Mesh-Covered Stents for Carotid Intervention: Rationale, Device Designs, Imaging, and Data to Date

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John Paul II Hospital, Krakow, Poland
Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Grant/Research Support</td>
<td>• ABBOTT</td>
</tr>
<tr>
<td>• Consulting Fees/Honoraria</td>
<td>• ABBOTT, Balton, InspireMD, Medtronic</td>
</tr>
</tbody>
</table>
Rationale
CAS (and CEA) are—and will remain—emboli-generating procedures

Figure 1. Microembolic profile during unprotected CAS. The mean MES counts during various phases of the procedure are displayed.

*Circulation* 2001;104:1999-2002
Post-procedural Embolization with conventional carotid stents

DW-MRI post CAS

Mean total lesion area

Schofer J et al, JACC Cardiovasc interv 2008
Does Free Cell Area Influence the Outcome in Carotid Artery Stenting?

M. Bosiers, G. de Donato, K. Deloose, J. Verbist, P. Peeters, F. Castriota, A. Cremonesi and C. Setacci

Overview of event rates related to the different stents

<table>
<thead>
<tr>
<th>Stent name</th>
<th>Total population</th>
<th>Symptomatic population</th>
<th>Asymptomatic population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>All events</td>
<td>Post-procedural events</td>
</tr>
<tr>
<td>X-act</td>
<td>1.9%</td>
<td>1.9%</td>
<td></td>
</tr>
<tr>
<td>Nexstent</td>
<td>3.3%</td>
<td>3.3%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Wallstent</td>
<td>2.3%</td>
<td>1.2%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Precise</td>
<td>4.1%</td>
<td>3.1%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Protégé</td>
<td>3.0%</td>
<td>3.0%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Acculink</td>
<td>4.2%</td>
<td>3.7%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Exponent</td>
<td>11.8%</td>
<td>5.9%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Total</td>
<td>3179</td>
<td>2.83%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

2/3 CAS neuro events (stroke, TIA) are POST-procedural

Eur J Vasc Endovasc Surg Vol 33, February 2007
FREE CELL AREA drives CAS neurologic adverse events (and majority occur post-procedure)

<table>
<thead>
<tr>
<th>Free cell area</th>
<th>Total population</th>
<th>Symptomatic population</th>
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<tbody>
<tr>
<td></td>
<td>All events</td>
<td>Post-procedural events</td>
</tr>
<tr>
<td>&lt;2.5 vs [2.5, 5]</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;2.5 vs [5, 7.5]</td>
<td>0.054</td>
<td>0.072</td>
</tr>
<tr>
<td>&lt;2.5 vs &gt;7.5</td>
<td>0.27</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Eur J Vasc Endovasc Surg Vol 33, February 2007
Conventional Carotid Stent

Plaque protrusion may lead to early and late distal embolization

J. Schofer, P. Musialek et al. TCT 2014
Conventional Carotid Stent
current best-in-class Hybrid stent

current best-in-class Closed-cell stent
ANY data on incidence of PLAQUE PROLAPSE in conventional carotid stents?
Post-procedural **PLAQUE PROLAPSE** through **conventional stent** struts

Suzuki M et al.
ESC 2014
Presentation
www.escardio.org

81 y.o. Female, Symptomatic

1/3 stents = **Precise**
2/3 stents = **Carotid Wallstent**

Images: Dr M. Suzuki
ESC 2014
www.escardio.org

*Eur Heart J.* 2014;35(Abstr Suppl):178
Post-procedural PLAQUE PROLAPSE through conventional stent struts

De Donato et al. *Eur J Vasc Endovasc Surg* 2013;45:579-587

<table>
<thead>
<tr>
<th></th>
<th>Closed cell (n = 17)</th>
<th>Open cell (n = 13)</th>
<th>Hybrid cell (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque prolapse&lt;sup&gt;b&lt;/sup&gt;</td>
<td>17.6%, (3)</td>
<td>61.5%, (8)</td>
<td>30%, (3)</td>
</tr>
</tbody>
</table>

<sup>b</sup> At least 10 appreciable tissue prolapses between the stent struts per patient.
Conventional Carotid Stent

Image Courtesy Dr Juan Rigla, MD PhD
Perceptual Imaging Lab, University of Barcelona
Conventional Carotid Stent

Plaque protrusion may lead to early and late distal embolization

J. Schofer, P. Musialek et al.  TCT 2014
CREST

Freedom from Primary End Point (%)

0  1  2  3  4
Year of Follow-up

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>CAS</th>
<th>1262</th>
<th>1100</th>
<th>787</th>
<th>460</th>
<th>162</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA</td>
<td>1240</td>
<td>1099</td>
<td>770</td>
<td>430</td>
<td>145</td>
<td></td>
</tr>
</tbody>
</table>

30 d
<table>
<thead>
<tr>
<th>Event</th>
<th>CAS (N = 1262)</th>
<th>CEA (N = 1240)</th>
<th>Periprocedural Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients</td>
<td>percentage points</td>
<td>Absolute Treatment Effect of CAS vs. CEA (95% CI)</td>
</tr>
<tr>
<td>Death</td>
<td>9 (0.7±0.2)</td>
<td>0.4 (−0.2 to 1.0)</td>
<td>2.25 (0.69 to 7.30)†</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td>P Value</td>
</tr>
<tr>
<td>Any</td>
<td>52 (4.1±0.6)</td>
<td>1.8 (0.4 to 3.2)</td>
<td>1.79 (1.14 to 2.82)</td>
</tr>
<tr>
<td>Major ipsilateral</td>
<td>11 (0.9±0.3)</td>
<td>0.5 (−0.1 to 1.2)</td>
<td>2.67 (0.85 to 8.40)</td>
</tr>
<tr>
<td>Major nonipsilateral‡</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Minor ipsilateral</td>
<td>37 (2.9±0.5)</td>
<td>1.6 (0.4 to 2.7)</td>
<td>2.16 (1.22 to 3.83)</td>
</tr>
<tr>
<td>Minor nonipsilateral‡</td>
<td>4 (0.3±0.2)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>14 (1.1±0.3)</td>
<td>−1.1 (−2.2 to −0.1)</td>
<td>0.50 (0.26 to 0.94)</td>
</tr>
<tr>
<td>Any periprocedural stroke or postprocedural ipsilateral stroke</td>
<td>52 (4.1±0.6)</td>
<td>1.8 (0.4 to 3.2)</td>
<td>1.79 (1.14 to 2.82)</td>
</tr>
<tr>
<td>Major stroke</td>
<td>11 (0.9±0.3)</td>
<td>0.2 (−0.5 to 0.9)</td>
<td>1.35 (0.54 to 3.36)</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>41 (3.2±0.5)</td>
<td>1.6 (0.3 to 2.8)</td>
<td>1.95 (1.15 to 3.30)</td>
</tr>
<tr>
<td>Any periprocedural stroke or death or postprocedural ipsilateral stroke</td>
<td>55 (4.4±0.6)</td>
<td>2.0 (0.6 to 3.4)</td>
<td>1.90 (1.21 to 2.98)</td>
</tr>
<tr>
<td>Primary end point (any periprocedural stroke, myocardial infarction, or death or postprocedural ipsilateral stroke)</td>
<td>66 (5.2±0.6)</td>
<td>0.7 (−1.0 to 2.4)</td>
<td>1.18 (0.82 to 1.68)</td>
</tr>
</tbody>
</table>

† The periprocedural period was defined, according to the study protocol, as the 30-day period after the procedure.
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<th>Periprocedural Period</th>
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<tbody>
<tr>
<td></td>
<td>no. of patients (%) ± SE</td>
<td>percentage points</td>
<td>Hazard Ratio for CAS vs. CEA (95% CI)</td>
</tr>
<tr>
<td>Death</td>
<td>9 (0.7±0.2)</td>
<td>4 (0.3±0.2)</td>
<td>0.4 (−0.2 to 1.0)</td>
</tr>
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<td>Stroke</td>
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<td>0</td>
<td>4 (0.3±0.2)</td>
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<td>37 (2.9±0.5)</td>
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<tr>
<td>Minor nonipsilateral</td>
<td>4 (0.3±0.2)</td>
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<td>0.0 (−0.4 to 0.4)</td>
</tr>
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<td>14 (1.1±0.3)</td>
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</tr>
<tr>
<td>Major stroke</td>
<td>11 (0.9±0.3)</td>
<td>8 (0.6±0.2)</td>
<td>0.2 (−0.5 to 0.9)</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>41 (3.2±0.5)</td>
<td>21 (1.7±0.4)</td>
<td>1.6 (0.3 to 2.8)</td>
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<tr>
<td>Primary end point (any periprocedural stroke, myocardial infarction, or death or postprocedural ipsilateral stroke)</td>
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<td>56 (4.5±0.6)</td>
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<td>0.18†</td>
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<td>Stroke</td>
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<td></td>
<td></td>
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<td>1.79 (1.14 to 2.82)</td>
<td>0.01</td>
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<td>0.5 (-0.1 to 1.2)</td>
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<td>0.09</td>
</tr>
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<td>NA</td>
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<td>2.16 (1.22 to 3.83)</td>
<td>0.009</td>
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<tr>
<td>Minor nonipsilateral</td>
<td>4 (0.3±0.2)</td>
<td>4 (0.3±0.2)</td>
<td>0.0 (-0.4 to 0.4)</td>
<td>1.02 (0.25 to 4.07)</td>
<td>0.98†</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>14 (1.1±0.3)</td>
<td>28 (2.3±0.4)</td>
<td>-1.1 (-2.2 to -0.1)</td>
<td>0.50 (0.26 to 0.94)</td>
<td>0.03</td>
</tr>
<tr>
<td>Any periprocedural stroke or postprocedural ipsilateral stroke</td>
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<td>29 (2.3±0.4)</td>
<td>1.8 (0.4 to 3.2)</td>
<td>1.79 (1.14 to 2.82)</td>
<td>0.01</td>
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<td>0.52</td>
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<td>1.95 (1.15 to 3.30)</td>
<td><strong>0.01</strong></td>
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<td>0.005</td>
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<td>56 (4.5±0.6)</td>
<td>0.7 (-1.0 to 2.4)</td>
<td>1.18 (0.82 to 1.68)</td>
<td>0.38</td>
</tr>
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## CREST

<table>
<thead>
<tr>
<th>No. of patients (%) ±SE</th>
<th>Percentage points</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td></td>
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</tr>
<tr>
<td>CAS (N = 1262)</td>
<td>9 (0.7 ± 0.2)</td>
<td>4 (0.3 ± 0.2)</td>
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<tr>
<td>CEA (N = 1240)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
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<td>4 (0.3 ± 0.2)</td>
</tr>
<tr>
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<td>4 (0.3 ± 0.2)</td>
</tr>
<tr>
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<td>28 (2.3 ± 0.4)</td>
</tr>
<tr>
<td>Any periprocedural stroke or postprocedural ipsilateral stroke</td>
<td>52 (4.1 ± 0.6)</td>
<td>29 (2.3 ± 0.4)</td>
</tr>
<tr>
<td>Major stroke</td>
<td>7 (0.6 ± 0.2)</td>
<td>3 (0.2 ± 0.2)</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>11 (3.3 ± 0.3)</td>
<td>4 (0.3 ± 0.2)</td>
</tr>
<tr>
<td>Any periprocedural stroke or death or postprocedural ipsilateral stroke</td>
<td>55 (4.4 ± 0.6)</td>
<td>29 (2.3 ± 0.4)</td>
</tr>
<tr>
<td>Primary end point (any periprocedural stroke, myocardial infarction, or death or postprocedural ipsilateral stroke)</td>
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<td>56 (4.5 ± 0.6)</td>
</tr>
</tbody>
</table>

We need to do better.

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2015+
Conventional Carotid Stent

Plaque protrusion may lead to early and late distal embolization.

J. Schofer, P. Musialek et al. TCT 2014
Anti-Embolic Carotid Stent

Plaque protrusion may lead to early and late distal embolization
Device Designs
Device Designs

n=3
## Competition Carotid Stents

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Material Type</th>
<th>Diameter (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terumo/Microvention</td>
<td>Mesh</td>
<td>0.38</td>
</tr>
<tr>
<td>Inspire MD</td>
<td>Mesh</td>
<td>0.15</td>
</tr>
<tr>
<td>W.L. Gore</td>
<td>Mesh</td>
<td>0.44</td>
</tr>
<tr>
<td>Abbott Vascular</td>
<td>2.36</td>
<td></td>
</tr>
<tr>
<td>Boston Scientific</td>
<td>1.89</td>
<td></td>
</tr>
<tr>
<td>Ev3/Covidien/Medtronic</td>
<td>1.397</td>
<td></td>
</tr>
<tr>
<td>Cordis/Cardinal Health</td>
<td>4.93</td>
<td></td>
</tr>
<tr>
<td>Invatec/Medtronic</td>
<td>2.36</td>
<td></td>
</tr>
<tr>
<td>Cristallo Ideale</td>
<td>3.23</td>
<td></td>
</tr>
</tbody>
</table>

**Bench marking by Microvention**

<table>
<thead>
<tr>
<th>Diameter</th>
<th>375-500µm</th>
<th>150-180µm</th>
<th>500µm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Advertising by Inspire MD**

Table by Terumo, used with permission
RoadSaver

= MicroVena

= Casper

*Not available in the United States.*
RoadSaver (Terumo) = Casper (MicroVena)

Nitinol mesh INSIDE the nitinol frame
RoadSaver: Push-Pull Stent Delivery System

re-sheathable up to 50% stent length release

CE Mark – January 2014
GORE® Carotid Stent

Open Cell NiTi Frame

Closed Cell 500 μm PTFE lattice on outside of NiTi Frame

Permanently Bound CBAS Heparin on all device surfaces

Courtesy WL Gore & Associates / by permission
# GORE® Carotid Stent System Sizing Summary

<table>
<thead>
<tr>
<th>GORE® CAROTID STENT PART NUMBER</th>
<th>UNCONSTRAINED STENT DIMENSIONS (mm)</th>
<th>REFERENCE VESSEL DIAMETER (mm)</th>
<th>MINIMUM INTRODUCER OR GUIDING SHEATH CATHETER ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS5530</td>
<td>5 x 30</td>
<td>3.7 – 4.5</td>
<td></td>
</tr>
<tr>
<td>GCS5540</td>
<td>5 x 40</td>
<td>4.5 – 5.4</td>
<td></td>
</tr>
<tr>
<td>GCS6630</td>
<td>6 x 30</td>
<td>5.4 – 6.3</td>
<td></td>
</tr>
<tr>
<td>GCS6640</td>
<td>6 x 40</td>
<td>6.3 – 7.2</td>
<td>0.073&quot; (1.85 mm) White Tip</td>
</tr>
<tr>
<td>GCS7730</td>
<td>7 x 30</td>
<td>7.2 – 8.1</td>
<td></td>
</tr>
<tr>
<td>GCS7740</td>
<td>7 x 40</td>
<td>8.1 – 9.0</td>
<td>0.080&quot; (2.03 mm) Gray Tip</td>
</tr>
<tr>
<td>GCS8830</td>
<td>8 x 30</td>
<td>9 x 30</td>
<td></td>
</tr>
<tr>
<td>GCS8840</td>
<td>8 x 40</td>
<td>10 x 30</td>
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<tr>
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<td>6 x 8 x 30</td>
<td>10 x 40</td>
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<td>6 x 8 x 40</td>
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<tr>
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<tr>
<td>GCS7930</td>
<td>7 x 9 x 30</td>
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<td>GCS7940</td>
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</tr>
<tr>
<td>GCS8030</td>
<td>8 x 10 x 30</td>
<td>10 x 40</td>
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<tr>
<td>GCS8040</td>
<td>8 x 10 x 40</td>
<td>10 x 40</td>
<td></td>
</tr>
</tbody>
</table>

Table by WL Gore & Associates / used with permission

**NB. The Gore carotid stent is not available outside the SCAFFOLD Study**
The Gore Stent Delivery System

Attributes
- Single handed delivery
- 5Fr Introducer Sheath Compatible (White Tip)
- 6Fr Introducer Sheath Compatible (Gray Tip)
- Hypotube Design
  - Allows for complete closure of hemostatic valve
- 135 cm Working Length
- 30 cm Rx

NB. The Gore carotid stent is not available outside the SCAFFOLD Study
*Not available in the United States; available in Europe and a number of other geographies
# CGuard™ Embolic Prevention Stent System

## System specifications

<table>
<thead>
<tr>
<th></th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent type</td>
<td>Nitinol – self expanding</td>
</tr>
<tr>
<td>Micronet aperture size</td>
<td>150-180 µm</td>
</tr>
<tr>
<td>Guidewire</td>
<td>0.014”</td>
</tr>
<tr>
<td>Stent sizes</td>
<td></td>
</tr>
<tr>
<td>- Diameter</td>
<td>6-10mm</td>
</tr>
<tr>
<td>- Length</td>
<td>20-60mm</td>
</tr>
</tbody>
</table>

CE Mark – March 2014
CGuard™ Embolic Prevention Stent System

Images by InspireMD, used with permission
Pore Size

* Average in lesion at expanded state
<table>
<thead>
<tr>
<th>Name</th>
<th>RoadSaver <em>aka</em> Casper</th>
<th>Gore® Carotid Stent</th>
<th>CGuard™ Embolic Prevention Stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent frame</td>
<td>closed-cell Nitinol</td>
<td>open-cell Nitinol</td>
<td>open-cell Nitinol</td>
</tr>
<tr>
<td>Mesh position in relation to frame</td>
<td>inside</td>
<td>outside</td>
<td>outside</td>
</tr>
<tr>
<td>Mesh material</td>
<td>Nitinol</td>
<td>PTFE</td>
<td>PET</td>
</tr>
<tr>
<td>Mesh structure</td>
<td>braided</td>
<td>inter-woven</td>
<td>single-fiber knitted</td>
</tr>
<tr>
<td>Pore size</td>
<td>375 µm</td>
<td>500 µm</td>
<td>150 - 180 µm</td>
</tr>
</tbody>
</table>

PTFE = Polytetrafluoroethylene  
PET = poliethylenephthalat
Data

histology / animal
Gore Mesh-Covered Carotid Stent
Preclinical Studies

- Canine artery model
- Biologically acceptable tissue response
  - All sidebranches and devices patent through 56 days
  - Full device endothelialization at 30 days
  - Comparatively less medial compression

PA Schneider VERVE 2014, animal data WL Gore / by permission
RoadSaver Histology and REM after 6 months

Proximal  Mid  Distal
CGuard EPS 90 days / pig
CGuard EPS 30 & 90 days/pig

BMS = non mesh-covered CGuard nitinol frame; InspireMD data / used with permission
Imaging angio
Roadsaver / Casper

Angio/CAS images courtesy P. Pieniazek / Krakow
Gore Carotid Stent

Angio/CAS images courtesy Dr. C. Schönholz
Imaging
IVUS
Initial series of CGuard™ IVUS studies indicates...

- Excellent stent expansion and apposition ✓
- ZERO tissue protrusion though mesh-and-struts ✓

Piotr Musialek @ LINC 2015
Mesh-Covered Stents for Carotid Intervention

Imaging
OCT
RoadSaver

Courtesy of Dr. Max Amor, Essey les Nancy

Data by Terumo / used with permission
CGuard™ EPS

Thrombotic material trapped between the stent MicroNET and the vessel wall.

Image Courtesy Dr. Juan Rigla, MD PhD
Perceptual Imaging Lab, University of Barcelona
Mesh-Covered Stents for Carotid Intervention

Imaging

CT
CGuard  5 months follow-up

Images  M.Urbanczyk / Z.Moczulski / M.Irzyk / P.Banyś
JP2 Hospital, Krakow, Poland
RCCA & RICA

LICA CGuard
5 months follow-up

Images  M.Urbanczyk / Z.Moczulski / M.Irzyk / P.Banyś
Jp2 Hospital, Krakow, Poland
published Evidence
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, DP Hil,† 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.
Evaluation of PET Mesh Covered Stent in Patients with Carotid Artery Disease

The CARENET-Trial
(CARotid Embolic protection using microNET)

Joachim Schofer (PI)
Piotr Musialek (Co-PI)
On behalf of the CARENET Investigators

Joachim Schofer, MD,PhD, Hamburg University Cardiovascular Center, Hamburg Germany
Piotr Musialek, MD, PhD, Jagiellonian University Medical College at John Paul II Hospital, Krakow, Poland,
Ralf Kolvenbach, MD, PhD, Augusta Hospital, Dusseldorf, Germany,
Horst Sievert, MD, PhD, Cardiovascular Center Frankfurt, Frankfurt, Germany
CGuard™ embolic prevention stent
CARENET – Study Design

Prospective, multi-center, all-comer

Objectives:
To evaluate the periprocedural safety and efficacy of the CGuard stent in the treatment of carotid lesions in thirty consecutive patients with symptomatic and asymptomatic carotid artery stenosis, suitable for CAS

Sites:
- Joachim Schofer (PI), Hamburg University Cardiovascular Center
- Piotr Musialek (Co-PI), Jagiellonian University Medical College
- Ralf Kolvenbach, Augusta Hospital
- Horst Sievert, Cardiovascular Center Frankfurt

Endpoints:
- Acute /30-day Cerebral Embolization by DWI (incidence, volume)
- 30 day MACCE (death, stroke, MI)

J. Schofer, P. Musialek et al. JACC Intv 2015;8:1229-34
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J. Schofer, P. Musialek et al. JACC Intv 2015;8:1229-34
DW-MRI: the *unforgiving* testimony of what you’ve done to the TARGET ORGAN...
The Power of DW-MRI...

48h after LICA-CAS

M. Urbanczyk, P. Banys, Dept. Radiology, JP2 Hospital, Krakow, Poland
CARENET DW-MRI analysis

<table>
<thead>
<tr>
<th>DW-MRI analysis @ 48 h</th>
<th>CARENET (n=27)</th>
</tr>
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<tbody>
<tr>
<td>Incidence of new ipsilateral lesions</td>
<td>37.0%</td>
</tr>
<tr>
<td>Average lesion volume (cm³)</td>
<td>0.039 ± 0.08</td>
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<tr>
<td>Maximum lesion volume (cm³)</td>
<td>0.445</td>
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</tbody>
</table>

see patient fluxogram

*External Core Lab analysis (US)*

† bilateral lesions

J. Schofer, P. Musialek et al. *JACC Intv* 2015;8:1229-34
# CARENET DW-MRI analysis

## DW-MRI analysis @ 48 hours

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<tr>
<th></th>
<th>CARENET (n=27)</th>
<th>PROFI (all) (n=62)</th>
<th>ICSS† (n=56)</th>
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<tr>
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<td><strong>68.0%</strong></td>
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<tr>
<td><strong>Average lesion volume (cm³)</strong></td>
<td>0.039 ± 0.08</td>
<td>1.375</td>
<td>-</td>
</tr>
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<td>0.445</td>
<td></td>
<td></td>
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</tbody>
</table>

≈50% reduction in new ipsilateral lesion incidence

---

*External Core Lab analysis (US)*


† bilateral lesions

J. Schofer, P. Musialek et al. *JACC Intv* 2015;8:1229-34
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<td>68.0%</td>
</tr>
<tr>
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<td>0.039</td>
<td>0.375</td>
<td>-</td>
</tr>
<tr>
<td><strong>Maximum lesion volume (cm(^3))</strong></td>
<td>0.415</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

>10-fold reduction in cerebral lesion volume

---

*External Core Lab analysis (US)*

Bijuklic et al. *JACC*, 2012; Bonati et al., *Lancet Neurol* 2010

\(^\d\) bilateral lesions

J. Schofer, P. Musialek et al. *JACC Intv* 2015;8:1229-34
Filter-protected CAS procedures

CARENET vs PROFI: DW-MRI analysis

DW-MRI analysis @ 48 hours

p < 0.005

INCIDENCE

new ipsilateral lesions (%)

34.6

CGuard

n=27

87.1

Conventional Carotid stent

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)
Filter-protected CAS procedures

CARENET vs PROFI: DW-MRI analysis

DW-MRI analysis @ 48 hours

VOLUME
new ipsilateral lesions (mL)

CGuard

Conventional Carotid stent (hybrid)

p < 0.005

0.59

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

*External Core Lab analysis (US)

J. Schofer, P. Musialek et al. *JACC Intv* 2015;8:1229-34
CARENET DW-MRI analysis

All but one peri-procedural ipsilateral lesions RESOLVED

<table>
<thead>
<tr>
<th>DW-MRI analysis @ 30 days*</th>
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<tbody>
<tr>
<td>Incidence of new ipsilateral lesions</td>
<td>1</td>
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<tr>
<td>Average lesion volume (cm³)</td>
<td>0.08 ± 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
Anti-Embolic Carotid Stent

Plaque protrusion may lead to early and late distal embolization

J. Schofer, P. Musialek et al. TCT 2014
Anti-Embolic Carotid Stent
CAS (and CEA) are—and will remain—emboli-generating procedures amenable to elimination with mesh.

**Figure 1.** Microembolic profile during unprotected CAS. The mean MES counts during various phases of the procedure are displayed.

CAS (and CEA) are – and will remain – emboli-generating procedures amenable to elimination with MicroNet + MicroNet protection during stent healing!

Figure 1. Microembolic profile during unprotected CAS. The mean MES counts during various phases of the procedure are displayed.

Prospective evaluation of All-comer percutaneous carotid revascularization in symptomatic and increased-risk asymptomatic carotid artery stenosis using CGuard™ Micronet-covered embolic prevention stent system:

The PARADIGM Study
Objective

- to evaluate feasibility and outcome of routine anti-embolic stent system use in unselected, consecutive patients referred for carotid revascularization ('all-comer' study)
Methods: The CAS Procedure

- **EPD** use mandatory; EPD selection according to the ‘Tailored CAS’ algorithm*

- **Liberal postdilatation** accepted in order to maximize potential for ‘endovascular full reconstruction’ (minimizing residual stenosis)

NB. 1. DWI evidence of effective MicroNet prevention against cerebral embolization (CARENET/PROFI)
2. Residual stenosis after CAS as independent predictor of in-stent restenosis

Cosottini M et al. Stroke Res 2010
Musialek P et al. J Endovasc Ther 2010
Wasser K et al. J Neurol 2012

PARADIGM

Endpoints:

- feasibility of endovascular Tx in unselected referrals using the study device in otherwise routine practice

- **device success** (able to deliver + implant + <30% DS)

- **procedure success** (device success w/o clinical compl.)
  (external neurologist, external non-invasive cardiologist)

- **clinical efficacy: MACNE** (death/stroke/MI)

- **in-stent velocities** (Duplex)

- 24-48h
- 30 days
- 12 months
- up to 5y
PARADIGM

- **ASYMPTOMATIC** patients treated interventionally only if at \(\uparrow\) stroke risk

- established lesion-level increased-risk criteria used:
  - thrombus-containing
  - tight, near-occlusive
  - documented progressive
  - irregular and/or ulcerated
  - contralateral ICA occlusion/stroke
  - asymptomatic ipsilateral brain infarct

PARADIGM: investigator – independent

- external study data verification
- external angiographic analysis
- external statistical analysis
Study Flow Chart (1)

97 carotid stenosis patient referrals*
(external >> internal)

Neuro-Vascular Team
- Neurologist
- Interventional Angiologist
- Vascular Surgeon
- Cardiologist

for carotid revascularization
73 patients

NOT for carotid revascularization
24 patients

n=19: lesion increased risk and/or severity criteria not met
n=2: ICA totally occluded on verification
n=2: ICA functionally occluded + h/o prior ipsil. large infarct with hemorrhagic transformation
n=1: severe haemodynamic instability (ICA stenosis asympt.)

*Dept. of Cardiac & Vascular Diseases, John Paul II Hospital, Krakow, Poland; 10.2014–03.2015
Study Flow Chart (2)

73 Patients for carotid revascularization

(92%)

CAS in n=67 Patients (bilateral in 3)

(1%)

CAS + CEA in n=1 Patient

(LICA-CEA and RICA-CAS) hybrid management

(7%)

CEA in n=5 Patients

n = 1 eGFR 14 => no contrast
n = 1 extreme access tortuosity
n = 1 severe aortic valve disease + calcific LICA (AVR + CEA)

n = 1 floating thrombus in CCA
n = 1 ICA diameter < 2.0 mm + contralateral occlusion

71 ICAs treated endovascularly in 68 patients
### Clinical characteristics of study patients (n=68)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age, mean±SD (min–max)</td>
<td>69 ±7 (55–83)</td>
</tr>
<tr>
<td>male, % (n)</td>
<td>66% (45)</td>
</tr>
<tr>
<td>symptomatic, % (n)</td>
<td>53% (36)</td>
</tr>
<tr>
<td>symptomatic ≤ 14 days, % (n)</td>
<td>28% (19)</td>
</tr>
<tr>
<td>acutely symptomatic (emergent CAS), % (n)</td>
<td>9% (6)</td>
</tr>
<tr>
<td>index lesion (CAS), % (n)</td>
<td></td>
</tr>
<tr>
<td>RICA</td>
<td>52% (35)</td>
</tr>
<tr>
<td>LICA</td>
<td>44% (30)</td>
</tr>
<tr>
<td>RICA+LICA</td>
<td>4% (3)</td>
</tr>
<tr>
<td>CAD, % (n)</td>
<td>65% (44)</td>
</tr>
<tr>
<td>h/of MI, % (n)</td>
<td>27% (18)</td>
</tr>
<tr>
<td>CABG or PCI in the past, % (n)</td>
<td>38% (26)</td>
</tr>
<tr>
<td>PCI as bridge to CAS, % (n)</td>
<td>16% (11)</td>
</tr>
<tr>
<td>AFib (h/o or chronic), % (n)</td>
<td>6% (4)</td>
</tr>
<tr>
<td>diabetes, % (n)</td>
<td>35% (24)</td>
</tr>
<tr>
<td>h/o neck or chest radiotherapy, % (n)</td>
<td>4% (3)</td>
</tr>
</tbody>
</table>
PARADIGM: Results (1)

- Percutaneous treatment using the intended MicroNet-covered embolic prevention stent system CGuard (ie, no other stents used during the study period)
  - Device success: 100%
  - Procedure success: 100%
  - Transient Dopamine infusion: 19% (n=14)
  - Debris in EPD: 18% (n=13)
  - Access site complications: 0% (n=0)
  - Vascular plug closure: 45% (n=32)
# PARADIGM: Results (2)

## Index lesion qualitative characteristics \( (n=71\) lesions)

<table>
<thead>
<tr>
<th></th>
<th>All ((n=71))</th>
<th>Symptomatic ((n=37))</th>
<th>Asymptomatic ((n=34))</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>thrombus, % ((n))</td>
<td>15% (11)</td>
<td>24% (9)</td>
<td>6% (2)</td>
<td>0.025</td>
</tr>
<tr>
<td>near occl./string, % ((n))</td>
<td>21% (15)</td>
<td>30% (11)</td>
<td>12% (4)</td>
<td>0.084</td>
</tr>
<tr>
<td>proggresive*, % ((n))</td>
<td>27% (19)</td>
<td>11% (4)</td>
<td>44% (15)</td>
<td>0.003</td>
</tr>
<tr>
<td>ulcerated, % ((n))</td>
<td>41% (29)</td>
<td>46% (17)</td>
<td>35% (12)</td>
<td>0.470</td>
</tr>
<tr>
<td>irregular, % ((n))</td>
<td>72% (51)</td>
<td>65% (24)</td>
<td>79% (27)</td>
<td>0.197</td>
</tr>
<tr>
<td>contralateral occl. , % ((n))</td>
<td>17% (12)</td>
<td>22% (8)</td>
<td>35% (12)</td>
<td>0.291</td>
</tr>
<tr>
<td>highly calcific, % ((n))</td>
<td>23% (16)</td>
<td>14% (5)</td>
<td>35% (12)</td>
<td>0.050</td>
</tr>
<tr>
<td>asymptomatic ipsilat. brain embolization/infarct</td>
<td>N/A</td>
<td>N/A</td>
<td>32% (11)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*verified on imaging

## CoreLab-Quantified
- **ICA reference diameter** \( 4.99 \pm 0.36\)mm \(\text{from 4.27 to 6.02}\)mm
- **Lesion length** \( 19.9 \pm 5.8\)mm \(\text{from 8.19 to 30.25}\)mm
**PARADIGM: Results (3)**

<table>
<thead>
<tr>
<th>Index lesion quantitative characteristics (n=71 lesions)</th>
<th>All (n=71 lesions)</th>
<th>Symptomatic n=37</th>
<th>Asymptomatic n=34</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before CAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSV, m/s</td>
<td>3.8 ± 1.3</td>
<td>3.7 ± 1.1</td>
<td>3.8 ± 1.5</td>
<td>0.862</td>
</tr>
<tr>
<td>EDV, m/s</td>
<td>1.3 ± 0.7</td>
<td>1.4 ± 0.6</td>
<td>1.3 ± 0.8</td>
<td>0.687</td>
</tr>
<tr>
<td>Diameter stenosis % (QA)</td>
<td>82 ± 9</td>
<td>79 ± 9</td>
<td>84 ± 9</td>
<td>0.021</td>
</tr>
<tr>
<td>CAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPD type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal*</td>
<td>35% (25)</td>
<td>44% (16)</td>
<td>26% (9)</td>
<td>0.092</td>
</tr>
<tr>
<td>Distal**</td>
<td>65% (46)</td>
<td>56% (21)</td>
<td>74% (25)</td>
<td></td>
</tr>
<tr>
<td>post-dilat balloon# peak pressure, mmHg</td>
<td>18.4 ± 3.4</td>
<td>17.5 ± 3.6</td>
<td>19.2 ± 2.9</td>
<td>0.037</td>
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<tr>
<td>After CAS</td>
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</tr>
<tr>
<td>Stent length (QA)§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nominal 30 mm (min-max)</td>
<td>29.66 ± 0.30</td>
<td>29.66 ± 0.28</td>
<td>29.65 ± 0.32</td>
<td>NA</td>
</tr>
<tr>
<td>Nominal 40 mm (min-max)</td>
<td>39.73 ± 0.34</td>
<td>39.69 ± 0.41</td>
<td>39.77 ± 0.28</td>
<td>(28.73-30.07)</td>
</tr>
<tr>
<td>Residual diam. stenosis</td>
<td>7 ± 4%</td>
<td>5 ± 4%</td>
<td>7 ± 5%</td>
<td>0.257</td>
</tr>
<tr>
<td>in-stent PSV, m/s</td>
<td>0.70 ± 0.28</td>
<td>0.66 ± 0.29</td>
<td>0.74 ± 0.27</td>
<td>0.266</td>
</tr>
<tr>
<td>in-stent EDV, m/s</td>
<td>0.17 ± 0.07</td>
<td>0.17 ± 0.07</td>
<td>0.18 ± 0.07</td>
<td>0.457</td>
</tr>
</tbody>
</table>

* Emboshield (n=7); FilterWire (n=14); Spider (n=25)
** Gore FlowReversal (n=4) or flow reversal with MoMa (n=21)

(NB. mean flow reversal time was 6min 48s, from 5min 18s to 11min 2s)
# Ø 4.5mm (n=5); Ø 5.0mm (n=36); Ø 5.5mm (n=29); Ø 6.0mm (n=1);
§ 30mm in 51 lesions; 40mm in 18 lesions (2 other lesions required two stents each)
PARADIGM: Results (4)

- Death/stroke/MI @ 48h: 0%
- Death/stroke/MI @ 30d: 0%
PARADIGM: Results (5)

n=71 arteries in 68 patients

PSV (m/s)  EDV (m/s)

baseline  CGuard 30 days
Procedure - Relevant Information
<table>
<thead>
<tr>
<th>Name</th>
<th>RoadSaver aka Casper</th>
<th>Gore® Carotid Stent</th>
<th>CGuard™ Embolic Prevention Stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-sheathable ?</td>
<td>yes*</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Crossing profile</td>
<td>5F</td>
<td>5F (smaller diam)</td>
<td>6F</td>
</tr>
<tr>
<td>Foreshortening</td>
<td>yes</td>
<td>unknown**</td>
<td>no #</td>
</tr>
<tr>
<td>Stent placement accuracy</td>
<td>–</td>
<td>N/D</td>
<td>++#</td>
</tr>
<tr>
<td>Ability to eliminate residual stenosis</td>
<td>N/D</td>
<td>N/D</td>
<td>yes #</td>
</tr>
<tr>
<td>Externally-analysed systematic DW MRI study data</td>
<td>unknown</td>
<td>unknown</td>
<td>yes ##</td>
</tr>
</tbody>
</table>

*up to 50% released length  
**probably not substantial  
## CARENET JACC Intv 2015;8:1229  
N/D = not determined  
CRF Cardiovascular Research Foundation At the heart of innovation  
P. Musialek @ TCT 2015
on-going Studies
CLEAR-ROAD: a Physician-initiated Carotid Trial Investigating the Efficacy of Endovascular Treatment of Carotid Arterial Disease With the Multi-layer RoadSaver Stent

This study is currently recruiting participants. (see Contacts and Locations)

Verified August 2015 by Flanders Medical Research Program

Sponsor:
Flanders Medical Research Program

Information provided by (Responsible Party):
Flanders Medical Research Program

Purpose

The objective of this clinical investigation is to evaluate the clinical outcome (up to 12 months) of treatment by means of stenting with the RoadSaver (Terumo) in subjects at high risk for carotid endarterectomy requiring carotid revascularization due to significant extra-cranial carotid artery stenosis.

Study Type: Interventional
Study Design: Endpoint Classification: Efficacy Study
 Intervention Model: Single Group Assignment
 Masking: Open Label
 Primary Purpose: Treatment

Primary Outcome Measures:
- 30-day rate of Major Adverse events (MAE)

Estimated Enrollment: 100
Study Start Date: April 2015
Estimated Study Completion Date: May 2017
Estimated Primary Completion Date: April 2016 (Final data collection date for primary outcome measure)

50% patient cohort recruitment threshold crossed
Italian registry - Roadsaver

Torino: Dr. C. Rabbia
Radiologist

Cotignola: Dr. A. Cremonesi
Cardiologist

Siena: Prof. C. Setacci
Vascular Surgeon

3 Italian Vascular Centers
RoadSaver Italian registry - Preliminary results

3 Centers
Cotignola, Siena, Torino

more than 100 cases
Italian registry - Preliminary results

- Subgroup analysis - MR
  - Magnetic Resonance evaluation of cerebral parenchyma before and 24 hours post-op

New lesions in **1 case** @ 24h (n=3 in the ipsilateral and n=2 in contralateral hemisphere)
GORE® Carotid Stent Clinical Study for the treatment of carotid Artery stenosis in patients at increased risk For adverse events From carOtid enDarterectomy

The Gore SCAFFOLD Clinical Study

PIs: P.A. Schneider and W.A. Gray

• Number of Subjects
  312 subjects (max 40 at each site)

• Primary Endpoint
  Composite of Major Adverse Events (MAE) defined as death, any stroke, or myocardial infarction through 30 days post index procedure plus ipsilateral stroke between 31 days and 1 year
  *All primary endpoint events will be determined by the study Clinical Events Committee

• 50% patient cohort recruitment threshold crossed

NCT # 01901874

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Data expected 2017
Physician-initiated prospective Italian Registry of carotid stenting with the C-Guard mesh-stent: the IRON-Guard registry. Rationale and design

Announced: J CARDIOVASC SURG 2015;56:787-91

Planned enrollment: n = 200 patients

Primary endpoint: clinical – MAE death/stroke/MI ≤ 30 days

CO-Principal Investigators
Carlo Setacci, Siena
Francesco Speziale, Rome

Investigators
Guido Bellandi, Arezzo
Piergiorgio Cao, Rome
Renato Casana, Milan
Patrizio Castelli, Varese
Roberto Chiesa, Milan

Gioachino Coppi, Modena
Alberto Cremonesi, Cotignola
Gianfranco Fadda, Nuoro
Augusto Farina, Crema
Paolo Frigatti, Udine
Andrea Gaggiano, Asti
Franco Grego, Padova
Massimo Lenti, Perugia
Nicola Mangialardi, Rome
Giustino Marcucci, Civitavecchia
Stefano Michelagnoli, Florence

Giovanni Nano, Milan
Franco Nessi, Turin
Claudio Novali, Cuneo
Giancarlo Palasciano, Tricase
Domenico Palombo, Genoa
Giovanni Paroni, San Giovanni Rotondo
Francesco Pompeo, Pozzilli
Claudio Rabbia, Turin
Massimo Sponza, Udine
Andrea Stella, Bologna
Enrico Vecchiati, Reggio Emilia
PARADIGM – Extend (aka PARADIGM-101)

PARADIGM – 101 recruitment completed

Patient #101 in 'PARADIGM-EXTEND' (a.k.a. 'PARADIGM 101')

subacute stroke

PI: P. Musialek / Krakow
remaining
Ununknowns
Remaining Unknowns (1)

- Is there a product/design-specific "gradient" in the embolic prevention efficacy?
Remaining Unknowns (1)

- Is there a product/design-specific "gradient" in the embolic prevention efficacy?
Remaining Unknowns (1)

- Is there a product/design-specific "gradient" in the embolic prevention efficacy?
Remaining Unknowns (2)

- **Large-scale** (multi-center, multi-hundred patient), controlled clinical endpoint data?

- Long-term treatment durability / ’no restenosis’ proof
  
  NB. so far – no worrying signal

- Role in **open (CEA)** vs. **endo (CAS)** balance

- Role in **primary** stroke prevention
Conclusions
Clinical evidence in October 2015...

- 1 peer-reviewed, published clinical study
  - multicenter, single-arm
  - **DWI** controlled (24-48h, 30d, external analysis)

*CARENET, JACC Intv 2015;8:1229-1234*
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  (CARENET, JACC Intv 2015;8:1229-1234)

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  - 1 with full 30-day data available in all-comers (others underway or planned)
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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
This concept has been desired.

And it works.

This is the future of Carotid Artery Stenting?
Improved technology for CAS — better EPDs (flow reversal and proximal occlusion) and better stents (membrane-covered, ultra-closed cell, and biodegradable). Several issues may improve CAS outcomes, such as the introduction of new and better stents. An ex vivo study showed that use of a polyurethane membrane-covered stent resulted in lower cerebral embolization rates.