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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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
Carotid Stenosis
Decision-making

Pharmacotherapy + Intervention
ISOlated Pharmacotherapy

Risk of Procedure

P Musialek @ LINC 2019
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

P Musialek @ LINC 2019
MicroNet mesh preventing prolapse

Tomyuki Umemoto et al.  
EuroIntervention 2017

Musialek & Stabile  
EuroIntervention 2017
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

*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**

- **CGuard**
  - n=27
  - Volume: 0.04 mL
- **Conventional Carotid stent (hybrid)**
  - n=31
  - Volume: 0.59 mL

* 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>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of new ipsilateral lesions</td>
</tr>
<tr>
<td>Average lesion volume (cm³)</td>
</tr>
<tr>
<td>Permanent lesions at 30 days</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 CGuard™ 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.)

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

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

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

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 – 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

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Count</th>
<th>Ipsi. Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-12 mo</td>
<td>251</td>
<td>0</td>
</tr>
<tr>
<td>12-24 mo</td>
<td>185</td>
<td>0</td>
</tr>
<tr>
<td>24-36 mo</td>
<td>93</td>
<td>0</td>
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Ipsi. = Ipsilateral stroke
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<th>24-36 mo</th>
</tr>
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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>
</tbody>
</table>

- Cerebellal:
- Brainstem:

n=251
n=185
n=93
# PARADIGM – Extend

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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any stroke</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Stroke-related death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

1-12 mo:
- 0 ipsilateral stroke
- 0 any stroke
- 0 stroke-related death

12-24 mo:
- 0 ipsilateral stroke
- 1 any stroke (cerebellal)
- 0 stroke-related death

24-36 mo:
- 0 ipsilateral stroke
- 1 any stroke (brain stem)
- 0 stroke-related death
<table>
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<tr>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>any stroke</strong></td>
<td>0</td>
<td>1 (cerebellal)</td>
<td>1 (brain stem)</td>
</tr>
<tr>
<td><strong>stroke-related death</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>MI or other non-cerebral VA</strong></td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
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<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>MI or other non-cerebral VA</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Any death</td>
<td>6 (CHF-2, Ca-2, PE-1, urosepsis -1)</td>
<td>5 (CHF-2, Ca-2, MI-1)</td>
<td>2 (Ca-1, MI-1)</td>
</tr>
</tbody>
</table>
## 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>
<th>In-Stent Velocities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-12 mo</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6 (CHF-2, Ca-2, PE-1, urosepsis -1)</td>
<td>PSV 0.82±0.48 m/s</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EDV 0.22±0.13 m/s</td>
</tr>
<tr>
<td>12-24 mo</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>5 (CHF-2, Ca-2, MI-1)</td>
<td>PSV 0.73±0.31 m/s</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EDV 0.19±0.09 m/s</td>
</tr>
<tr>
<td>24-36 mo</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2 (Ca-1, MI-1)</td>
<td>PSV 0.75±0.27 m/s</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>EDV 0.18±0.06 m/s</td>
</tr>
</tbody>
</table>

PSV: Peak Spectra Velocity, EDV: End Diastolic Velocity.
PARADIGM – Extend

By 36 months:
- Normal healing
- No ISR signal

PSV and EDV velocities:
- **In-stent velocities**
  - PSV: 0.82 ± 0.48 m/s
  - EDV: 0.22 ± 0.13 m/s
- **12-24 mo**
  - PSV: 0.73 ± 0.31 m/s
  - EDV: 0.19 ± 0.09 m/s
- **24-36 mo**
  - PSV: 0.75 ± 0.27 m/s
  - EDV: 0.18 ± 0.06 m/s
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

new DWI lesion in R hemisphere

"fresh" ischemia surrounding old lesions

chronic ischemic lesion in R hemisphere

RICA high-grade highly-thrombolytic stenosis

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

Normal stent image

Normal velocities

ECA patent

P Musialek @ VEITH 2018
Moving beyond routine CAS…

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)

P Musialek @ LINC 2019
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

Procedural result
Thrombus-containing/high-embolic risk lesions in iliacs or subclavians

CGuard™

Normal Result @ follow-up

P Musialek @ LINC 2019
Thrombus-containing/high-embolic risk lesions in iliacs or subclavians and

Procedural acute outcome
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 (!)
Large-diameter SVG disease problem

AK, 58y, NSTE Acute Myocardial Infarction

SVG ref diameter 7.5 mm (!)

Severely impared OM flow
Large-diameter SVG disease / NSTE-acute MI
post PCI/direct stenting with overlapping MicroNet–covered CGuard™ stents

NB. absence of distal embolism, 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

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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 need)
(V) Highly calcific disease
(note adequate radial force needed)
(V) Highly calcific disease
(note: adequate radial force provided)

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

CGuard™

Immediately SEALED

Thr?

MoMa, IVUS

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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)

Retrograde Cannula removed following successful wiring from the arch after ostial LCCA predilation from the top
Ostial CCA lesions
(note adequate radial force and placement precision)
Ostial CCA lesions
(note adequate radial force and placement precision)

2 overlapping cGuards

cGuard™

OPTIMAL angiographic + clinical + duplex result @ 12mo

(and LECA patent)
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Piotr Wilkołek
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

Note self-tapering
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
One swallow does not a summer 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

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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

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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/SES 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/filiter) 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 CoRnav MicroNet-Covered Embolic Protection Stent System (EPS) and RoadSaver/Casper were recently published and included routine DW-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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John Paul II Hospital, Krakow, Poland

Prospective evaluation of All-comer percutaneous carotid artery stenting using CGuard™ Micronet-covered embolic prevention stent system – clinical trial extension