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MicroNET-covered stents for embolic prevention in patients undergoing carotid revascularisation: twelve-month outcomes from the PARADIGM study

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Introduction

Large clinical series of carotid artery stenting (CAS) using conventional carotid stents have shown that 40-80% of adverse neurologic events within the first 30 days occur post-procedurally rather than intraprocedurally, and often several days after the procedure[1]. Indeed, first-generation carotid stent use is associated with post-procedural cerebral embolism[2] that largely results from intraluminal plaque prolapse through the struts[3], a phenomenon which is not eliminated by the classic closed-cell design[4].

Sequential cerebral imaging with diffusion-weighted magnetic resonance (including routine imaging at baseline, 24-48 hours and 30 days[5]) demonstrated that the MicroNET-covered embolic prevention stent CGuard™ (InspireMD, Tel Aviv, Israel)[5-9] minimises intraprocedural and eliminates post-procedural cerebral embolism[5-8,10], providing a basis for larger-scale clinical endpoint-oriented studies[11,12]. The device, combined with a tailored use of intraprocedural embolic protection (the MicroNET embolic prevention occurs only after stent deployment), demonstrated favourable short-term clinical outcomes (30-day death/stroke/MI rate <1%)[5,7,10], but its longer-term safety and efficacy need to be established.

Methods

PARADIGM[10] is a non-industry-funded, prospective academic study in all-referrals-tracked symptomatic and asymptomatic carotid stenosis with a multi-specialty NeuroVascular Team (NVT; angiologist/cardiologist, vascular surgeon, neurologist)[10] making decisions on revascularisation including establishment of indication and endovascular approach feasibility assessment. The study enrolled unselected, consecutive patients (flow chart in reference 10) with an independent neurologist evaluation at baseline, periprocedurally and at one and 12 months, and with events adjudication by an independent clinical events committee (CEC)[10]. Details regarding methodology are provided in **Supplementary Appendix 1** and in reference 10.

Results

Over 12 months, 108 consecutive patients with NVT-indicated carotid revascularisation were enrolled[10]. The endovascular route of revascularisation was considered feasible in 101 subjects (70% men, 55% symptomatic including symptoms within the preceding 14 days in 22% of the study cohort and 9 strokes-in-evolution);

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7/108 patients were referred for carotid endarterectomy (CEA)[10]. In the CAS cohort (106 arteries), 25 lesions (23.6%) were thrombotic on both duplex ultrasound (DUS) and angiography. With all procedures neuroprotected, proximal (flow reversal) device use was overall nearly 50%, with a higher prevalence in symptomatic lesions[10]. Stents were routinely coronary-like optimised, using large-diameter balloons[10] and higher pressures[10] than conventional CAS[1], leading to single-digit residual diameter stenosis[10]. Heparinisation was consistent with the device instructions for use (activated clotting time throughout the procedure of >250 s)[10]. Study device use was 100% (zero other stent type[s] CAS)[10] throughout the study period.

CLINICAL EVENTS BY 12 MONTHS

By 30 days there was one (0.9%) adverse event – periprocedural, clinically asymptomatic extension of a prior cerebral infarct zone in a hypotensive patient (CEC-adjudicated as minor stroke)[10]. No death, large stroke or myocardial infarction occurred by 30 days[10]. By 12 months, there were no patient withdrawals, and no patient was lost to follow-up. Between 30 days and 12 months, there were no strokes or stroke-related deaths but 4 non-stroke deaths occurred, including 1 cardiac death (heart failure exacerbation) and 3 non-cardiac deaths (urosepsis, pulmonary embolism, and microcellular pulmonary cancer).

DUPLEX ULTRASOUND

Preprocedural peak systolic velocity (PSV) was 3.68 (2.66, 4.50) m/s and end-diastolic velocity (EDV) was 1.10 (0.80, 1.60) m/s. At 30 days, PSV and EDV were normal[12] at 0.60 (0.47, 0.80) m/s and 0.15 (0.12, 0.22) m/s, and remained overall normal at 12 months – PSV 0.74 (0.53, 0.98) m/s and EDV 0.20 (0.14, 0.27) m/s (p=0.14). PSV data are shown in **Figure 1**, inclusive of the single in-stent restenosis. The isolated restenosis (PSV of 3.9 m/s) was asymptomatic and was treated uneventfully using a drug-eluting balloon. No stent thrombosis occurred throughout 12 months (0%).

Prior to CAS, 6/106 (5.6%) external carotid arteries (ECAs) were occluded on the target lesion side, whereas 3/100 (3.0%; severe ECA stenosis prior to CAS in all) occluded at CAS. No ECA occlusion occurred between CAS and 30 days and there was no new ECA occlusion at 12 months (post-procedural ECA occlusion rate 0%).

Discussion

Midterm results of our routine use of the novel MicroNET-covered embolic prevention stent (i) show lack of procedure- and/or device-related adverse clinical events between 30 days and 12 months, and (ii) indicate an effective protection against ipsilateral stroke extending post-procedurally.

Normal overall in-stent velocities at 30 days and 12 months **(Figure 1)**, and normal ECA patency are consistent with normal healing[12] of this particular dual-layer device in the absence of any device thrombosis or any in-stent restenosis excess[12-14].

Further discussion is provided in **Supplementary Appendix 2**.

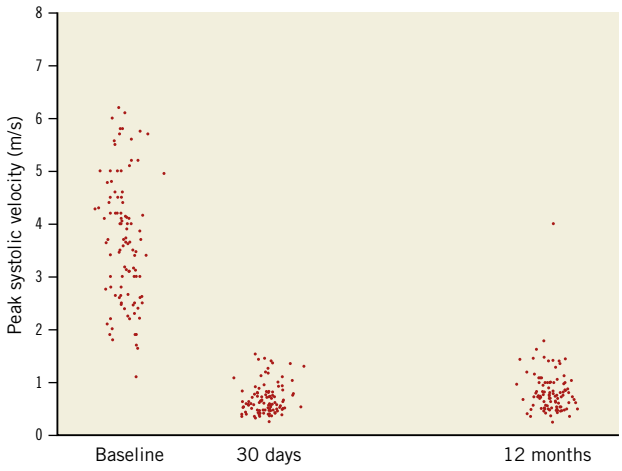

Figure 1. *Peak systolic velocity prior to CGuard CAS, and at 30 days and 12 months after the procedure. Individual patient/artery data for all study subjects.*

Limitations

PARADIGM is a single-centre study indicating that larger patient series and extended follow-up are required. The multicentre, multi-specialty PARADIGM study extension (PARADIGM-Extend, ClinicalTrials.gov Identifier: NCT04271033) is continuing enrolment up to its (close) target of 555 consecutive patients.

With a protocol-mandated bias towards the endovascular route using (and challenging) the study device[15] in symptomatic and increased-stroke-risk patients in the absence of the "entry" bias of randomised studies[15], this investigation differs fundamentally from typical series with symptomatic and/or higher-risk lesions being treated preferentially using CEA[16,17].

Further limitations are discussed in **Supplementary Appendix 3**.

Conclusion

Clinical and DUS data from this symptomatic and increased-stroke-risk consecutive patient series are consistent with the MicroNET-covered carotid stent providing effective protection against cerebral events which extends post-procedurally and with the normal healing profile of the device.

Impact on daily practice

A low (<1%)[5,7,10] periprocedural complication rate with routine use of the MicroNET-covered carotid stent in cohorts including largely symptomatic or increased-stroke-risk clinically asymptomatic carotid stenosis patients is critically important, shifting the carotid revascularisation paradigm[13,14]. One fundamental message from the present PARADIGM study update is the durability of clinical results for at least one year without any significant restenosis and without any late thrombosis.

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Conflict of interest statement

P. Musialek reports being on the speaker bureau, proctoring, consulting, research support, and being on the advisory board of Abbott, InspireMD and Medtronic. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Expanded methods.
Supplementary Appendix 2. Discussion (continued).
Supplementary Appendix 3. Limitations.

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Supplementary data

Supplementary Appendix 1. Expanded methods

In clinically asymptomatic lesions, intervention was mandated only in case of increased stroke risk CS features [10]. The study had no exclusion criteria other than lack of indication to carotid revascularisation [10]. Details of the clinical decision-making process and the CAS procedure have been described previously [10]. In PARADIGM, there is an independent neurological evaluation before CAS, at 48 hours and 30±5 days, and then yearly (±1 month). Duplex ultrasound imaging is performed at baseline and at 30 days and then yearly. There is external source data verification and statistical analysis [10].

The study device is the MicroNET-covered embolic prevention stent system (CGuard^{TM}; InspireMD) that consists of an open-cell nitinol frame wrapped into a proprietary single-fibre-knitted MicroNET sleeve that is attached outside to the stent frame at its distal and proximal edges [5,7,9]. The stent shows a relatively high radial force that is similar to the PRECISE® stent (Cordis, Cardinal Health, Milpitas, CA, USA) [7] and extremely high conformability to vascular anatomy in vitro [7] and in vivo [12] (note the largest, amongst the current carotid stents, open-cell size of 21.66 mm^2). The high conformability and radial force enable, with post-implantation balloon optimisation of the device [12], achieving a residual stenosis-free result of CAS that respects the internal and common carotid artery anatomy ("endovascular reconstruction") [12]. On the other hand, MicroNET (with its cell area of only 0.023-0.032 mm^2) flexibility enables effective plaque coverage and protection against cerebral embolism even in a theoretical case of residual plaque prolapse through the large cells of the nitinol frame [9].

Detailed definitions of study endpoints are provided in ref. 12.

Statistical analysis

Nominal variables were presented as counts and percentages and compared using χ^2 or Fisher's exact test. Continuous variables were presented as median with the first (Q1) and the third quartile (Q3) and compared using the Mann-Whitney U test. P-values less than 0.05 were considered to indicate statistical significance.

Supplementary Appendix 2. Discussion (continued)

Lack of post-procedural adverse events that might be attributable to the study device and/or the CAS procedure as determined in the present study is consistent with a recent series of 200 CGuard™ CAS in mostly asymptomatic patients demonstrating no adverse neurologic events during the stent healing and throughout 12 months [10]. With their rigorous DUS follow-up (similar to ours), Capoccia et al [11] identified only one case of clinically asymptomatic ISR, in line with a normal CAS ISR rate [11].

The totality of first-generation CAS data demonstrate long-term equivalence of CAS and surgery (CEA) [13]. However, first-generation-stent (and mostly filter-protected) CAS may be associated with a relative excess of (mostly minor) strokes by 30 days [13,14], a historical finding that has been used repeatedly as an argument against CAS as a first-line carotid revascularisation modality [14]. By removing the atherosclerotic plaque, CEA removes any post-procedural problem related to the plaque [1,14]. For CAS, one fundamental solution to address the post-procedural problem of the plaque is to effectively sequestrate (isolate) the plaque from the lumen of the artery [1,7,9,14]. Indeed, evidence is accumulating that, with the MicroNET, plaque sequestration CAS may be able to minimise the incidence of post-procedural stroke [1,5,9,14]. Accumulating evidence suggests that novel technologies, including optimised intraprocedural cerebral protection with a high use of proximal systems plus an embolic prevention stent, taken together with appropriate operator training and increasing experience, play a fundamental role in establishing CAS as a safe(r) alternative to CEA [1,13,14]. Our present work indicates that an effective MicroNET-covered stent protection against post-procedural neurologic events extends at least midterm in the absence of any procedure- or device-related issues.

Supplementary Appendix 3. Limitations

With the DW-MRI evidence of the MicroNET-covered stent inhibition of periprocedural and elimination of post-procedural cerebral embolism in four prior studies [5-8], we were not able to justify performing routine sequential DW-MRI in the present investigation that was focused on clinical outcomes. However, PARADIGM is a single-centre study indicating that larger and multicentric patient series and extended follow-up are required. To address this need, a multicentre multi-specialty extension of the study (PARADIGM-Extend, ClinicalTrials.gov Identifier: NCT04271033) continues enrolment up to the target 555 consecutive patients.

It needs to be noted that PARADIGM is a non-randomised study and it involves no comparator device. However, as an all-comer study that reflects consecutive patient management in our routine clinical practice (note the absence of subjects treated outside the study), PARADIGM is largely free from a patient selection bias that constitutes a significant limitation of randomised trials [1,13-15].