenosis >30% and 3 to nondeployment of a study stent. Among the patients with the novel stent implanted who received 1-year Doppler velocity imaging, 2.5% (7/284; 95% CI: 1.0%-5.0%) had >70% in-stent restenosis. Three patients were adjudicated as having TLR during the 1-year period; all 3 patients with TLR were asymptomatic. The TLR rate at 1 year was 1.0% (3/299; 95% CI: 0.2%-2.9%), and freedom from TLR at 1 year by Kaplan-Meier analysis was 99.03% (**Central Illustration**).

DISCUSSION

This pivotal trial showed historically low event rates in patients with obstructive carotid disease at high risk for adverse CEA events, in a cohort including 25% symptomatic patients, comparing favorably with similar patients treated with all forms of carotid revascularization in clinical trials.

The trial's 30-day and 1-year primary endpoint rates are fully consistent with the large peer-reviewed body of literature from Europe published since this device's CE-mark approval in 2014. These include postmarket CAS studies[5-8] and a randomized controlled trial of CGuard vs the CREST-1 study device (ACCULINK, Guidant).[9] The extensive and congruent body of evidence from these peer-reviewed European studies represent 1,758 patients with 30-day outcomes.[10] The aggregate rate for 30-day DSMI in these European studies was 1.1%,[10] validating the DSMI rate observed in the current study, 0.95%. The aggregate rate for DSMI at 30 days and ipsilateral stroke at 1 year in these studies was 1.2%, which is concordant with the primary endpoint rate observed in this study.

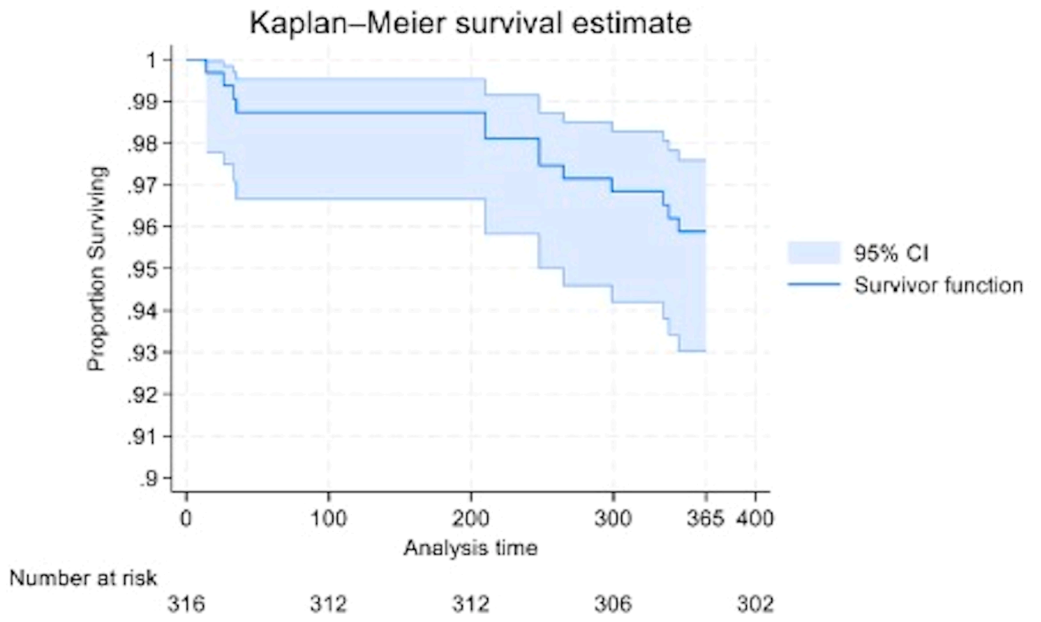
In the context of prior CAS pivotal trials in high-risk patients used for device approval in the United States,[20,22] this study demonstrated the lowest ever periprocedural AE rates (DSMI through 30 days) at 0.95% (3/316) in the ITT analysis. **Figure 3** provides numerical and graphical comparisons of 30-day outcomes of this study those of other IDE studies. Also, the rate of 30-day DSMI in C-GUARDIANS ITT analysis compares favorably with rates in FDA studies of transcarotid arterial revascularization employing a first-generation (single-layer) stent.[23,24]

In the subset of FDA IDE carotid stenting trials with available 1-year outcomes, the current study showed the lowest rate of primary endpoint events (DSMI at 30 days and ipsilateral stroke through 1 year). The 1-year primary endpoint rate was 1.93% in the ITT analysis, the lowest among those reporting 12-month ipsilateral stroke data.

This study's DSMI rates are lower than the DSMI rates for the CEA patients seen in the most recent contemporary standard risk randomized asymptomatic trials, ACT 1 (Carotid Angioplasty and Stenting Versus Endarterectomy in Asymptomatic Subjects Who Are at Standard Risk for Carotid Endarterectomy With Significant Extracranial Carotid Stenotic Disease) (2.6%) and ACST-2 (Second Asymptomatic Carotid Surgery Trial) (3.2%),[22] despite having 25% symptomatic patients in the study. Although these results are not directly comparable, given our high-risk for CEA cohort of patients, the favorable decline in historical DSMI rates seen in this trial support the neuroprotective benefits of this unique micro mesh covered stent.

A mechanistic understanding of the neuroprotective effect of this novel stent was gained from the randomized controlled trial comparing a conventional single-layer stent (nickel-titanium, self-expanding stent) to this stent,[9] which was powered to detect a 50% reduction in ipsilateral diffusion-weighted MRI lesion average volume 48 hours post-procedure. In this randomized trial comparing a single-layer nickel-titanium, self-expanding stent to this novel stent utilizing the same embolic protection system, there was a significant reduction (92.3%) in the total volume of MRI permanent cerebral lesions at 30 days, in addition to a less frequent

FIGURE 2 **Kaplan-Meier Estimate: Primary Endpoint (ITT)**



Kaplan-Meier curve shows freedom from perioperative composite and ipsilateral stroke between 31 days and 1 year. The overall composite event-free rate is 98.07% at 1 year. Brackets denote the beginning and end of intervals. Number at risk represents the number of patients at risk of events at the beginning of each interval. Number of events are cumulative. ITT = intention to treat.

number and smaller volume of postprocedure MRI cerebral lesions.

Considering that this trial showed the most favorable outcomes among pivotal CAS clinical trials with independent adjudication of events, including standard-risk randomized controlled trials such as CREST and ACT-I, and in light of the large volume of peer-review published evidence from the EU,[25,26] this stent system is probably safe and effective in patients with standard surgical risk carotid stenosis, who present with fewer co-morbidities than this study's patient population. Further U.S. trials will evaluate performance of CGuard in acute stroke interventions[27] and in carotid stenting using the transcarotid route.[28]

STUDY LIMITATIONS. As a single arm trial, there is inherent potential for selection bias; however, this study design is representative of other pivotal carotid IDE study designs. Additionally, the exclusion of patients with more challenging anatomy, such as heavily calcified vessels, along with the predominance of asymptomatic patients, may limit the applicability of the results to broader patient populations. The study population was predominantly composed of white males, which may further restrict the generalizability to more diverse demographic groups. Variations in operator experience and procedural techniques across sites may also influence outcomes. Lastly, the favorable outcomes observed in this study likely reflect not only the design features of the stent but may also be the cumulative impact of decades of procedural refinement, improved patient selection, and greater operator experience. Despite these limitations, the data provide valuable insights into the safety and efficacy of this novel stent within the study population. Further studies in real world populations and head-to-head randomized trials would provide additional important insights.

CONCLUSIONS

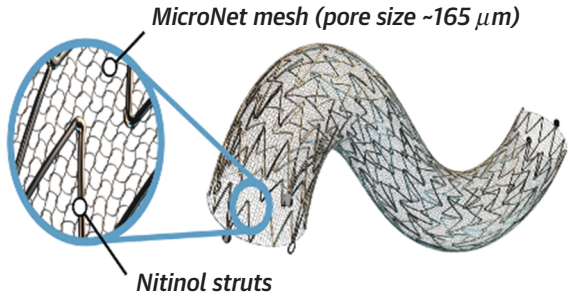
The C-GUARDIAN pivotal trial with independent neurologic assessment and AE adjudication demonstrated historically low rates of clinical AEs in the ITT population of 0.95% and 1.93% for the 30-day hierarchical DSMI endpoint and the 1-year primary endpoint, respectively. The superiority

CENTRAL ILLUSTRATION **The Safety and Efficacy of a Novel Carotid Stent System**

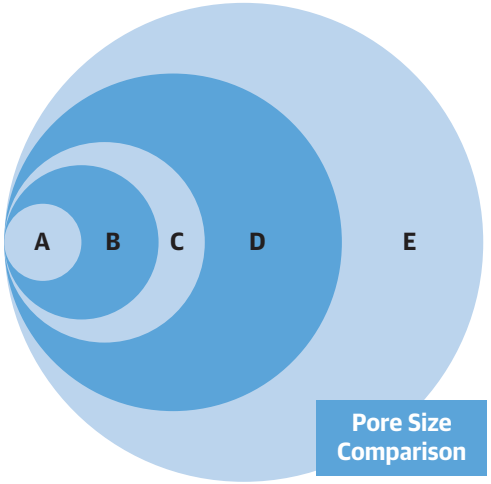
Pivotal IDE Trial: Safety and Efficacy of a Novel Carotid Stent System

Study Population (N = 316)

- High risk for CEA adverse events: 100%
- Symptomatic: 25%
- Calcified lesions: 36%
- Lesion length (mean): 19 mm
- Diameter Stenosis (mean): 90.2%



The novel carotid stent is a PET micro-mesh covered stent.



For visualization of the magnitude of the differences in plaque coverage.

A. PET MicroNet-covered CGuard stent (~165 μm)
B. Metallic micromesh dual-layer braided stent (~375 μm)
C. PTFE-covered open-cell nitinol stent (~500 μm)
D. Typical single-layer closed-cell stent (~1,050 μm)
E. Typical single-layer open-cell stent (~1,900 μm)

30-Day Results (ITT)

DSMI through 30-day (0.95%)
- Death (all cause): 0.32%
- Stroke: 0.95%
- MI: 0%

Outcomes Through 1 Year (ITT)

Primary Endpoint (1.93%)
DSMI through 30D & Ips Stroke through 1-year

TLR at 12 Months (1.00%)

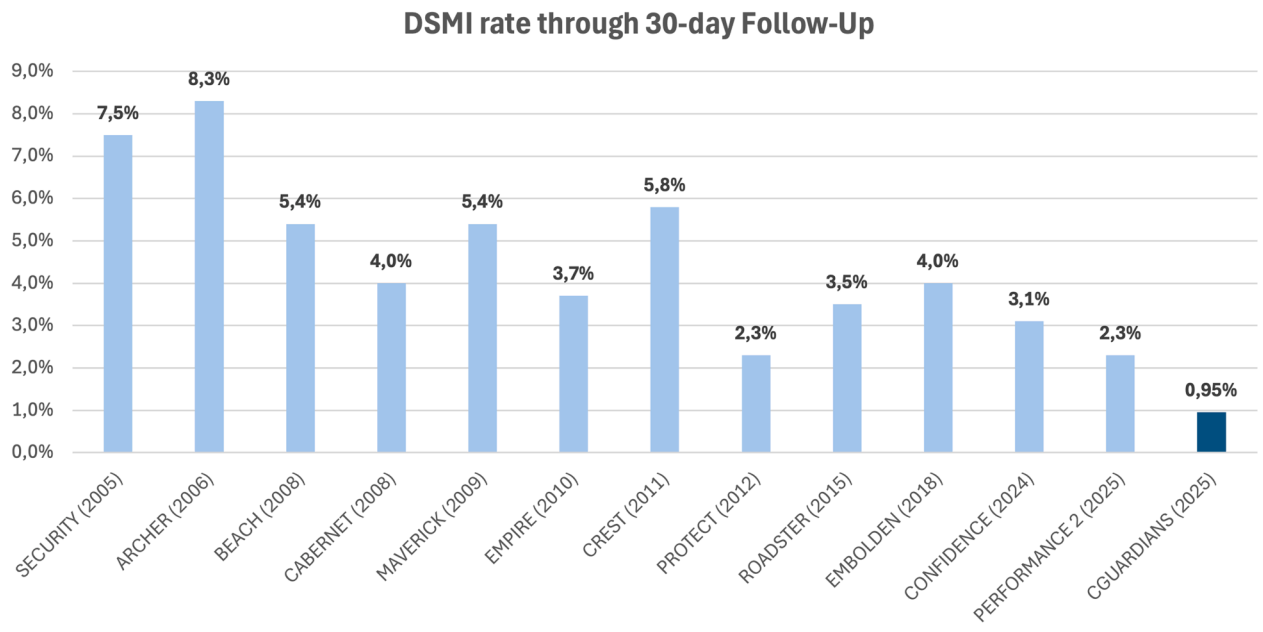
- Lowest reported rate of DSMI through 30-day and ipsilateral stroke between 31 and 365 days of any CAS/TCAR pivotal trial suggests a beneficial effect of the MicroNet-covered stent.
- Low rates of TLR through 1-year are consistent with treatment durability.

Metzger DC, et al. JACC Cardiovasc Interv. 2025;■(■):■–■.

CAS/TCAR = carotid artery stenting/transcarotid arterial revascularization; CEA = carotid artery stenting; DSMI = death, all stroke, myocardial infarction; IDE = investigational device exemption; ITT = intention to treat; MI = myocardial infarction; PET = polyethylene terephthalate; TCAR = transcarotid arterial revascularization; TLR = target lesion revascularization.

test of the composite primary endpoint of the trial to the prespecified performance goal demonstrated that this study met the criteria for success for the primary endpoint of the trial with $P < 0.001$. No unexpected adverse device effects or unexpected serious adverse device effects were reported. These results demonstrate that CGuard stent is safe, effective, and durable, and supports the proposed neuroprotective effect of the micro mesh-covered stent.

FIGURE 3 30-Day Safety Composite of DSMI in CAS IDE Studies



The 30-day death, all stroke, myocardial infarction (DSMI) rates across carotid artery stenting (CAS) studies. IDE = investigational device exemption.

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PERSPECTIVES

WHAT IS KNOWN? The safety and efficacy of carotid artery stenting is largely determined by the incidence of periprocedural and postprocedural plaque embolization. First-generation (single-layer) carotid stents were associated with a higher incidence of minor strokes than carotid endarterectomy due to incomplete plaque containment. Randomized clinical trial MRI evidence shows that the MicroNet-covered stent design prevents cerebral embolism. Multiple postapproval CAS studies in Europe using the MicroNet-covered stent (CGuard) have reported low rates of DSMI at 30 days and ipsilateral strokes at 1 year, but an FDA IDE study has been lacking.

WHAT IS NEW? This prospective, multicenter FDA approval study of the CGuard carotid stent with independent adjudication of AEs demonstrated the lowest reported periprocedural event (30-day death/stroke/MI rate of 0.95%) and 1-year combined primary endpoint rate (1.93%) of any carotid revascularization FDA trial in the ITT analysis.

WHAT IS NEXT? Further U.S. trials of the CGuard MicroNet-covered device using the trans-carotid route in managing acute stroke are warranted.

REFERENCES

1. Roubin GS, Yadav S, Iyer SS, Vitek J. Carotid stent-supported angioplasty: a neurovascular intervention to prevent stroke. *Am J Cardiol*. 1996;78:8-12.

2. White CJ, Brott TG, Gray WA, et al. Carotid artery stenting: JACC state-of-the-art review. *J Am Coll Cardiol*. 2022;80:155-170.

3. Gray WA, Yadav JS, Verta P, et al. The CAPTURE registry: predictors of outcomes in carotid artery stenting with embolic protection for high surgical risk patients in the early post-approval setting. *Catheter Cardiovasc Interv*. 2007;70:1025-1033.

4. Brott TG, Howard G, Roubin GS, et al. Long-term results of stenting versus endarterectomy for carotid-artery stenosis. *N Engl J Med*. 2016;374:1021-1031.

5. Schofer J, Musiałek P, Bijuklic K, et al. A prospective, multicenter study of a novel mesh-covered carotid stent: the CGuard CARENET Trial (Carotid Embolic Protection Using MicroNet). *JACC Cardiovasc Interv*. 2015;8:1229-1234.

6. Mazurek A, Borratynska A, Malinowski KP, et al. MicroNet-covered stents for embolic prevention in patients undergoing carotid revascularisation: twelve-month outcomes from the PARADIGM study. *EuroIntervention*. 2020;16:e950-e952.

7. Sirignano P, Stabile E, Mansour W, et al. 1-Year results from a prospective experience on CAS using the CGuard® Stent System: the IRONGUARD 2 study. *JACC Cardiovasc Interv*. 2021;14:1917-1923.

8. Tigkiropoulos K, Papoutsis I, Abatzis-Papadopoulos M, et al. Thirty-day results of the novel CGuard®-covered stent in patients undergoing carotid artery stenting. *J Endovasc Ther*. 2021;28:542-548.

9. Karpenko A, Bugurov S, Ignatenko P, et al. Randomized controlled trial of conventional versus MicroNet-covered stent in carotid artery revascularization. *JACC Cardiovasc Interv*. 2021;14:2377-2387.

10. Musialek P, Bonati LH, Bulbulia R, et al. Stroke risk management in carotid atherosclerotic disease: a clinical consensus statement of the ESC Council on Stroke and the ESC Working Group on Aorta and Peripheral Vascular Diseases. *Cardiovasc Res*. 2025;121(1):13-43.

11. U.S. Food and Drug Administration. *SECURITY_PMA SP. SECURITY Premarket Approval Application (PMA) Number: P040038b*. 2005. Accessed November 4, 2025. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P040038

12. Gray WA, Hopkins LN, Yadav S, et al. Protected carotid stenting in high-surgical-risk patients: the ARCHeR results. *J Vasc Surg*. 2006;44:258-268.

13. White CJ, Iyer SS, Hopkins LN, Katzen BT, Russell ME. Carotid stenting with distal protection in high surgical risk patients: the BEACH trial 30 day results. *Catheter Cardiovasc Interv*. 2006;67:503-512.

14. Iyer SS, White CJ, Hopkins LN, et al. Carotid artery revascularization in high-surgical-risk patients using the Carotid WALLSTENT and FilterWire EX/EZ: 1-year outcomes in the BEACH Pivotal Group. *J Am Coll Cardiol*. 2008;51:427-434.

15. Hopkins LN, Myla S, Grube E, et al. Carotid artery revascularization in high surgical risk patients with the NexStent and the Filterwire EX/EZ: 1-year results in the CABERNET trial. *Catheter Cardiovasc Interv*. 2008;71:950-960.

16. Higashida RT, Popma JJ, Apruzzese P, Zimetbaum P. Evaluation of the Medtronic exponent self-expanding carotid stent system with the Medtronic GuardWire temporary occlusion and aspiration system in the treatment of carotid stenosis: combined from the MAVErIC I and MAVErIC II trials. *Stroke*. 2010;41:e102-e109.

17. Clair DG, Hopkins LN, Mehta M, et al. Neuroprotection during carotid artery stenting using the GORE flow reversal system: 30-day outcomes in the EMPiRE Clinical Study. *Catheter Cardiovasc Interv*. 2011;77:420-429.

18. Matsumura JS, Gray W, Chaturvedi S, Yamanouchi D, Peng L, Verta P. Results of carotid artery stenting with distal embolic protection with improved systems: Protected Carotid Artery Stenting in Patients at High Risk for Carotid Endarterectomy (PROTECT) trial. *J Vasc Surg*. 2012;55:968-976.

19. Gray WA, Mehta M, Alani F, et al. Use of a novel embolic filter in carotid artery stenting: 30-Day results from the EMBOLDEN Clinical Study. *Catheter Cardiovasc Interv*. 2018;92:1128-1135.

20. Gray WA, Metzger DC, Zidar J, et al. The PERFORMANCE II trial: a prospective multicenter investigation of a novel carotid stent system. *JACC Cardiovasc Interv*. 2025;18:367-376.

21. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). *J Am Coll Cardiol*. 2018;72:2231-2264.

22. Halliday A, Bulbulia R, Bonati LH, et al. Second asymptomatic carotid surgery trial (ACST-2): a randomised comparison of carotid artery stenting versus carotid endarterectomy. *Lancet*. 2021;398:1065-1073.24.

23. Kwolek CJ, Jaff MR, Leal JI, et al. Results of the ROADSTER multicenter trial of transcarotid stenting with dynamic flow reversal. *J Vasc Surg*. 2015;62:1227-1234.

24. Kashyap VS, Schneider PA, Foteh M, et al, ROADSTER 2 Investigators. Early outcomes in the ROADSTER 2 study of transcarotid artery

revascularization in patients with significant carotid artery disease. *Stroke*. 2020;51:2620–2629.

25. Karpenko A, Bugurov S, Ignatenko P, et al. Randomized controlled trial of conventional versus MicroNet-covered stent in carotid artery revascularization: 12-month outcomes. *JACC Cardiovasc Interv*. 2023;16:878–880.

26. Mazurek A, Malinowski K, Rosenfield K, et al. Clinical outcomes of second- versus first-generation carotid stents: a systematic review and meta-analysis. *J Clin Med*. 2022;11:4819.

27. Zidan M, Voss YL, Wolf M, et al. The dual-layer CGuard stent is safe and effective in emergent carotid artery stenting and in tandem occlusions: a multi-centric study. *Clin Neuroradiol*. 2025;35:77–85.

28. Trystula M, Van Herzeele I, Kolvenbach R, et al. Next-generation transcarotid artery revascularization: TransCarotid flOw Reversal Cerebral Protection And CGUARD MicroNET-Covered Embolic Prevention Stent System To Reduce Strokes - TOPGUARD study. *J Cardiovasc Surg*. 2024;65:181–194.

KEY WORDS carotid stent, CGuard, in-stent restenosis