PARADIGM-EXTEND: Prospective Academic Trial of CGuard™ MicroNET-Covered Self-Expandable Stent System:

Cumulative 3-Year Clinical and Duplex Ultrasound Evidence for Safety, Efficacy and Durability of Stroke Prevention

Piotr Musialek, MD DPhil
on behalf of the PARADIGM-EXTEND Study Team

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Prospective evaluation of All-comer percutaneous carotid revascularization in symptomatic and increased-stroke-risk asymptomatic carotid artery stenosis using CGuard™ Micronet-covered embolic prevention stent system – clinical trial extension
Disclosure

Speaker name: Piotr Musialek

I have the following potential conflicts of interest to report:

- [✓] Consulting
- [ ] Employment in industry
- [ ] Stockholder of a healthcare company
- [ ] Owner of a healthcare company
- [ ] Other(s)

- [ ] I do not have any potential conflict of interest
Carotid Stenosis
Decision-making

PHARMACOTHERAPY
+ INTERVENTION

ISOLATED
PHARMACOTHERAPY

?
Carotid Stenosis
Decision-making

Risk of Procedure

Pharmacotherapy + Intervention

Isolated Pharmacotherapy
Conventional Carotid Stents
Do Have A Problem
Conventional Carotid Stents

Do Have A Problem

Human carotid artery treated using a conventional stent; OCT

Image courtesy Joan Rigla, MD PhD; Perceptual Imaging Lab, University of Barcelona
• CEA excludes the plaque

• In CAS, the stent should exclude the plaque too
• CEA excludes the plaque

• In CAS, the stent should exclude the plaque too
CGuard™ embolic prevention system
MicroNet mesh preventing prolapse

Tomyuki Umemoto et al.  
*EuroIntervention* 2017

Musialek & Stabile  
*EuroIntervention* 2017
MicroNet mesh preventing prolapse

Tomyuki Umemoto et al.  
*EuroIntervention* 2017
A Prospective, Multicenter Study of a Novel Mesh-Covered Carotid Stent

The CGuard CARENET Trial
(Carotid Embolic Protection Using MicroNet)

Joachim Schofer, MD,* Piotr Musiałek, MD, DPHIL,† Klaudija Bijuklic, MD,* Ralf Kolvenbach, MD,† Mariusz Trystula, MD,† Zbigniew Siudak, MD,†§ Horst Sievert, MD||

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.

Per-Protocol DW-MRI cerebral imaging at B/L, 24-48h after CAS, and at 30 days
Filter-protected CAS procedures

**CARENET vs PROFI:** DW-MRI analysis

**DW-MRI analysis @ 48 hours**

<table>
<thead>
<tr>
<th></th>
<th>CGuard</th>
<th>Conventional Carotid stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>27</td>
<td>31</td>
</tr>
<tr>
<td>S =</td>
<td>34.6%</td>
<td>87.1%</td>
</tr>
<tr>
<td>p =</td>
<td>&lt; 0.005</td>
<td></td>
</tr>
</tbody>
</table>

*see patient fluxogram
Bijuklic et al. *JACC*, 2012;59

J. Schofer, P. Musialek et al. *JACC Intv* 2015;8:1229-34
Bijuklic et al. (manuscript in preparation)
Filter-protected CAS procedures

CARENET vs PROFI: DW-MRI analysis

DW-MRI analysis @ 48 hours

VOLUME

new ipsilateral lesions (mL)

p < 0.005

0.59

Conventional Carotid stent (hybrid)

CGuard

0.04

n=27

n=31

* see patient fluxogram
Bijuklic et al. JACC, 2012:59

J. Schofer, P. Musialek et al. JACC Intv 2015;8:1229-34
Bijuklic et al. (manuscript in preparation)
CARENET DW-MRI analysis*

All but one peri-procedural ipsilateral lesions RESOLVED

<table>
<thead>
<tr>
<th>DW-MRI analysis @ 30 days*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of new ipsilateral lesions</td>
<td>1</td>
</tr>
<tr>
<td>Average lesion volume (cm$^3$)</td>
<td>$0.08 \pm 0.00$</td>
</tr>
<tr>
<td>Permanent lesions at 30 days</td>
<td>1</td>
</tr>
</tbody>
</table>

*External Core Lab analysis (US)

J. Schofer, P. Musialek et al. JACC Intv 2015;8:1229-34

=> near-elimination of post-procedural embolism!
Novel PARADIGM in carotid revascularisation: Prospective evaluation of All-comer peRcutaneous cArotiD revascularisation in symptomatic and Increased-risk asymptomatic carotid artery stenosis using CGuard™ Micronet-covered embolic prevention stent system

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1. Jagiellonian University Department of Cardiac & Vascular Diseases, John Paul II Hospital, Krakow, Poland; 2. Department of Vascular Surgery, John Paul II Hospital, Krakow, Poland; 3. Neurology Outpatient Department, John Paul II Hospital, Krakow, Poland; 4. Department of Radiology, John Paul II Hospital, Krakow, Poland; 5. Jagiellonian University Department of Interventional Cardiology, John Paul II Hospital, Krakow, Poland; 6. KCRI, Krakow, Poland
Objective

- to evaluate feasibility and outcome of routine anti-embolic stent system use in unselected, consecutive patients referred for carotid revascularization (‘all-comer’ study)
Prospective evaluation of All-comer percutaneous carotid revascularization in symptomatic and Increased-risk asymptomatic carotid artery stenosis using the C Guard™ Micronet-covered embolic prevention stent system

The PARADIGM Study
PARADIGM study: referrals flow chart

139 carotid stenosis patient referrals

- Neurologist
- Interventional angiologist
- Vascular surgeon
- Cardiologist

Neuro Vascular Team

for carotid revascularisation
108 patients

NOT for carotid revascularisation
31 patients

n=24: increased stroke risk and/or lesion severity criteria not met
n=2: ICA totally occluded on verification
n=2: ICA functional occluded + h/o prior ipsilateral large cerebral infarct with haemorrhagic transformation
n=1: major post-stroke disability, ICA functionally occluded
n=1: severe circulatory failure (ICA stenosis asympt.)
n=1: malignancy with limited life expectancy (ICA stenosis asympt.)

PARADIGM study: revascularisation flow chart
108 patients for carotid revascularisation

(93%)
CAS in n=100 patients (bilateral in 5)

(1%)
CAS+CEA in n=1 patient (LICA-CEA and RICA-CAS) hybrid management

(6%)
CEA in n=7 patients

106 ICAs treated endovascularly in 101 patients using exclusively the MicroNet-covered embolic prevention stent system

n=1 eGRF 14 → no contrast
n=2 hostile access
n=1 major ICA kink/loop
n=1 severe aortic valve disease + calcific LICA (AVR+CEA)
n=1 floating thrombus in CCA
n=1 ICA diameter <2.0 mm + contralateral ICA occlusion

PARADIGM

Methods (cont’d):

- **ASYMPTOMATIC** patients treated interventionally only if at **stroke risk**
- established lesion-level increased-risk criteria used:
  - thrombus-containing
  - documented progressive
  - irregular and/or ulcerated
  - contralateral ICA occlusion/stroke
  - asymptomatic ipsilateral brain infarct


*PARADIGM* design and 30-day outcome data
PARADIGM – Extend continues as an ALL-Comer Study

- 251 patients / 263 arteries
- NeuroVascular Team decision-making on revascularization
- Age 51-87 years, 57.1% symptomatic
- Crossed the trial first follow-up window (30d)
- 100% CGuardEPS use, Proximal/distal EPD ≈ 50% : 50%
- Angiographic diameter stenosis was reduced from 83±9% to only 6.7±5% (p<0.001, ‘CEA-like’ effect of CAS)
PARADIGM – Extend

251 patients / 263 arteries

- *Peri-procedural outcome*
  0 death/major stroke – 0%
  1 minor stroke – 0.4%
  1 MI (type2) – 0.4%

- *By 30 days*
  1 haemorrhagic transformation of prior ischaemic cerebral infarct, leading to death – 0.4%
PARADIGM – Extend

- 1-12 mo: n=251
- 12-24 mo: n=185
- 24-36 mo: n=93
PARADIGM – Extend

- **1-12 mo**
  - n=251
  - 0 ipsilateral stroke

- **12-24 mo**
  - n=185
  - 0 ipsilateral stroke

- **24-36 mo**
  - n=93
  - 0 ipsilateral stroke
<table>
<thead>
<tr>
<th>Time</th>
<th>Ipsilateral Stroke</th>
<th>Any Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-12 mo</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12-24 mo</td>
<td>0</td>
<td>1 (cerebellal)</td>
</tr>
<tr>
<td>24-36 mo</td>
<td>0</td>
<td>1 (brain stem)</td>
</tr>
<tr>
<td></td>
<td>1-12 mo</td>
<td>12-24 mo</td>
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<tr>
<td>---------------</td>
<td>---------</td>
<td>----------</td>
</tr>
<tr>
<td>n</td>
<td>251</td>
<td>185</td>
</tr>
<tr>
<td>Ipsilateral stroke</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any stroke</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Stroke-related death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Event</td>
<td>1-12 mo</td>
<td>12-24 mo</td>
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<tr>
<td>-----------------------------------</td>
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<td>----------</td>
</tr>
<tr>
<td>Ipsilateral stroke</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any stroke</td>
<td>0</td>
<td>1 (cerebellal)</td>
</tr>
<tr>
<td>Stroke-related death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MI or other non-cerebral VA</td>
<td>0</td>
<td>3</td>
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</table>

n=251
n=185
n=93
# PARADIGM – Extend

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Ipsilateral Stroke</th>
<th>Any Stroke</th>
<th>Stroke-related Death</th>
<th>MI or Other Non-cerebral VA</th>
<th>Any Death</th>
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<tbody>
<tr>
<td>1-12 mo</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>(cerebellal)</td>
<td></td>
<td></td>
<td>(CHF-2, Ca-2, PE-1, urosepsis -1)</td>
<td></td>
</tr>
<tr>
<td>12-24 mo</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(brain stem)</td>
<td></td>
<td>(CHF-2, Ca-2, MI-1)</td>
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<tr>
<td>24-36 mo</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Ca-1, MI-1)</td>
<td></td>
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</table>

- n=251
- n=185
- n=93

P Musialek @ LINC 2019
<table>
<thead>
<tr>
<th>Event Type</th>
<th>1-12 mo</th>
<th>12-24 mo</th>
<th>24-36 mo</th>
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<tbody>
<tr>
<td>Ipsilateral stroke</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any stroke</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>(Cerebellal)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Stroke-related death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MI or other non-cerebral VA</td>
<td>0</td>
<td>3</td>
<td>2</td>
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<tr>
<td>(CHF-2, Ca-2, PE-1, urosepsis)</td>
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</tr>
<tr>
<td>Any death</td>
<td>6</td>
<td>5</td>
<td>2</td>
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<tr>
<td>(CHF-2, Ca-2, MI-1)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(Ca-1, MI-1)</td>
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<tr>
<td>In-stent velocities</td>
<td>PSV 0.82±0.48 m/s</td>
<td>PSV 0.73±0.31 m/s</td>
<td>PSV 0.75±0.27 m/s</td>
</tr>
<tr>
<td></td>
<td>EDV 0.22±0.13 m/s</td>
<td>EDV 0.19±0.09 m/s</td>
<td>EDV 0.18±0.06 m/s</td>
</tr>
</tbody>
</table>
By 36 months

- Normal healing
- No ISR signal

- Ipsilateral stroke
- Any stroke
- Stroke-related death
- MI or other non-cerebral VA
- Any death

<table>
<thead>
<tr>
<th>1-12 mo</th>
<th>12-24 mo</th>
<th>24-36 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=226</td>
<td>n=185</td>
<td>n=93</td>
</tr>
</tbody>
</table>

- PSV 0.82±0.48 m/s
- EDV 0.22±0.13 m/s

- PSV 0.73±0.31 m/s
- EDV 0.19±0.09 m/s

- PSV 0.75±0.27 m/s
- EDV 0.18±0.06 m/s
systematic

CEA-like effect of CAS

*EuroIntervention* 2016;12:e658-70
The Outcome Difference

Between the MicroNet-Covered Stent vs. Conventional Carotid Stent(s) driven by HIGH-RISK Plaques and Patients
chronic ischemic lesions in both hemispheres

"fresh" ischemia surrounding old lesions

new DWI lesion in R hemisphere

chronic ischemic lesion in R hemisphere

RICA high-grade thrombolytic stenosis

LICA chronic occlusion
Flow reversal time 7min 10sec
Intolerance in the last 80sec
(active aspiration still !! performed)
Final Result
Patient A/S, discharged home, unremarkable follow-up

Normal stent image

Normal velocities

ECA patent

P Musialek @ VEITH 2018
CGuard™ MicroNet Covered Stent:

ADDRESSING UNMET NEEDS IN OTHER VASCULAR BEDS
Thrombus-containing/high-embolic risk lesions in iliacs or subclavians
Thrombus-containing/high-embolic risk lesions in iliacs or subclavians

OPTIMAL procedural result

Normal 6mo follow-up
Thrombus-containing/high-embolic risk lesions in iliacs or subclavians

LSA

(movie)
Thrombus-containing/high-embolic risk lesions in iliacs or subclavians

**Procedural result**

Normal 6mo follow-up
Thrombus-containing/high-embolic risk lesions in iliacs or subclavians
Thrombus-containing/high-embolic risk lesions in iliacs or subclavians

CGuard™

Normal Result @follow-up
Thrombus-containing/high-embolic risk lesions in iliacs or subclavians and
Thrombus-containing/high-embolic risk lesions in iliacs or subclavians

OPTIMAL 6mo result

Pt ready for fem-fem (NB. several prior attempts to recanalize LCIA had failed)
Large-diameter SVG disease problem

AK, 58y, NSTE Acute Myocardial Infarction

SVG RD 7.5 mm (!)

Severely impaired OM flow
Large-diameter SVG disease problem

AK, 58y, NSTE Acute Myocardial Infarction

SVG ref diameter 7.5 mm (!)

Severely impaired OM flow

TIMI-2
Large-diameter SVG disease / NSTE-acute MI

post PCI/direct stenting with overlapping MicroNet–covered CGuard™ stents

NB. absence of distal embolizm, normal OM flow, no further troponin rise

OPTIMAL acute result
Large-diameter SVG disease treated with CGuards (angio @3mo)

overlapping CGuards

SVG

OM

cGuard™-reconstructed SVG

OM

OPTIMAL result @ 3mo
Large-diameter SVG disease treated with CGuards (CT-angio @6mo)

NOTE ostial placement precision feasibility

OPTIMAL result @ 6mo
(V) Highly calcific disease
(note: adequate radial force needed)
(V) Higly calcific disease
(note adequate radial force need)
(V) Highly calcific disease
(note: adequate radial force provided)

OPTIMAL result @ 6mo
Non-Healing Dissection with recurrent symptoms

CGuard™

Immediately SEALED

Thr?

MoMa, IVUS

P Musialek @ LINC 2019
Non-Healing Dissection with recurrent symptoms

CGuard™

Normal 12 mo Follow-up Result
Ostial CCA lesions

(note adequate radial force and placement precision need)

LCCA Retrograde Cannulation from the neck
(to wire and predilate the subtotal ostial LCCA; NB. failed access from the arch)

Lady 68 yo, retinal TIAs followed by retinal stroke while on OMT (mother to cathlab nurse)
Ostial CCA lesions
(note adequate radial force and placement precision)
Ostial CCA lesions
(note adequate radial force and placement precision)

OPTIMAL angiographic + clinical + duplex result @ 12mo
(and LECA patent)
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Agnieszka Zwolińska
PARADIGM

@ 36 months

Favourable Clinical Outcome

- NO device-related adverse events
- NO procedure-related events

sustained stroke prevention
Endovascular Solution for All-Comers

Endovascular Reconstruction of the Carotid Bifurcation

Prevention of embolism, High radial force, Conformability

P. Musialek @ VEITH 2018
This concept has been desired.

And it works.

This is the future of Carotid Artery Stenting.
This concept has been desired.

And it works.

This is the future of Carotid Artery Stenting!
man 3D OCT, symptomatic lesion

CGuard™
EPS

P Musialek @ LINC 2019
One swallow does not make but many swallows do: accumulating clinical evidence for nearly-eliminated peri-procedural and 30-day complications with mesh-covered stents transforms the carotid revascularisation field

Piotr Musialek 1, L. Neilson Hopkins 2, Adnan H. Siddiqui 3

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2Departments of Neurosurgery and Radiology, School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Jacobs Institute, Gates Vascular Institute Kaleida Health, Buffalo, New York, USA

Abstract

Atherosclerotic carotid artery stenosis (CS) continues to be a common cause of acute ischaemic stroke. Optimised medical therapy (OMT), the first-line treatment modality in CS, may reduce or delay – but it does not abolish – CS-related strokes. As per current AHA/ASA and ESC/ESVS/ESO guidelines, carotid artery stenting (CAS) is a less-invasive alternative to carotid endarterectomy (CEA) for CS revascularisation in primary and secondary stroke prevention.

Ten-year follow-up from the CREST trial in patients with symptomatic and asymptomatic CS confirmed equipoise of CAS and CEA in the primary endpoint. Nevertheless, CAS – using a widely open-cell, first-generation stent and first-generation distal filter neuroprotection – has been criticised for its relative excess of (mostly minor) strokes by 30 days, a significant proportion of which were post-procedural.

Atherosclerotic plaque protrusion through conventional carotid stent struts, confirmed on intravascular imaging, has been implicated as a leading mechanism of the relative excess of strokes with CAS vs. CEA, including delayed strokes with CAS. Different designs of mesh-covered carotid stents have been developed to prevent plaque prolapse. Several multi-centre/multi-specialty clinical studies with CGuard MicroNet-Covered Embolic Prevention Stent System (EPS) and RoadSaver/Casper were recently published and included routine DWI-MRI cerebral imaging peri-procedurally and at 30 days (CGuard EPS).

Data from more than 550 patients in mesh-covered carotid stent clinical studies to-date show an overall 30-day complication rate of ~1% with near-elimination of post-procedural events. While more (and long-term) evidence is still anticipated, these results – taken together with optimised intra-procedural neuroprotection in CAS (increased use of proximal systems including trans-carotid dynamic flow reversal) and the positive 12-month mesh-covered stent data reports in 2017 – are transforming the carotid revascularisation field today.

Establishing effective algorithms to identify the asymptomatic subjects at stroke risk despite OMT, and large-scale studies with mesh-covered stents including long-term clinical and duplex ultrasound outcomes, are the next major goals.

Key words: carotid artery stenting, mesh, stroke, endarterectomy, neuroprotection.
PARADIGM-EXTEND: Prospective Academic Trial of CGuard™ MicroNET-Covered Self-Expandable Stent System:

Cumulative 3-Year Clinical and Duplex Ultrasound Evidence for Safety, Efficacy and Durability of Stroke Prevention

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Prospective evaluation of All-comer percutaneous Atherectomy revascularization in symptomatic and Increased-stroke-risk asymptomatic carotid artery stenosis using CGuard™ Micronet-covered embolic prevention stent system – clinical trial extension