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

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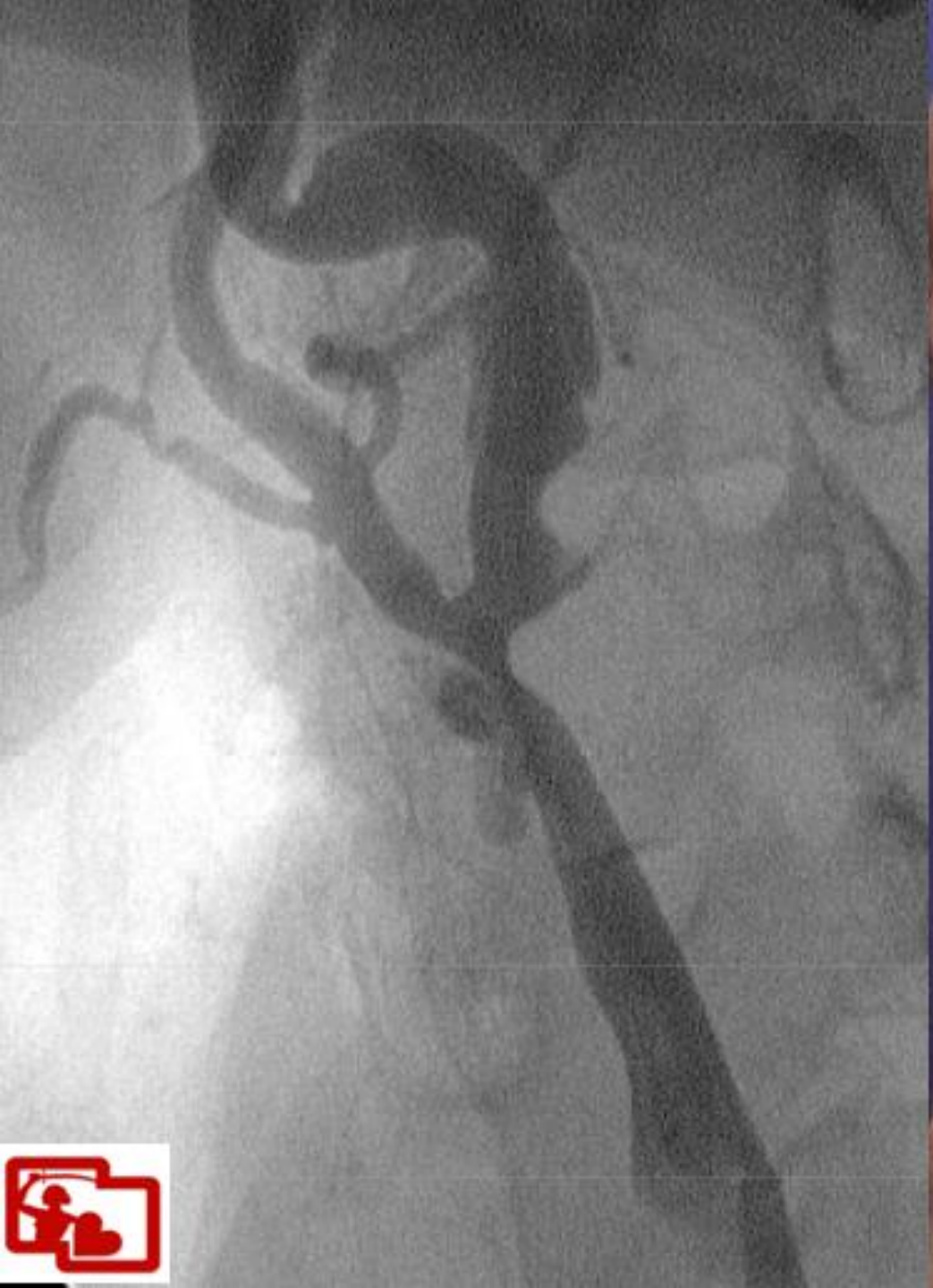
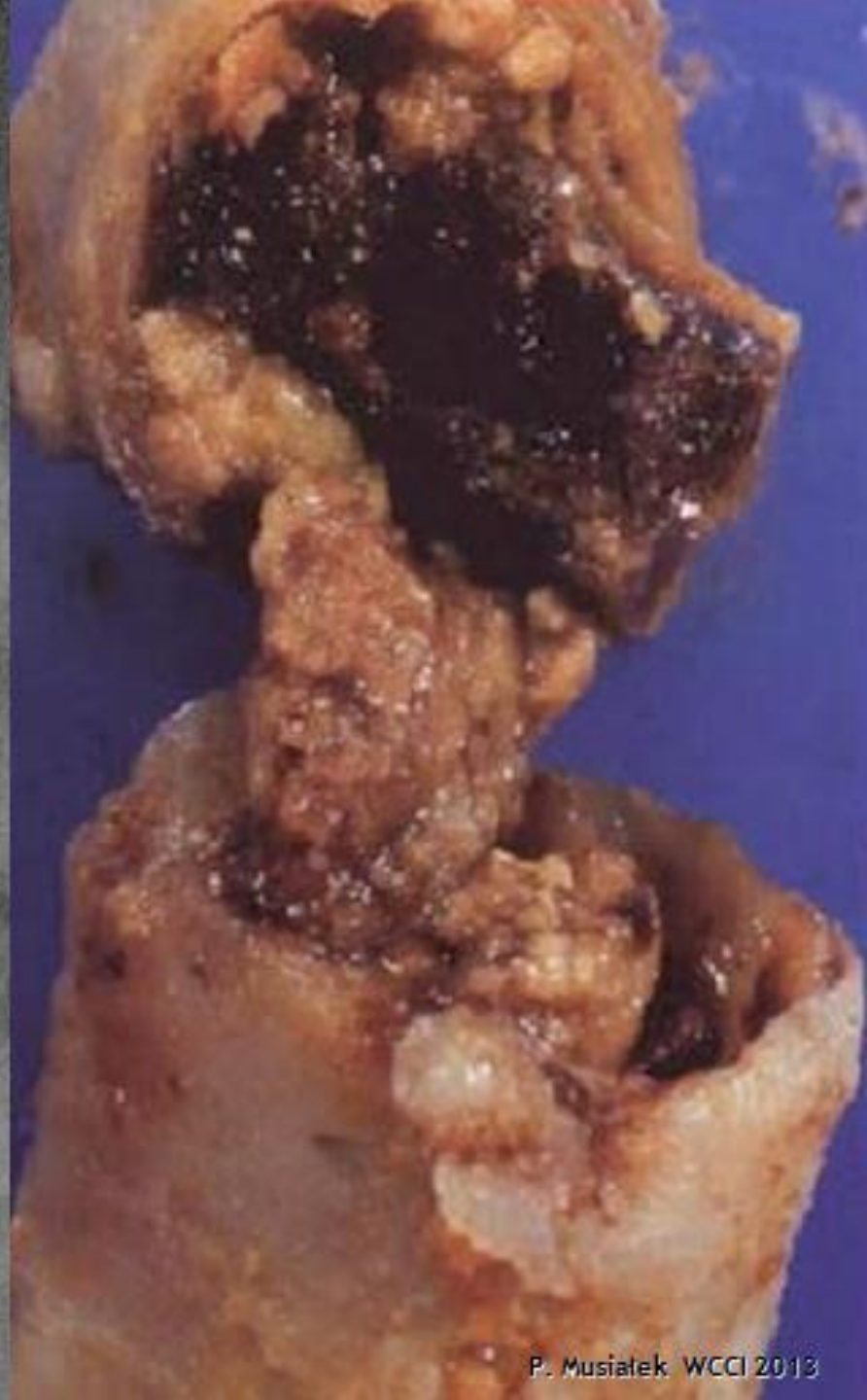
Disclosure Statement of Financial Interest

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

Affiliation/Financial Relationship	Company
• Grant/Research Support	• ABBOTT
• Consulting Fees/Honoraria	• ABBOTT, Balton, InspireMD, Medtronic

Rationale




P. Musiałek WCCI 2013

CAS (and CEA) *are* –and *will remain*– emboli-generating procedures

Effect of the Distal-Balloon Protection System on Microembolization During Carotid Stenting

Nadim Al-Mubarak, MD; Gary S. Roubin, MD, PhD; Jiri J. Vitek, MD, PhD; Sriram S. Iyer, MD; Gishel New, MD; Martin B. Leon, MD

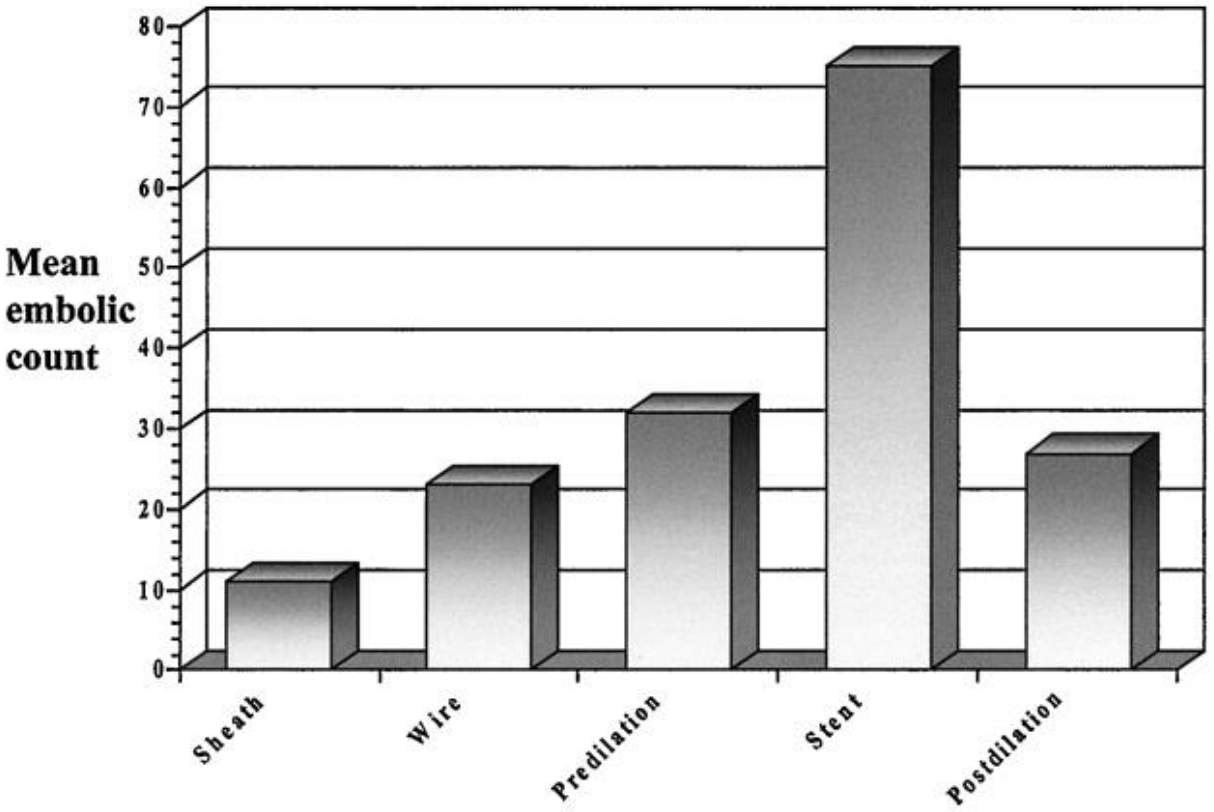
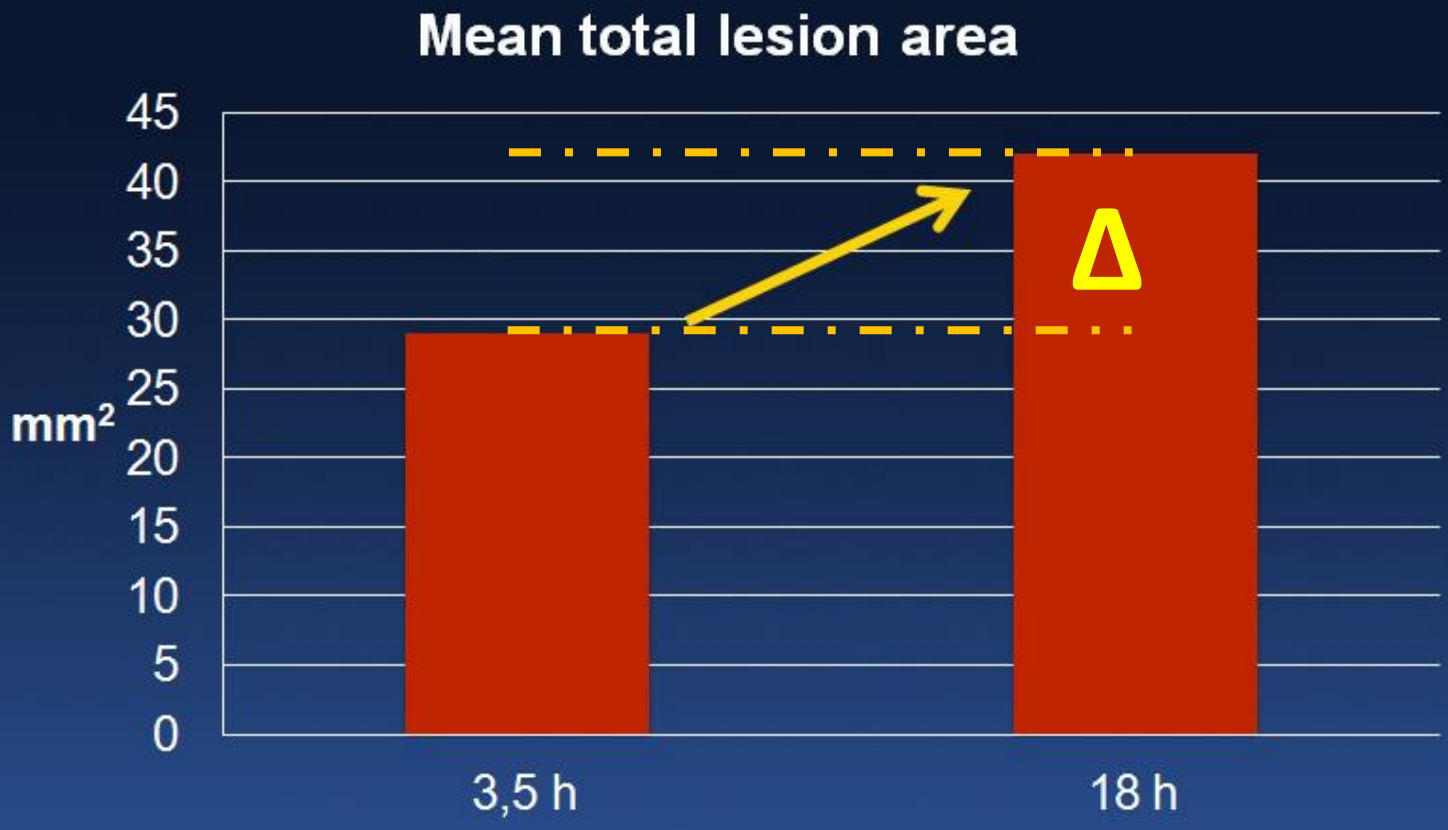


Figure 1. Microembolic profile during unprotected CAS. The mean MES counts during various phases of the procedure are displayed.

Circulation. 2001;104:1999-2002

Post-procedural Embolization with conventional carotid stents

DW-MRI post CAS



Schofer J et al, JACC Cardiovasc interv 2008

Does Free Cell Area Influence the Outcome in Carotid Artery Stenting?

M. Bosiers,[1*] G. de Donato,[2] K. Deloose,[1] J. Verbist,[3] P. Peeters,[3]
F. Castriota,[4] A. Cremonesi[4] and C. Setacci[4]

Overview of event rates related to the different stents

	Total population			Symptomatic population			Asymptomatic population		
	Patients	All events	Post-procedural events	Patients	All events	Post-procedural events	Patients	All events	Post-procedural events
Stent name									
X-act		1.9%	1.9%		2.2%	2.2%		1.7%	1.7%
Nexstent		3.3%	3.3%		0.0%	0.0%		4.2%	4.2%
Wallstent		2.3%	1.2%		2.3%	1.2%		2.3%	1.2%
Precise		4.1%	3.1%		6.3%	4.9%		2.0%	1.3%
Protégé		3.0%	3.0%		6.7%	6.7%		1.4%	1.4%
Acculink		4.2%	3.7%		7.7%	7.1%		1.7%	1.2%
Exponent		11.8%	5.9%		9.1%	9.1%		13.0%	4.3%
Total	3179	2.83%	1.9%		3.6%	2.73%	1862	2.25%	1.3%

2/3

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

Eur J Vasc Endovasc Surg Vol 33, February 2007

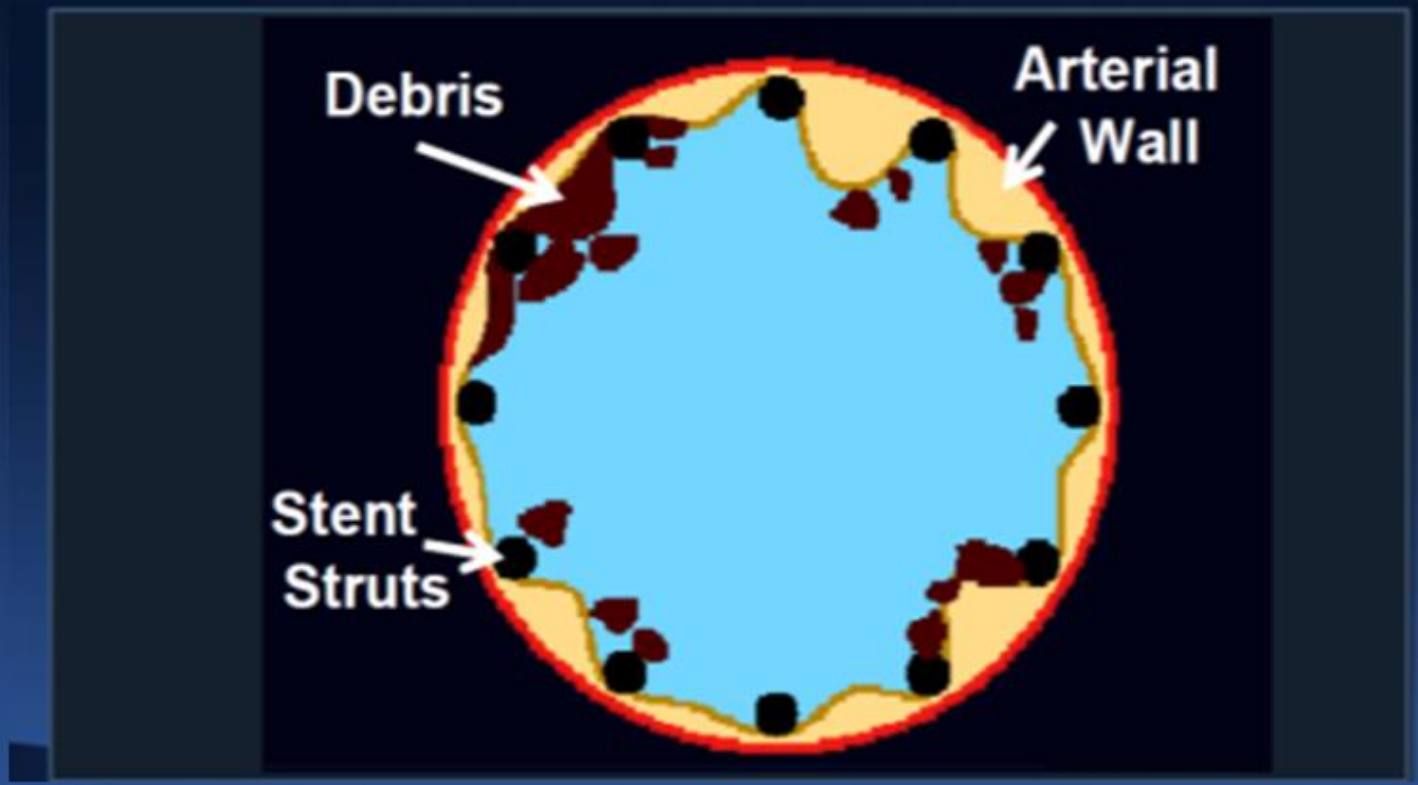
FREE CELL AREA drives CAS neurologic adverse events (and majority occur *post-procedure*)

Free cell area	Total population		Symptomatic population	
	All events	Post-procedural events	All events	Post-procedural events
<2.5 vs [2.5, 5]	1.00	1.00	1.00	1.00
<2.5 vs [5, 7.5]	0.054	0.072	0.048	0.024
<2.5 vs >7.5	0.27	0.006	0.0006	$2.8\ 10^{-6}$

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

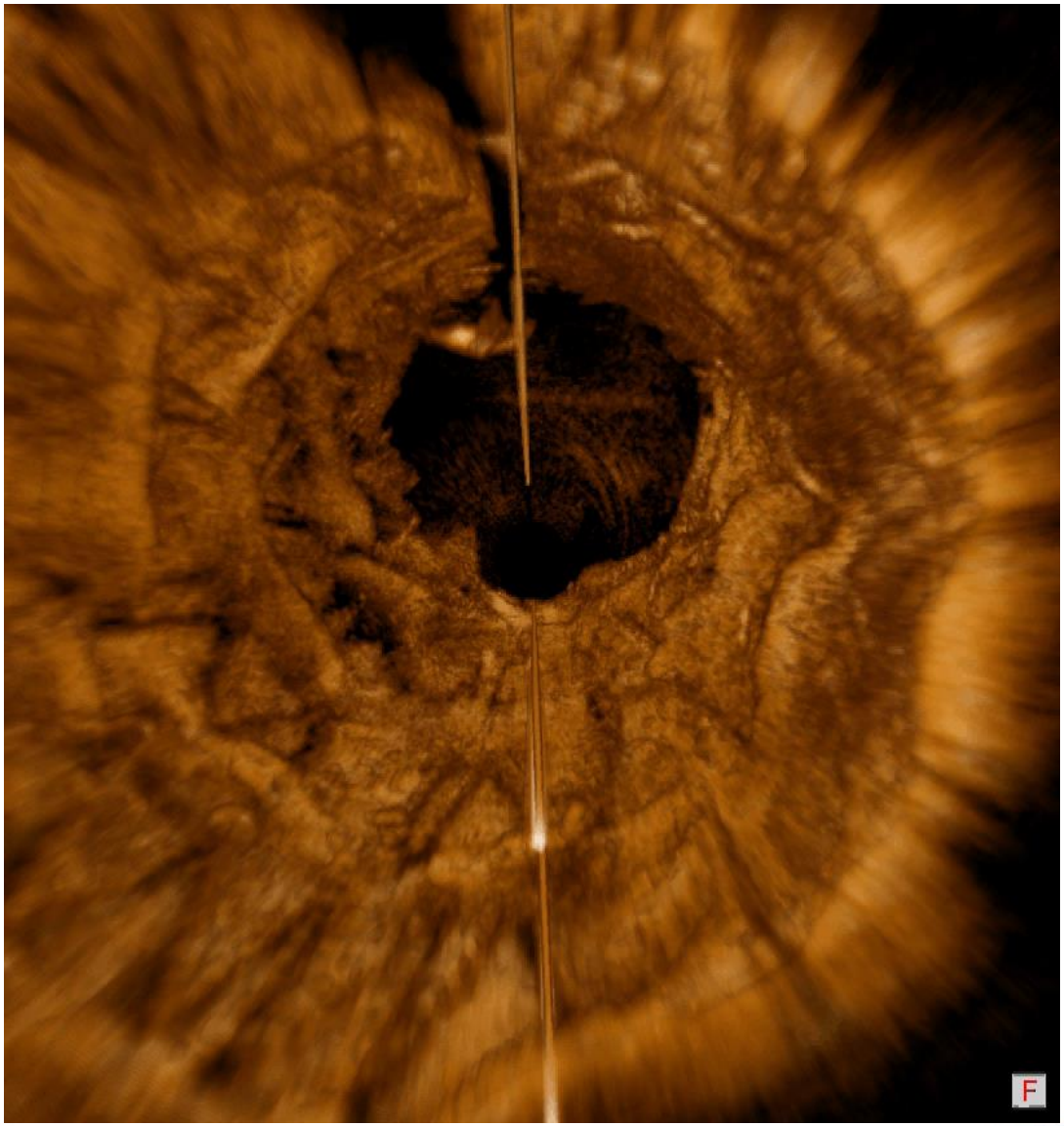
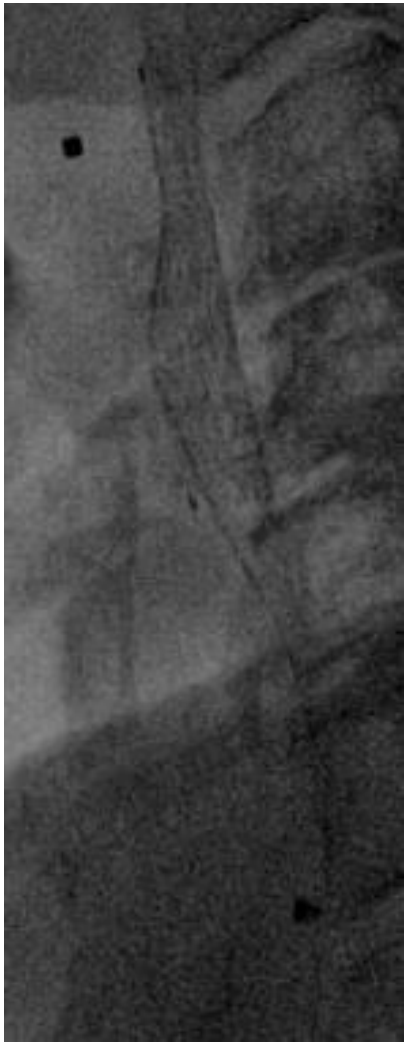
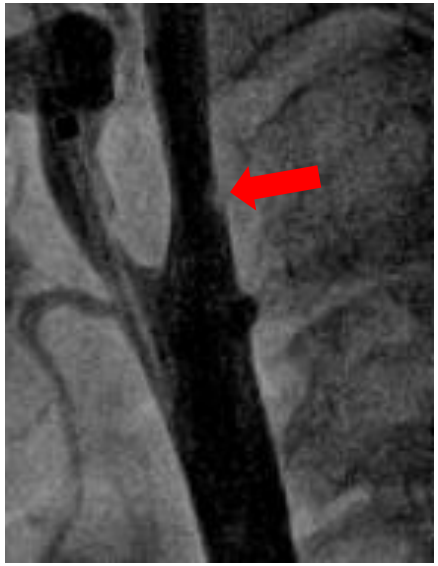


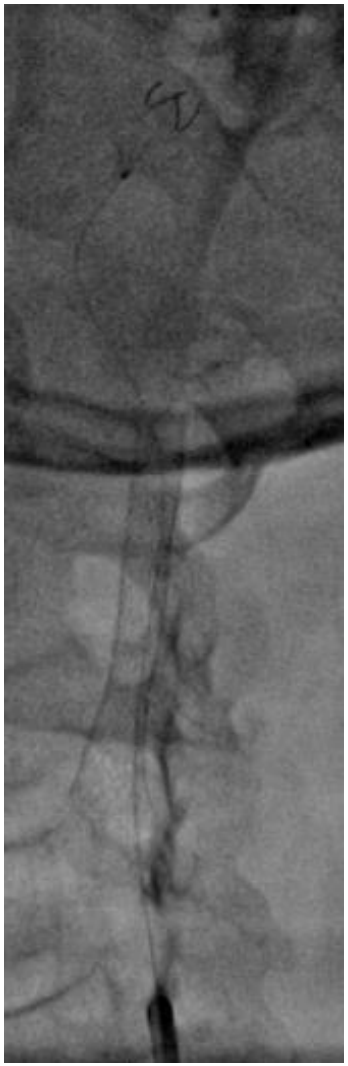
Image Courtesy Dr Juan Rigla, MD PhD
Perceptual Imaging Lab, Univerity of Barcelona

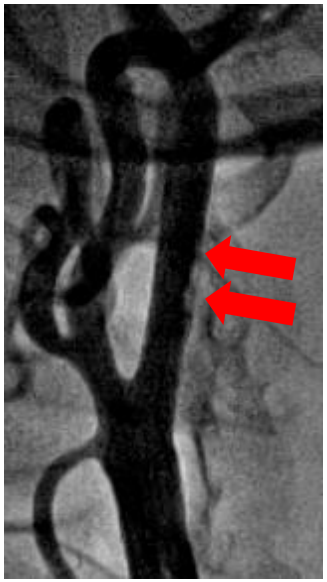
current best-in-class Hybrid stent

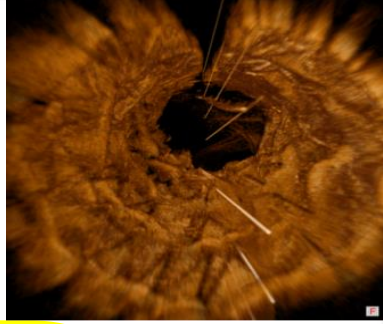




current best-in-class Closed-cell stent







ANY data

on incidence of

PLAQUE PROLAPSE

in

conventional carotid stents ?

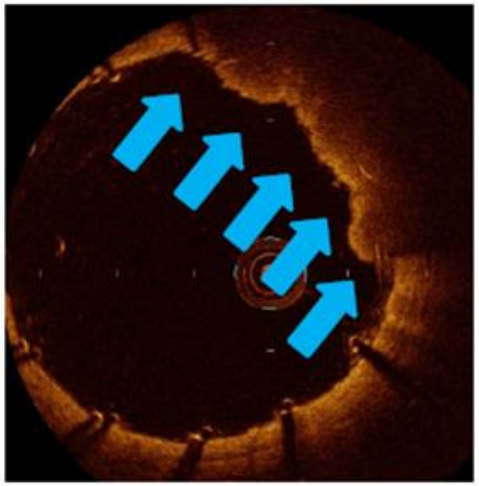
Post-procedural **PLAQUE PROLAPSE** through **conventional stent** struts

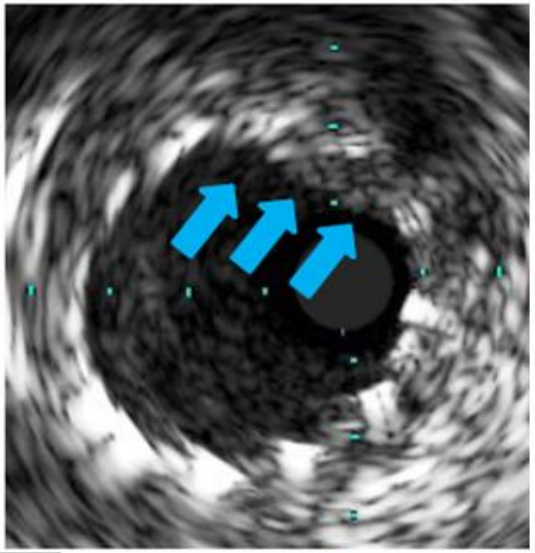
Suzuki M et al.
ESC 2014
Presentation
www.escardio.org

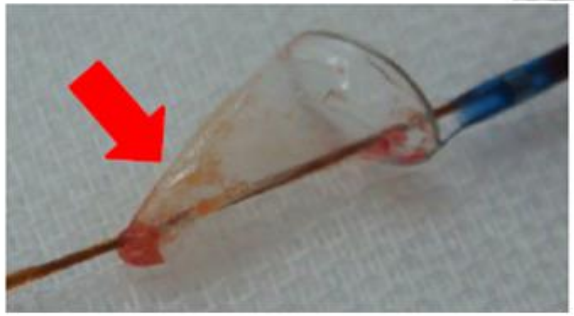
30.7%

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

81 y.o. Female, Symptomatic



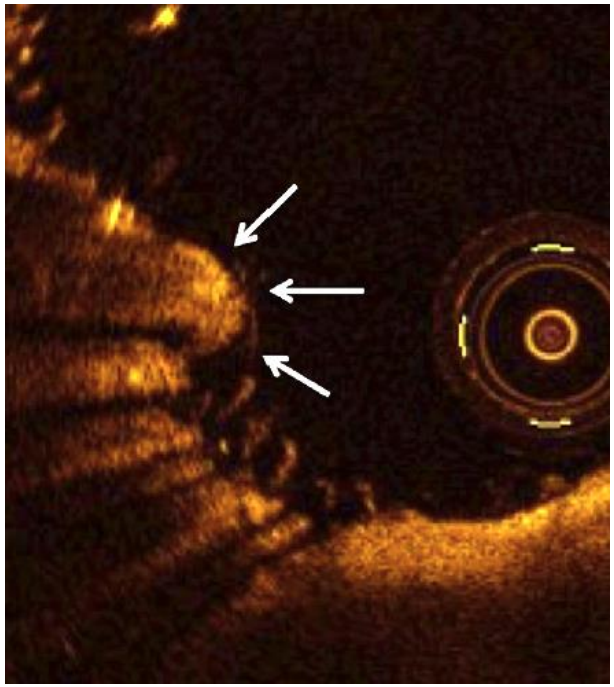




Images: Dr M. Suzuki
ESC 2014
www.escardio.org

Eur Heart J. 2014;35(Abstr Suppl):178

Post-procedural PLAQUE PROLAPSE through conventional stent struts

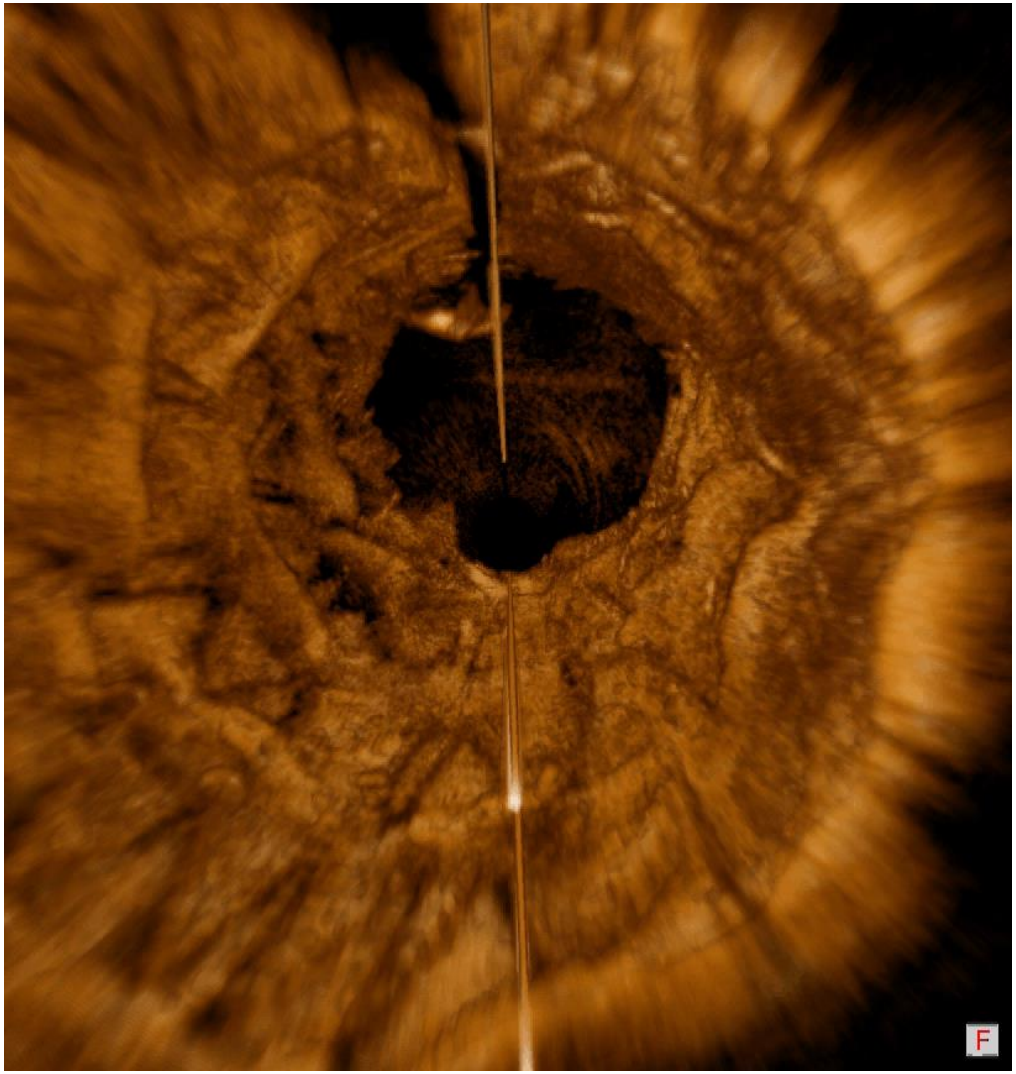


	Closed cell ($n = 17$)	Open cell ($n = 13$)	Hybrid cell ($n = 10$)
Plaque prolapse[b]	17.6%, (3)	61.5%, (8)	30%, (3)

[b] At least 10 appreciable tissue prolapses between the stent struts per patient.

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

Conventional Carotid Stent



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Perceptual Imaging Lab, Univerity of Barcelona

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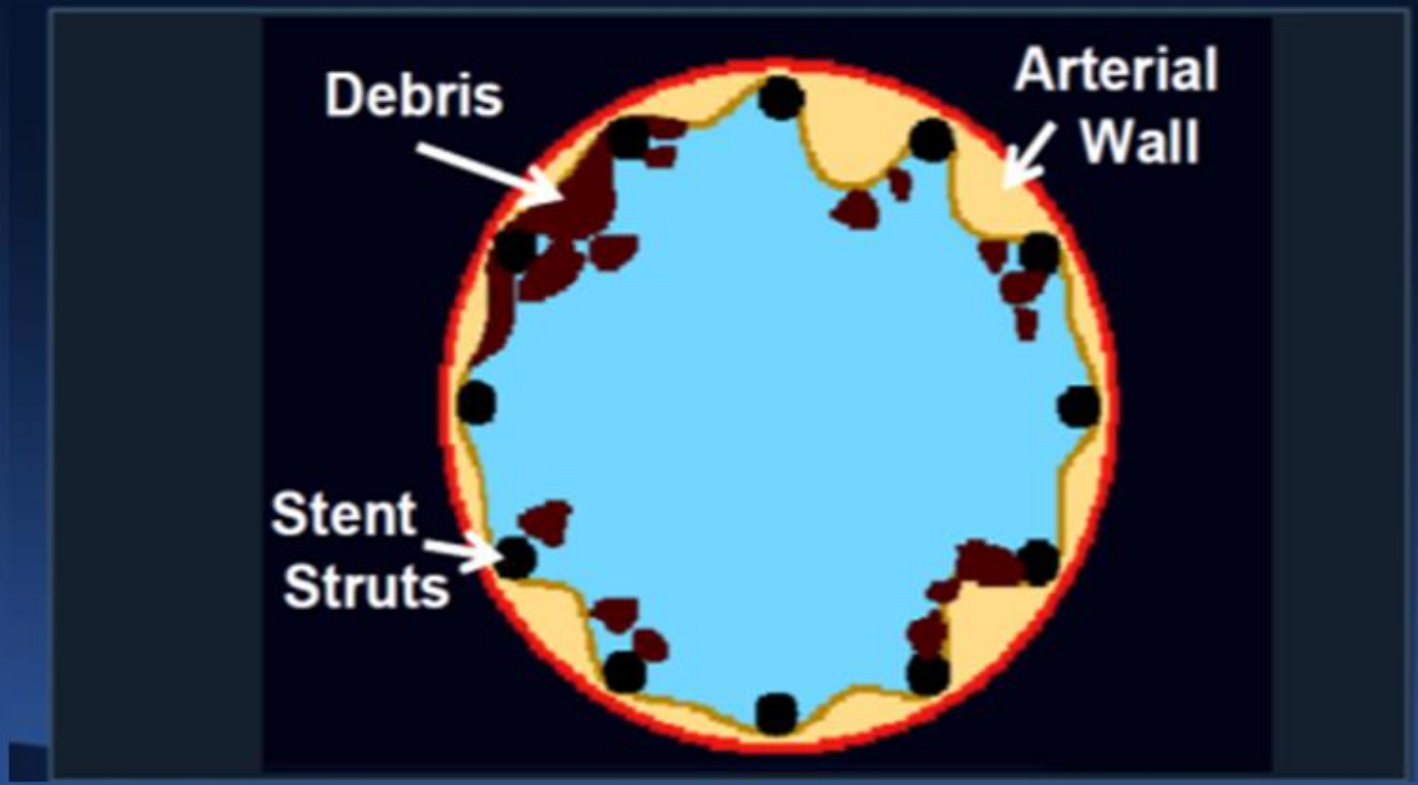
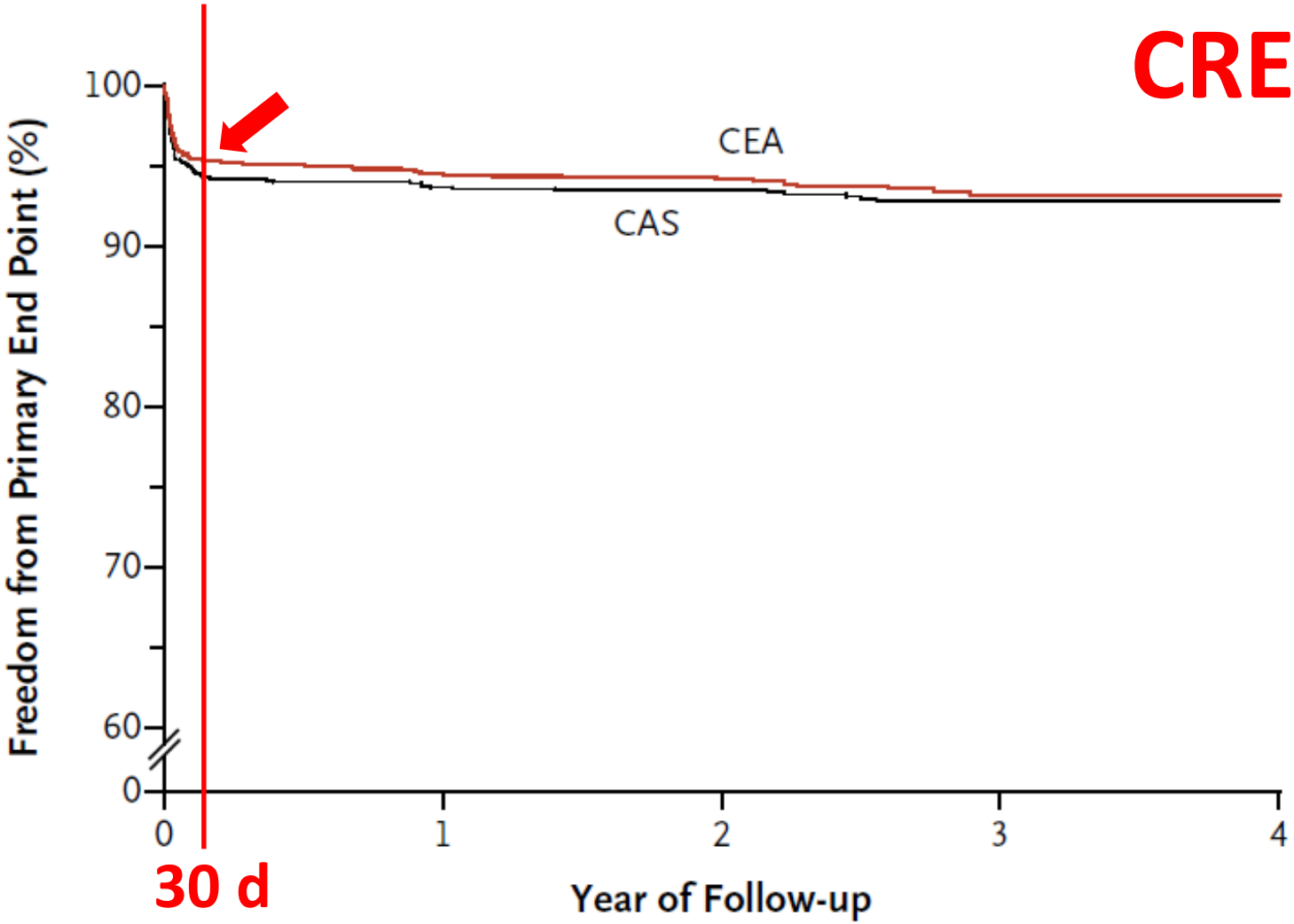


J. Schofer, P. Musialek et al. TCT 2014

N Engl J Med 2010;363:11-23.

CREST



No. at Risk

CAS	1262	1100	787	460	162
CEA	1240	1099	770	430	145

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N Engl J Med 2010;363:11-23.

			Periprocedural Period		
	CAS (N=1262)	CEA (N=1240)	Absolute Treatment Effect of CAS vs. CEA (95% CI)	Hazard Ratio for CAS vs. CEA (95% CI)	P Value
	no. of patients (% ±SE)		*percentage points*		
Death	9 (0.7±0.2)	4 (0.3±0.2)	0.4 (–0.2 to 1.0)	2.25 (0.69 to 7.30)†	0.18†
Stroke					
Any	52 (4.1±0.6)	29 (2.3±0.4)	1.8 (0.4 to 3.2)	1.79 (1.14 to 2.82)	0.01
Major ipsilateral	11 (0.9±0.3)	4 (0.3±0.2)	0.5 (–0.1 to 1.2)	2.67 (0.85 to 8.40)	0.09
Major nonipsilateral‡	0	4 (0.3±0.2)	NA	NA	NA
Minor ipsilateral	37 (2.9±0.5)	17 (1.4±0.3)	1.6 (0.4 to 2.7)	2.16 (1.22 to 3.83)	0.009
Minor nonipsilateral	4 (0.3±0.2)	4 (0.3±0.2)	0.0 (–0.4 to 0.4)	1.02 (0.25 to 4.07)	0.98†
Myocardial infarction	14 (1.1±0.3)	28 (2.3±0.4)	–1.1 (–2.2 to –0.1)	0.50 (0.26 to 0.94)	0.03
Any periprocedural stroke or postprocedural ipsilateral stroke	52 (4.1±0.6)	29 (2.3±0.4)	1.8 (0.4 to 3.2)	1.79 (1.14 to 2.82)	0.01
Major stroke	11 (0.9±0.3)	8 (0.6±0.2)	0.2 (–0.5 to 0.9)	1.35 (0.54 to 3.36)	0.52
Minor stroke	41 (3.2±0.5)	21 (1.7±0.4)	1.6 (0.3 to 2.8)	1.95 (1.15 to 3.30)	0.01
Any periprocedural stroke or death or post-procedural ipsilateral stroke	55 (4.4±0.6)	29 (2.3±0.4)	2.0 (0.6 to 3.4)	1.90 (1.21 to 2.98)	0.005
Primary end point (any periprocedural stroke, myocardial infarction, or death or postprocedural ipsilateral stroke)	66 (5.2±0.6)	56 (4.5±0.6)	0.7 (–1.0 to 2.4)	1.18 (0.82 to 1.68)	0.38

The periprocedural period was defined, according to the study protocol, as the 30-day period after the procedure

CREST

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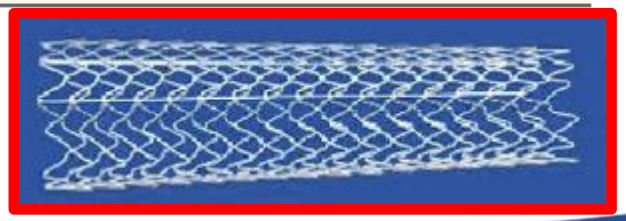

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Major stroke	1.[illegible]	[illegible]	[illegible] (–0.5 to 0.9)	[illegible]	[illegible]
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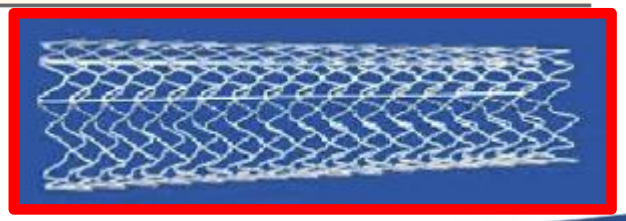
2015+

we need to do better



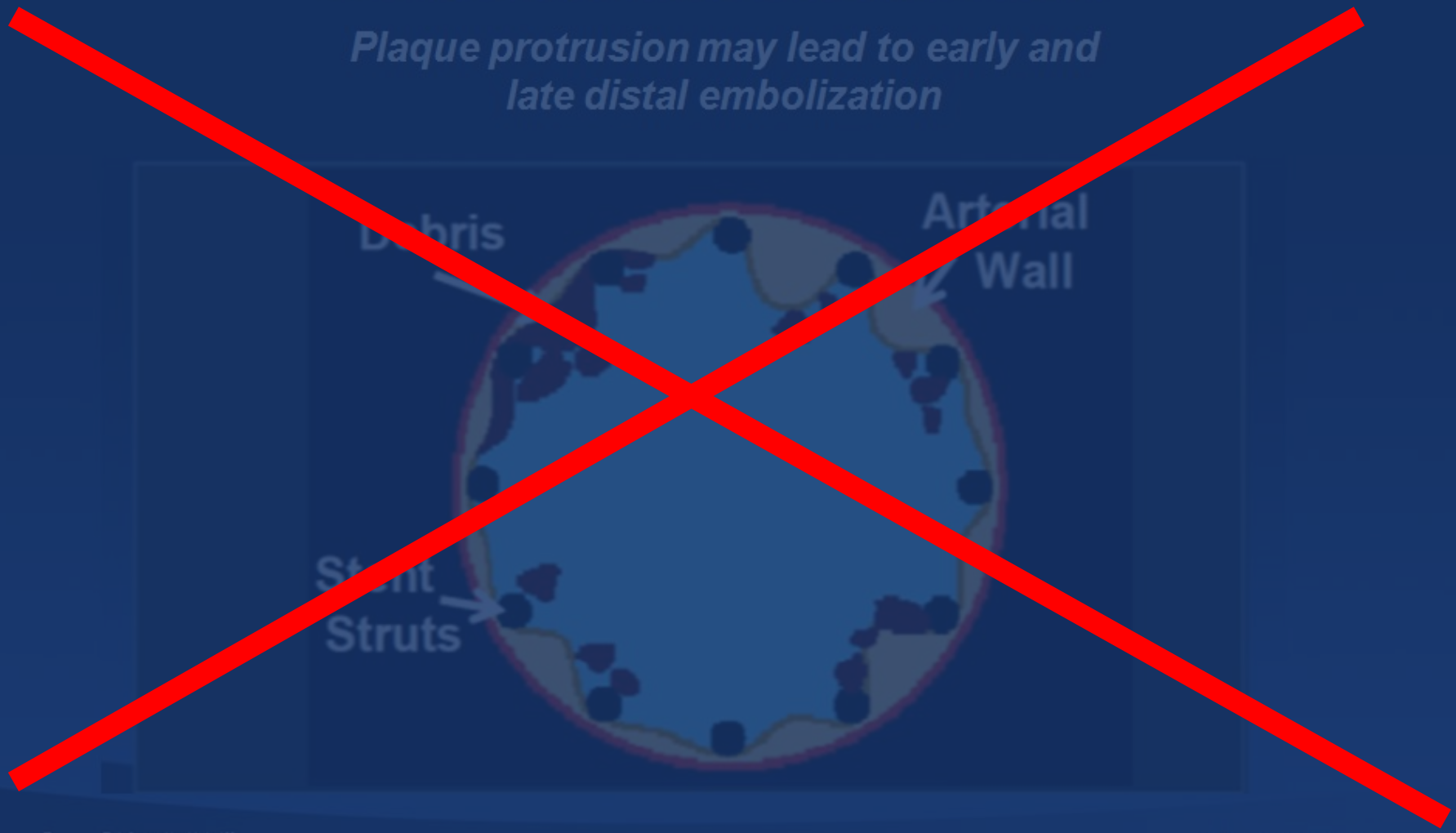


Conventional Carotid Stent

Plaque protrusion may lead to early and late distal embolization

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

Anti - Embolic Carotid Stent



Device Designs

Device Designs

n=3

Competition Carotid Stents

"Mesh" Stents









Terumo/ Microvention	Inspire MD	W.L. Gore	Abbott Vascular		Boston Scientific	Ev3/ Covidien/ Medtronic	Cordis/ Cardinal Health	Invatec/ Medtronic
Roadsaver	CGuard	Gore Carotid Stent	Acculink	XACT	Carotid Wallstent	Protégé	Precise Pro	Cristallo Ideale
0.38 mm²	0.15 mm²	0.44 mm²	2.36 mm²	1.89 mm²	1.397 mm²	4.93 mm²	2.36 mm²	3.23 mm²
Bench marking by Microvention								
375-500µm	150-180µm	500µm						
Advertising by Inspire MD								

TERUMO INTERVENTIONAL SYSTEMS

Table by Terumo, used with permission

TERUMO

RoadSaver

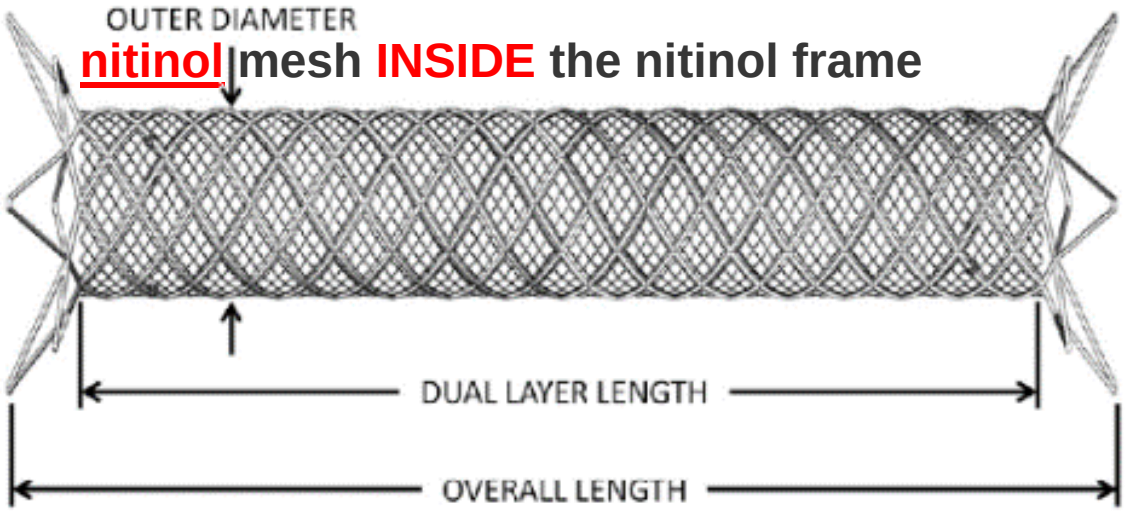
TERUMO **RoadSaver**

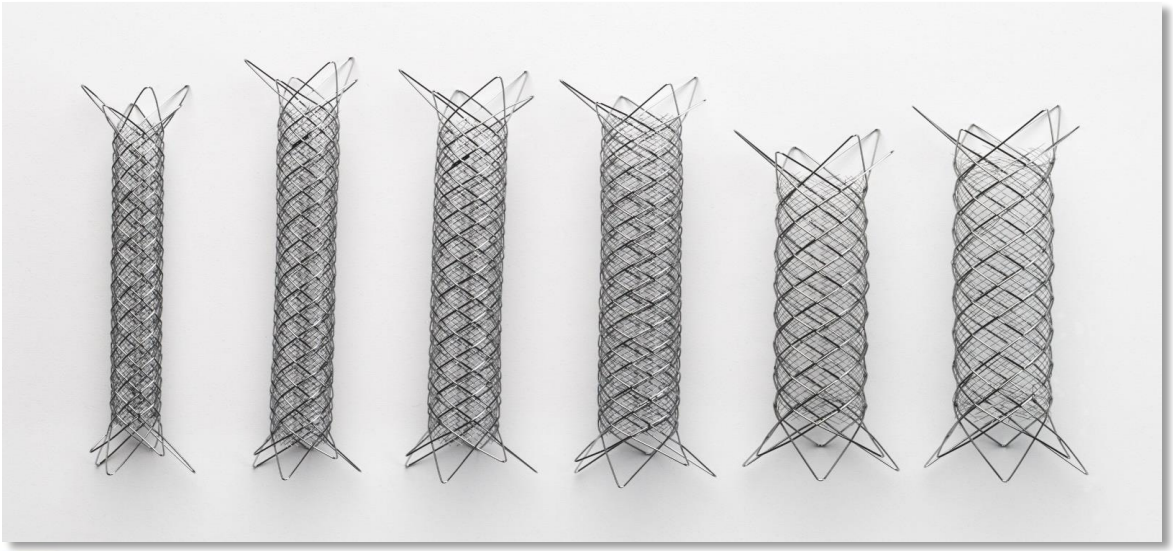
=

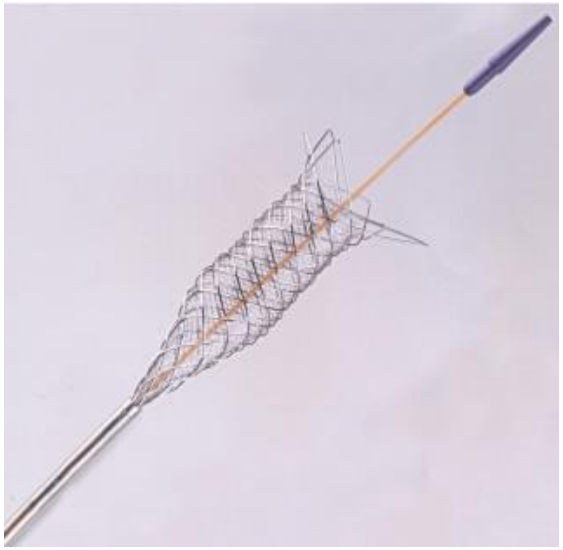
MICROVENA **Casper**

*Not available in the United States.

RoadSaver (Terumo) = Casper (MicroVena)

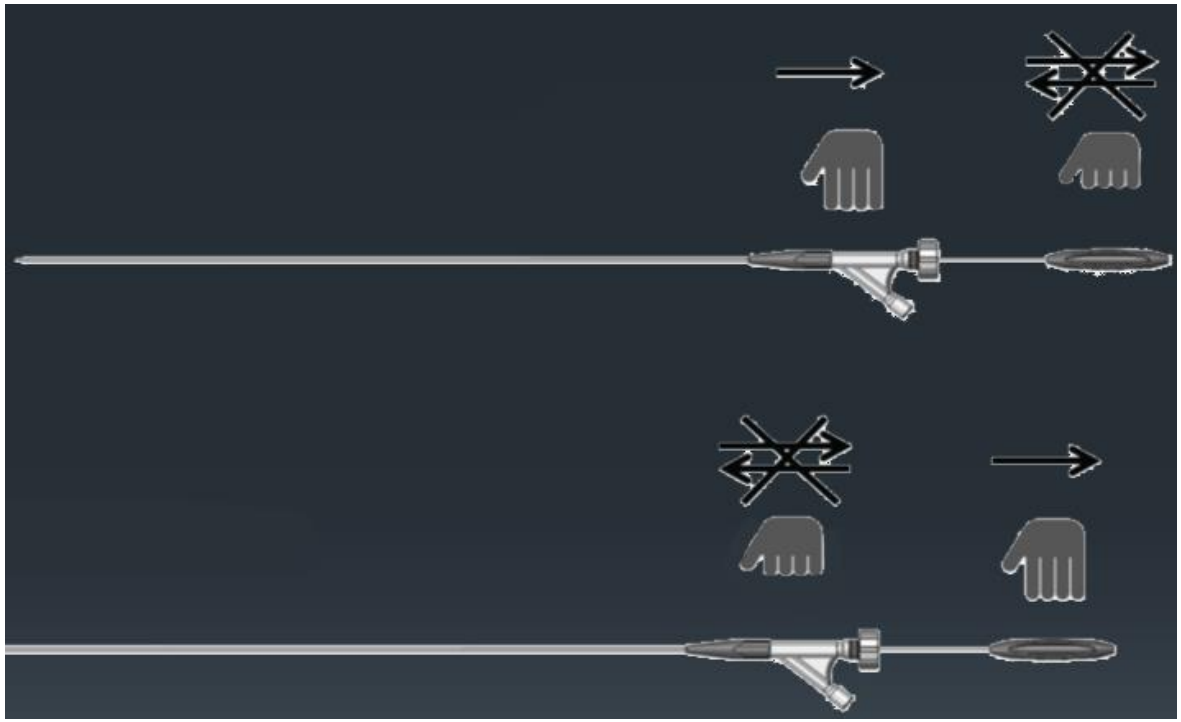




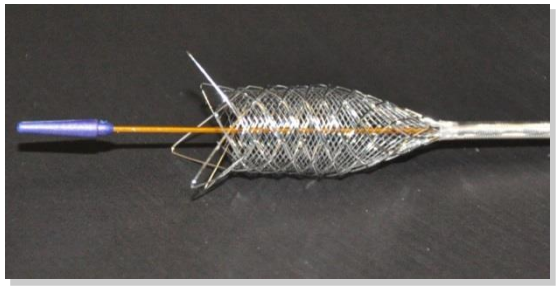


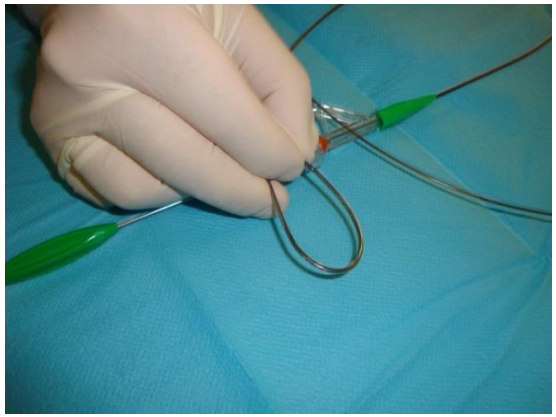
Images by Terumo / used with permission

RoadSaver: Push-Pull Stent Delivery System



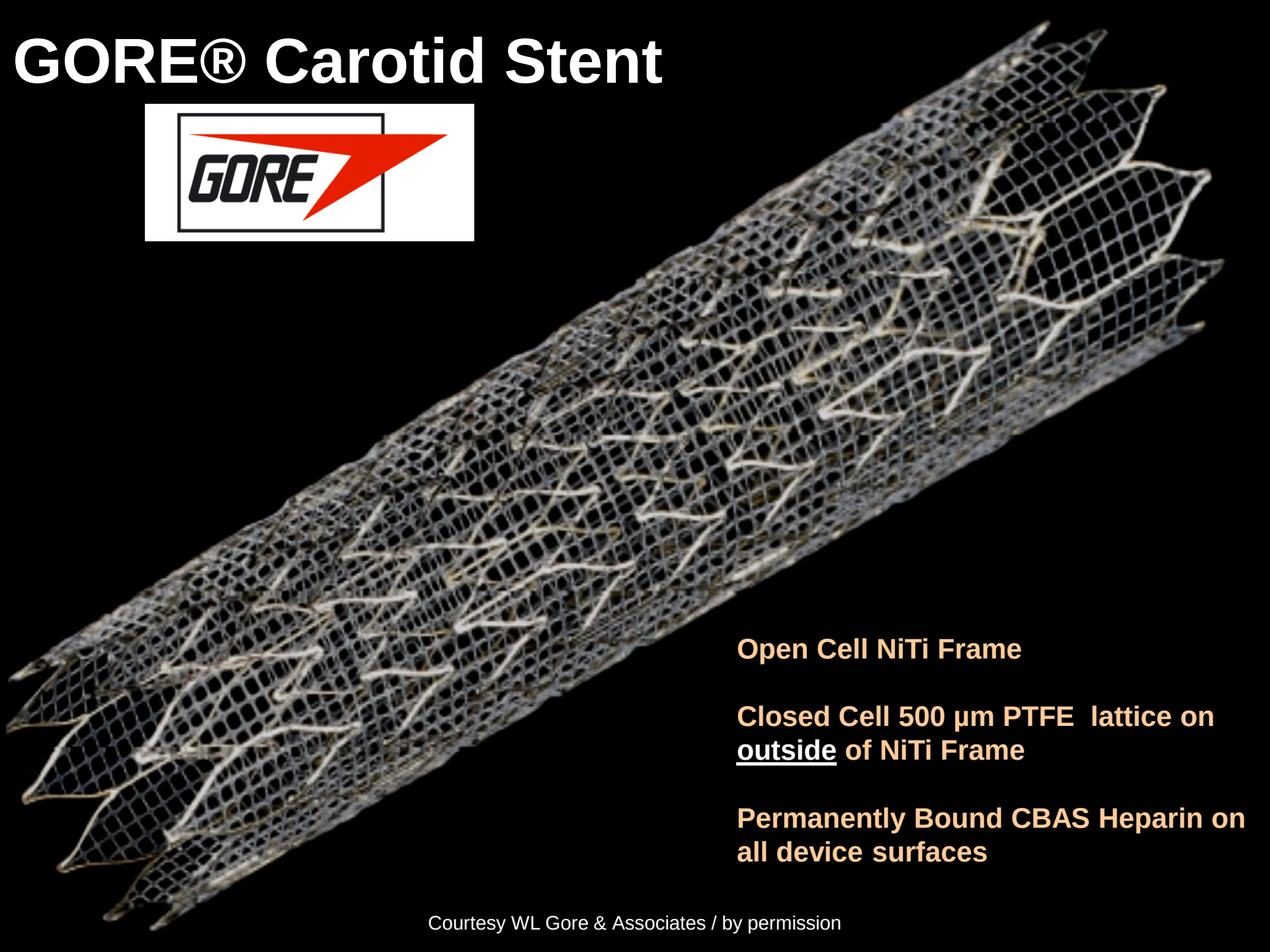
re-sheathable up to 50% stent length release





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

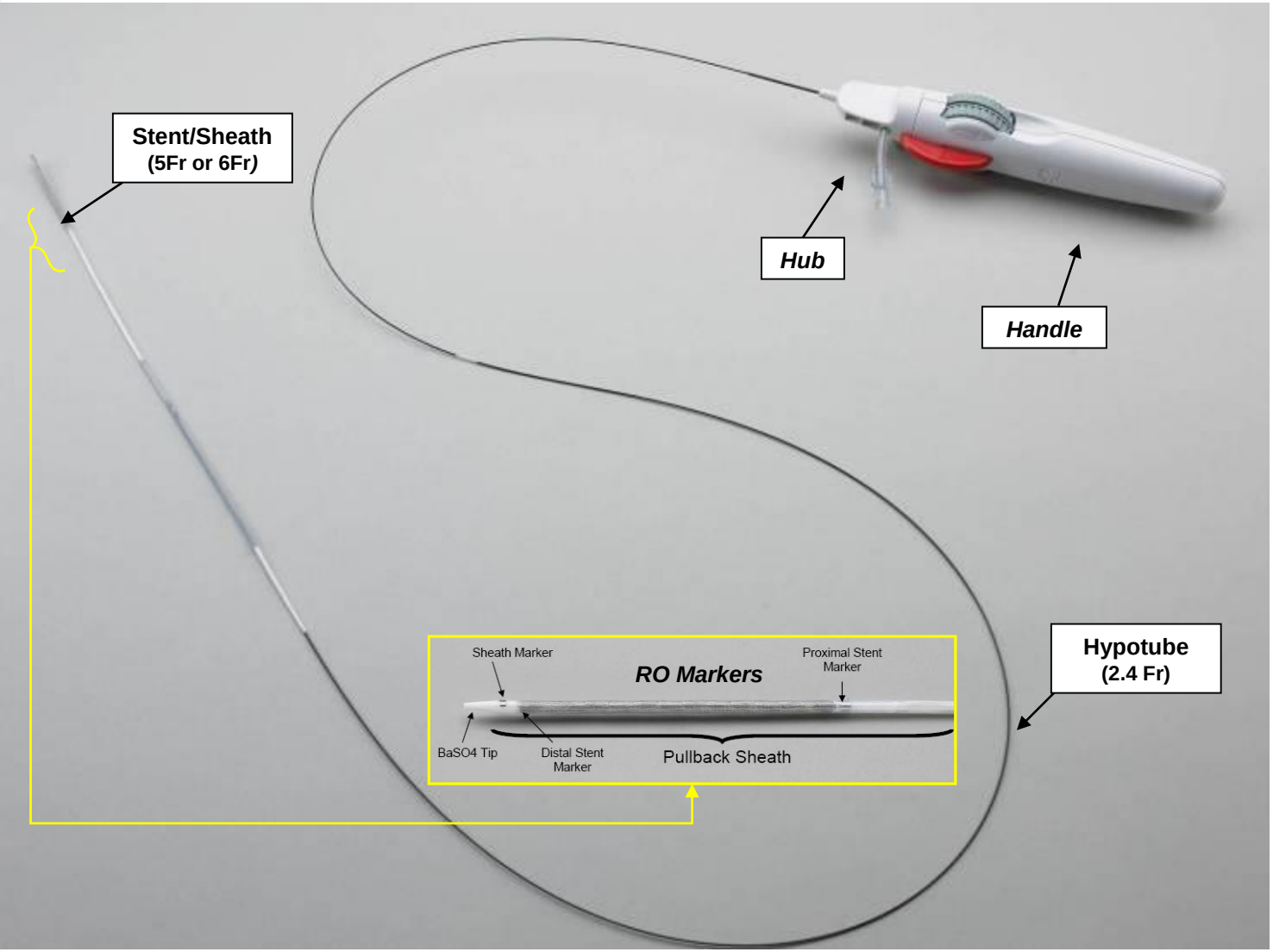
GORE® Carotid Stent System Sizing Summary

	GORE® Carotid Stent Part Number	Unconstrained Stent Dimensions (mm)	Reference Vessel Diameter (mm)	Minimum Introducer or Guiding Sheath Catheter ID
5 Fr	GCS5530	5 x 30	3.7 – 4.5	0.073" (1.85 mm) White Tip
	GCS5540	5 x 40		
	GCS6630	6 x 30	4.5 – 5.4	
	GCS6640	6 x 40		
	GCS7730	7 x 30	5.4 – 6.3	
	GCS7740	7 x 40		
	GCS8830	8 x 30	6.3 – 7.2	
	GCS8840	8 x 40		
	GCS6830	6 – 8 x 30	4.5 – 5.4 x 6.3 – 7.2	
	GCS6840	6 – 8 x 40		
6 Fr	GCS9930	9 x 30	7.2 – 8.1	0.080" (2.03 mm) Gray Tip
	GCS9940	9 x 40		
	GCS0030	10 x 30	8.1 – 9.0	
	GCS0040	10 x 40		
	GCS7930	7 – 9 x 30	5.4 – 6.3 x 7.2 – 8.1	
	GCS7940	7 – 9 x 40		
	GCS8030	8 – 10 x 30	6.3 – 7.2 x 8.1 – 9.0	
	GCS8040	8 – 10 x 40		

Table by WL Gore & Associates / used with permission

NB. The Gore carotid stent is <u>not avialable</u> outside the SCAFFOLD Study

The Gore Stent Delivery System



Attributes

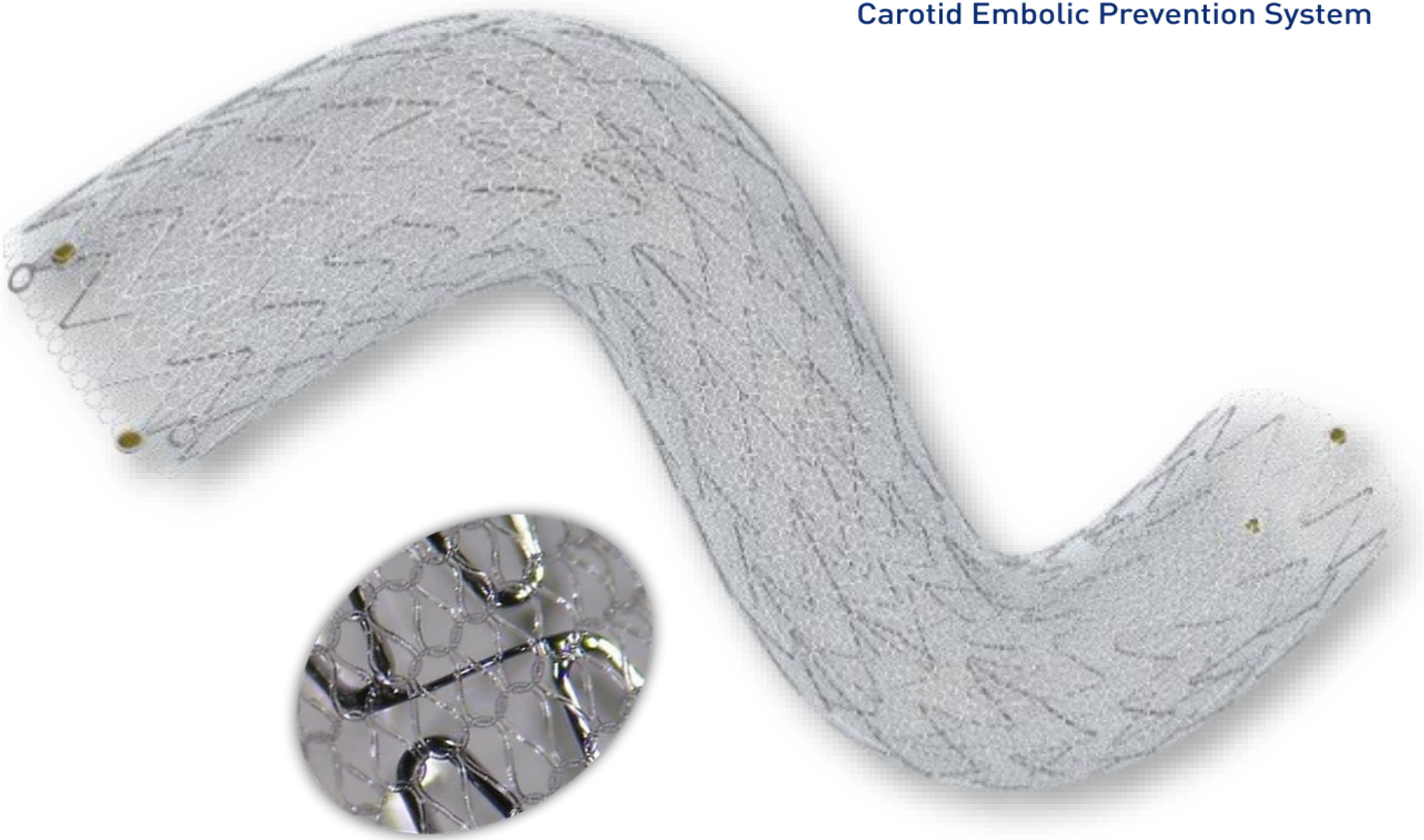
- Single handed delivery
- 5Fr Introducer Sheath Compatible (White Tip)
- 6Fr Introducer Sheath Compatible (Gray Tip)
- Hypotube Design
  - Allows for complete closure of hemostatic valve
- 135 cm Working Length
- 30 cm Rx

NB. The Gore carotid stent is not avialable outside the SCAFFOLD Study

InspireMD

CGUARD™

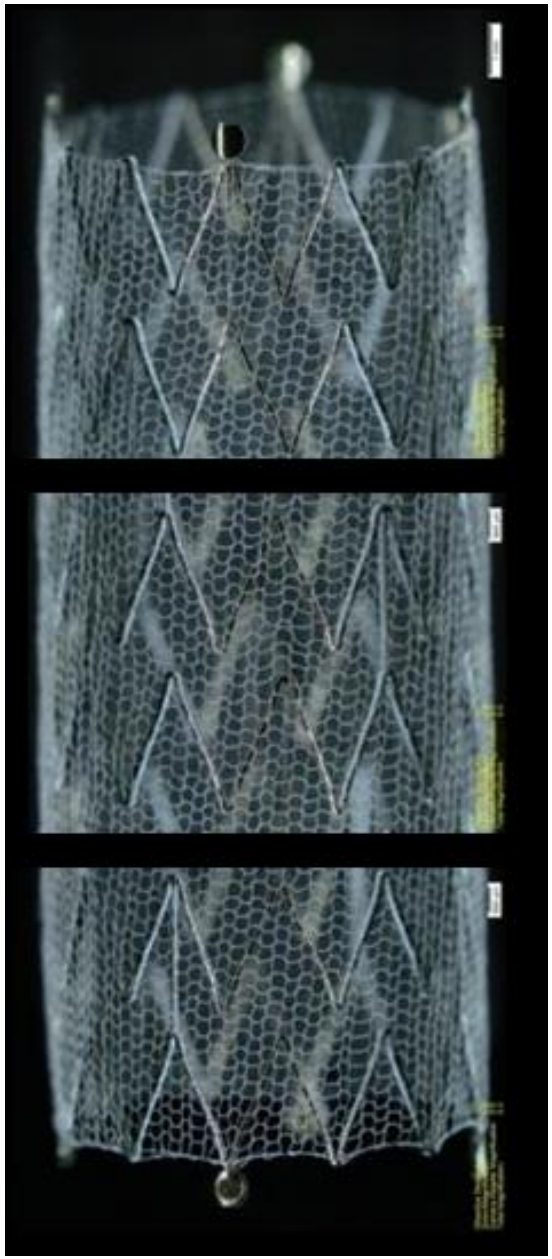
Carotid Embolic Prevention System



*Not available in the United States; available in Europe and a number of other geographies

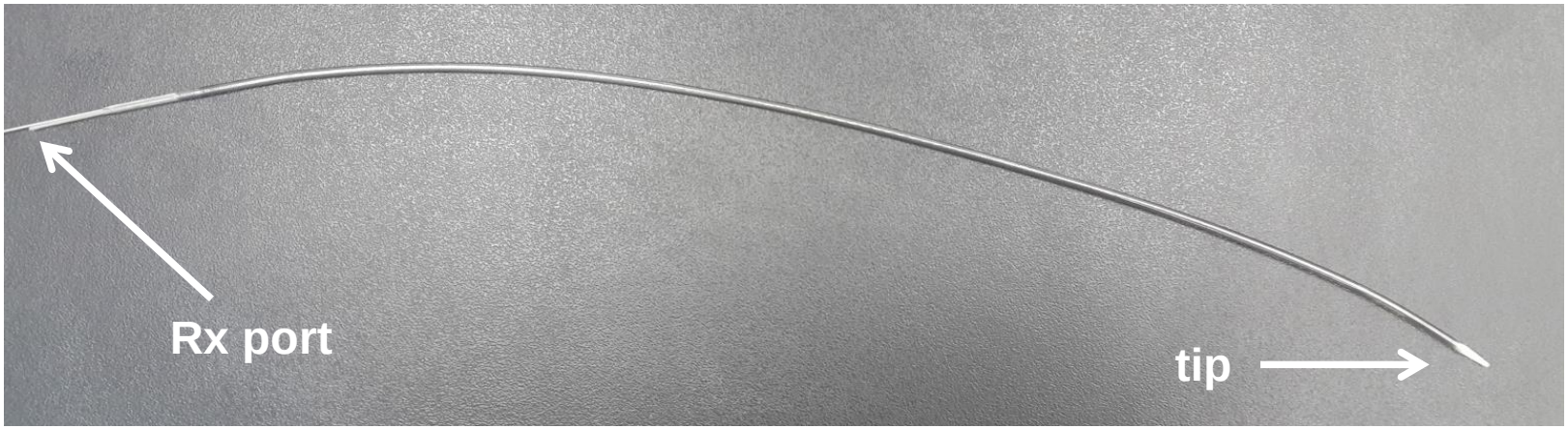
CGuard™ Embolic Prevention Stent System

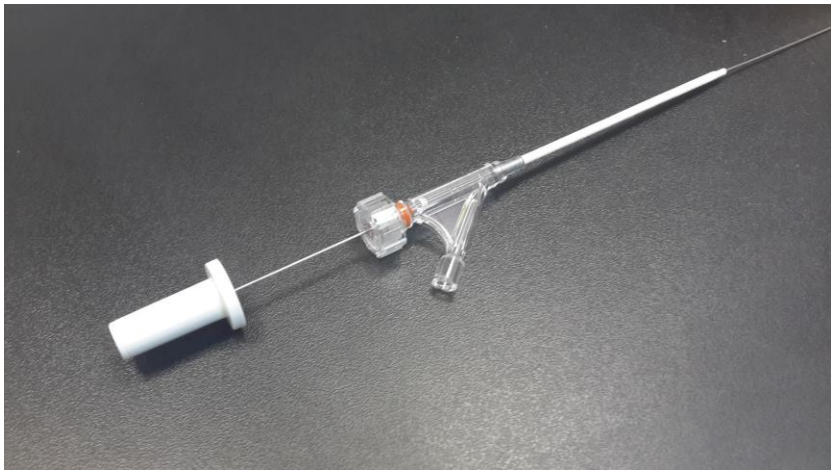
System specifications	
Stent type	Nitinol – self expanding
Micronet aperture size	150-180 μm
Guidewire	0.014”
Stent sizes - Diameter - Length	 6-10mm 20-60mm



CE Mark – March 2014

CGuard™ Embolic Prevention Stent System



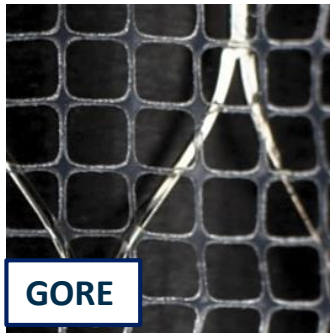


Images by InspireMD, used with permission

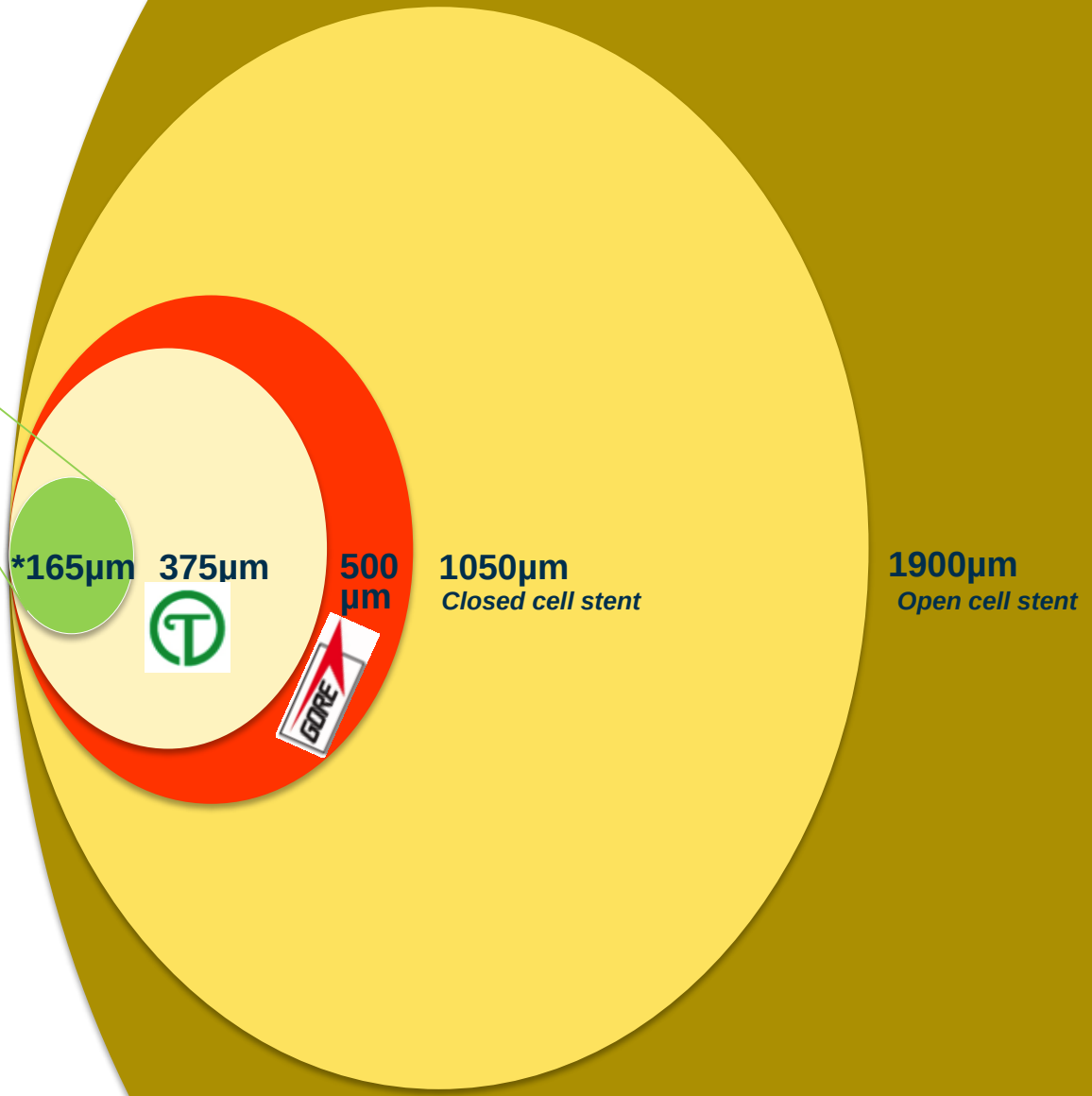
Pore Size

CGUARD™

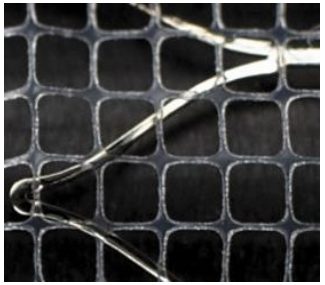
ROADSAVER=CASPER



GORE



* Average in lesion at expanded state

			
Name	**RoadSaver *aka* Casper**	**Gore® Carotid Stent**	**CGuard™ Embolic Prevention Stent**
Stent frame	**closed-cell Nitinol**	**open-cell Nitinol**	**open-cell Nitinol**
Mesh position in re--lation to frame	**inside**	**outside**	**outside**
Mesh material	**Nitinol**	**PTFE**	**PET**
Mesh structure	**braided**	**inter-woven**	**single-fiber knitted**
Pore size	**375 µm**	**500 µm**	**150 - 180 µm**

PTFE = Polytetrafluoroethylene

PET = poliethylenteraphtalat

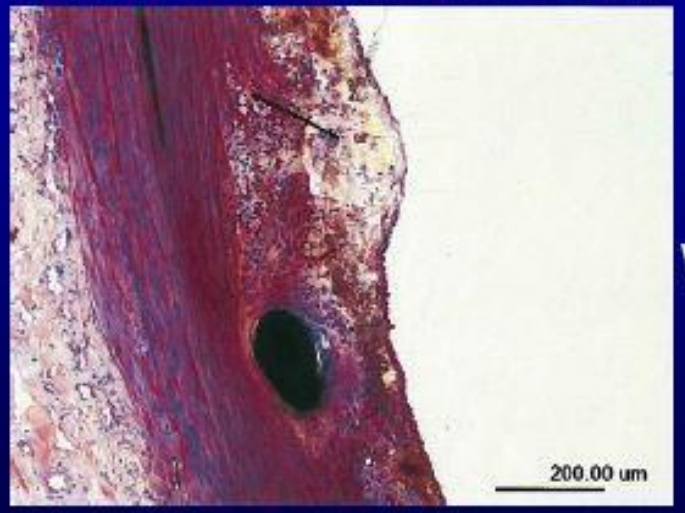
Data

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

GORE Stent

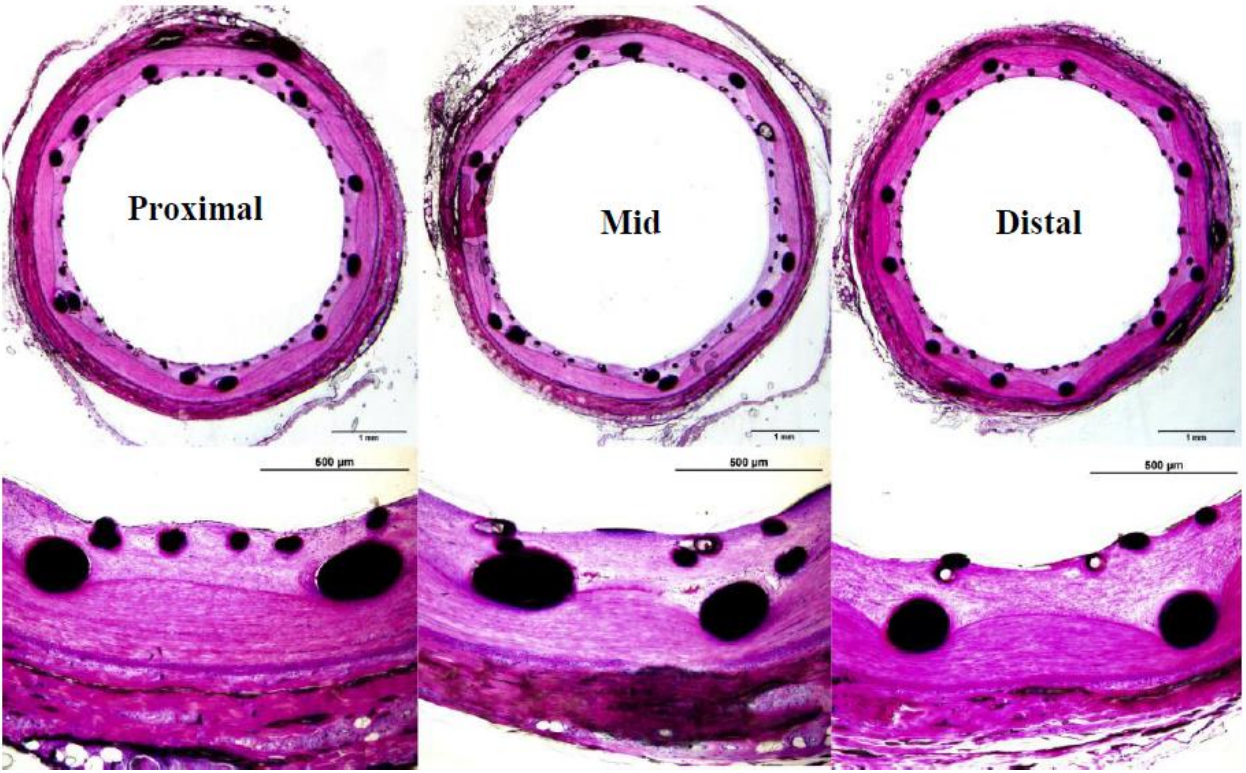


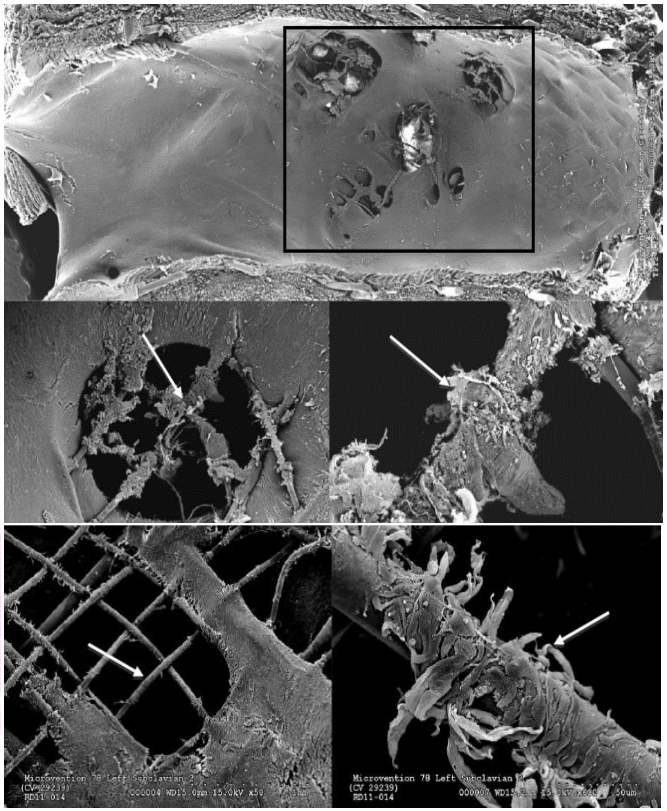
Carotid WALLSTENT

PA Schneider VERVE 2014, animal data WL Gore / by permission

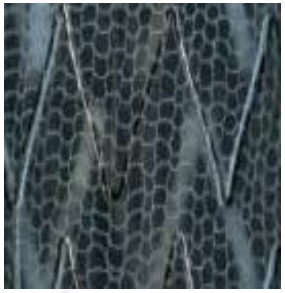
RoadSaver

Histology and REM after 6 months

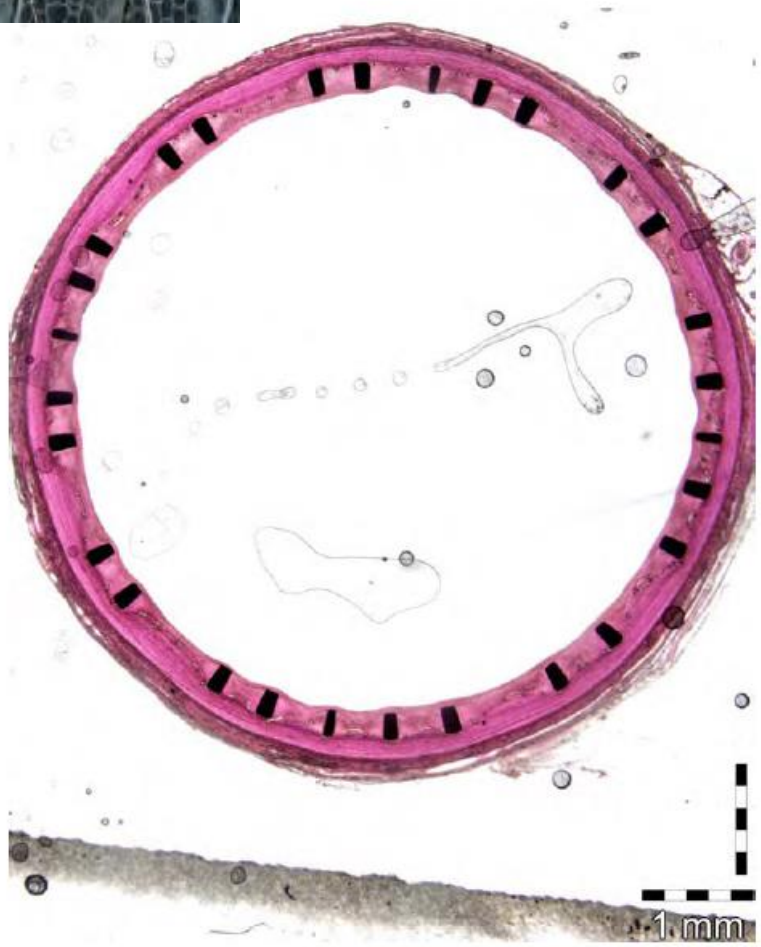




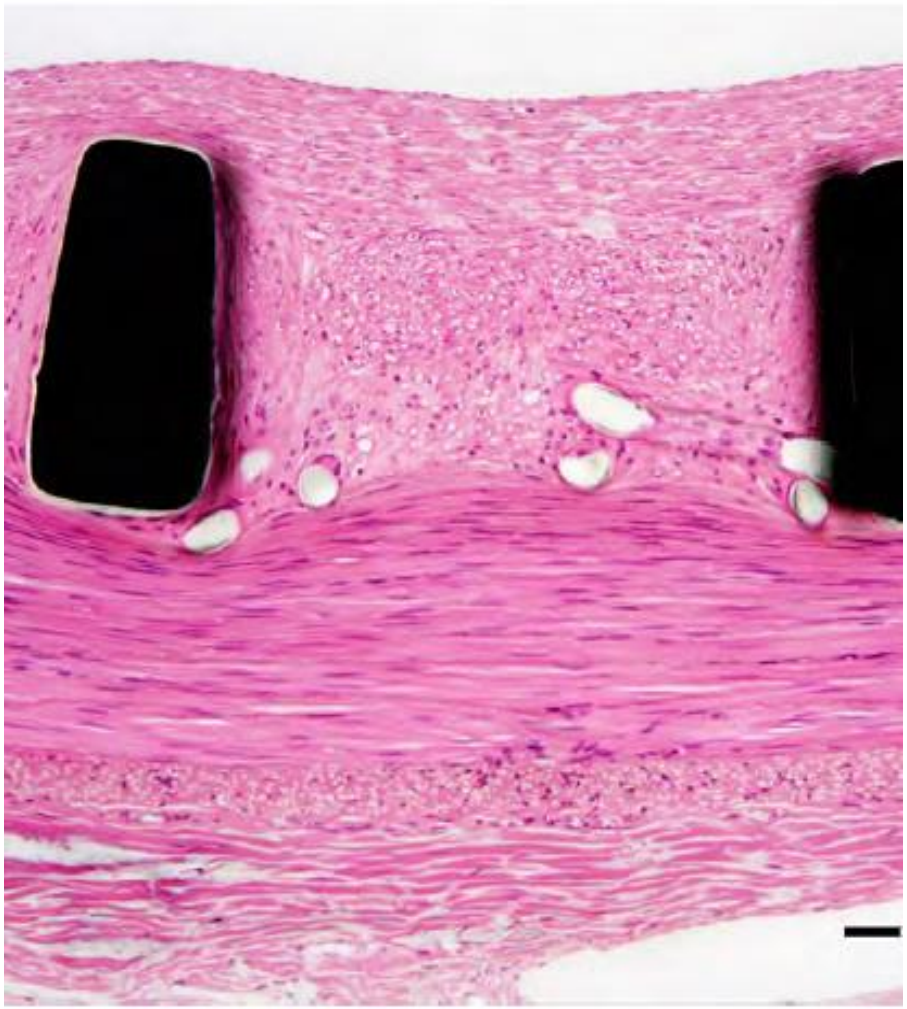
Data by Terumo / used with permission



CGuard EPS 90 days / pig

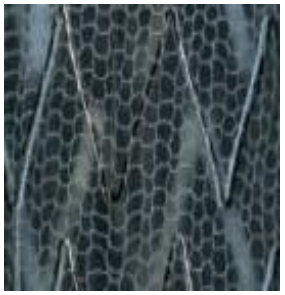


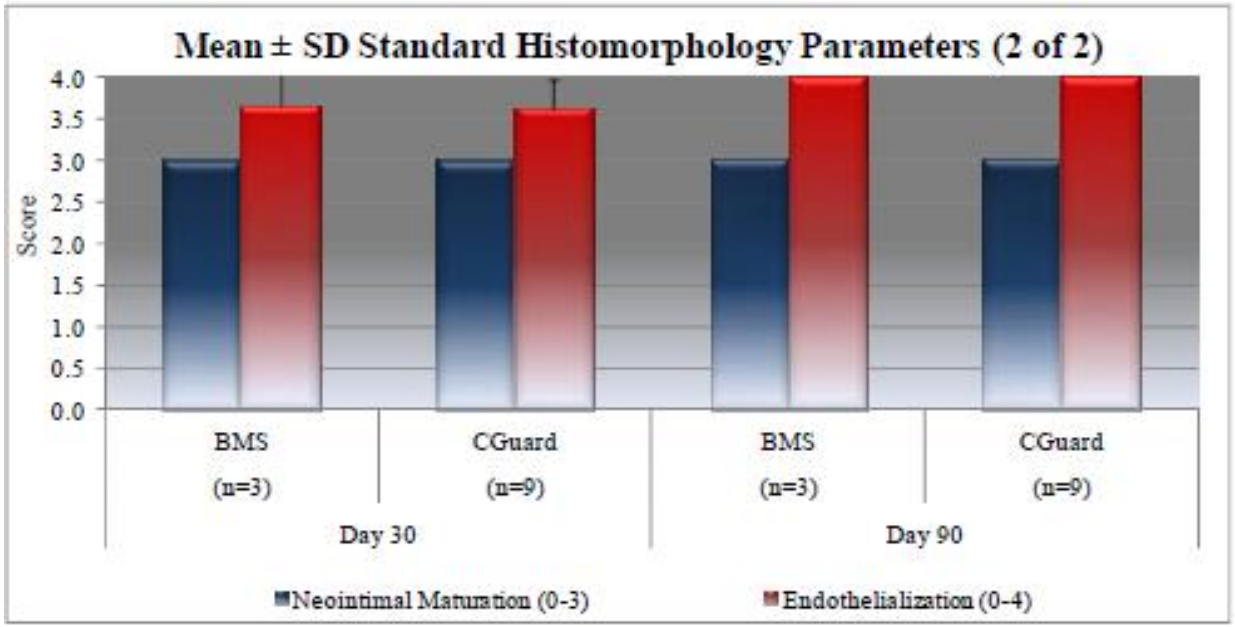
12-105 LCCA-S 3 13-1689-3 1.25x H&E.tif



CA-S 3 13-1689-3 10x H&E.tif

CGuard EPS 30 & 90 days/pig





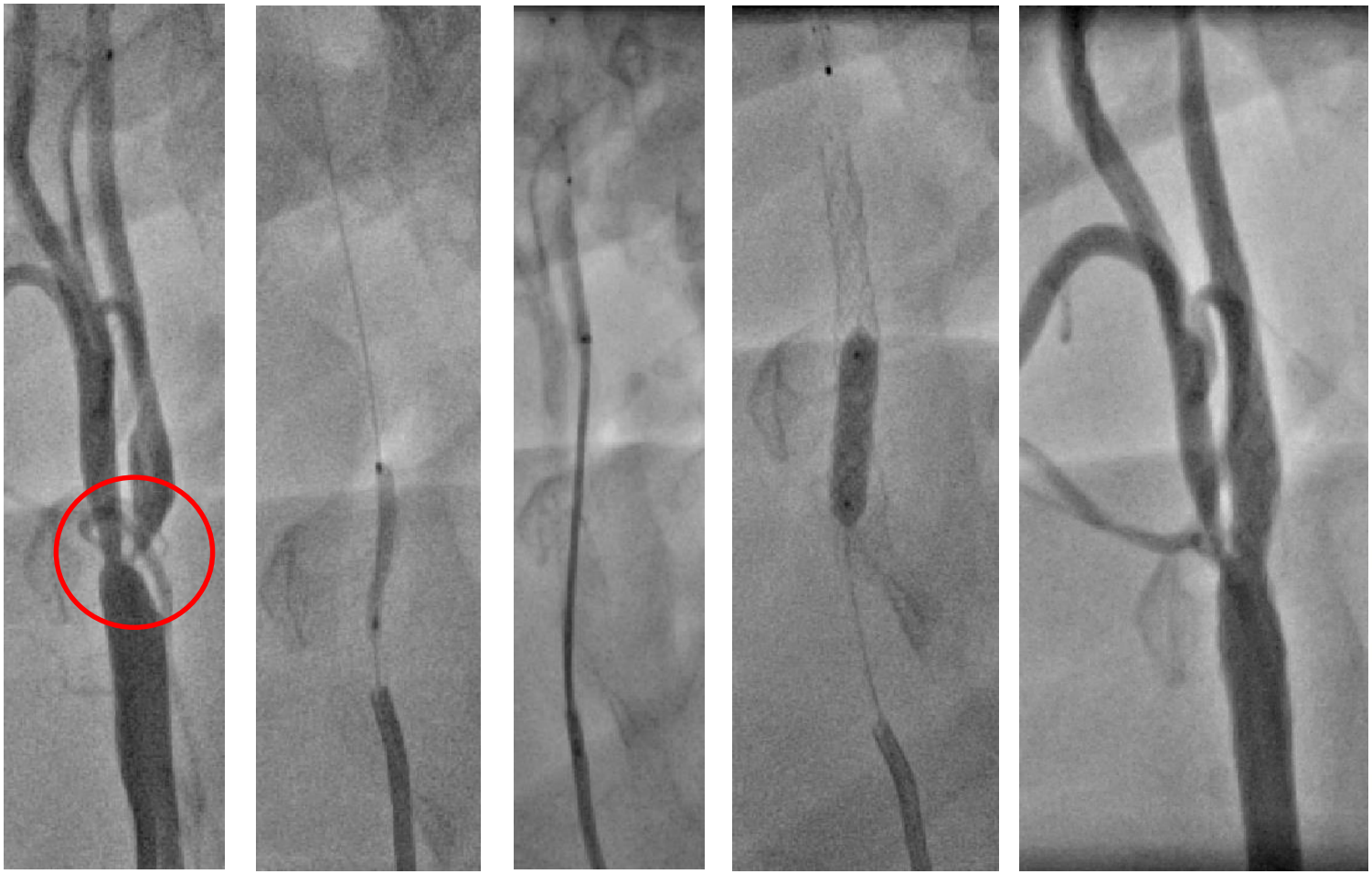
Mean ± SD and Median Standard Histomorphology Parameters								
Parameter	Day 30				Day 90			
	BMS (n=3)		CGuard (n=9)		BMS (n=3)		CGuard (n=9)	
Injury (0-3)	0.00 ± 0.01	0.00	0.00 ± 0.01	0.00	0.01 ± 0.02	0.00	0.00 ± 0.01	0.00
Inflammation (0-3)	0.43 ± 0.23	0.51	0.41 ± 0.22	0.36	0.17 ± 0.16	0.11	0.09 ± 0.08	0.07
Neointimal Fibrin (0-3)	1.13 ± 0.23	1.00	0.82 ± 0.37	1.00	0.00 ± 0.00	0.00	0.00 ± 0.00	0.00
Adventitial Fibrosis (0-3)	0.00 ± 0.00	0.00	0.02 ± 0.07	0.00	0.00 ± 0.00	0.00	0.00 ± 0.00	0.00
Neointimal Maturation (0-3)	3.00 ± 0.00	3.00	3.00 ± 0.00	3.00	3.00 ± 0.00	3.00	3.00 ± 0.00	3.00
Endothelialization (0-4)	3.67 ± 0.42	3.80	3.62 ± 0.35	3.80	4.00 ± 0.00	4.00	4.00 ± 0.00	4.00

BMS = non mesh-covered CGuard nitynol frame; InspireMD data / used with permission

Imaging

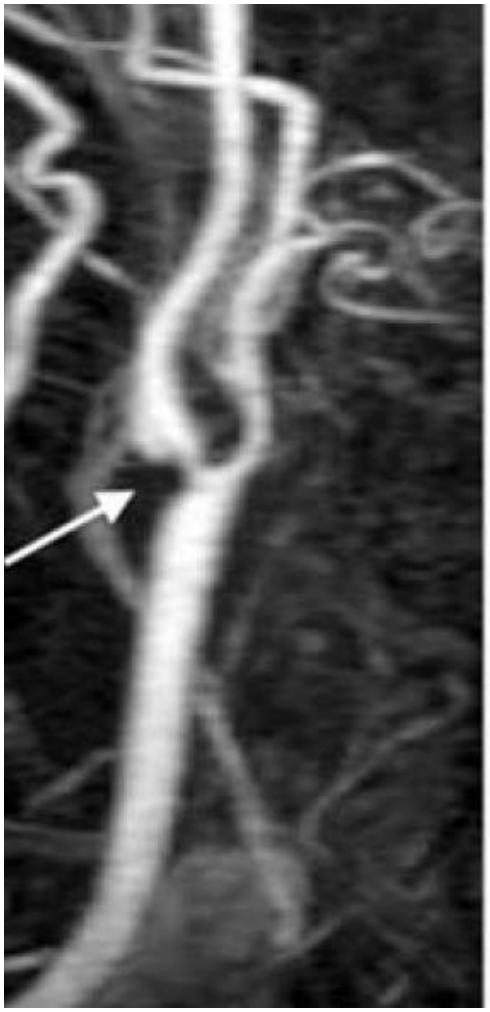
angio

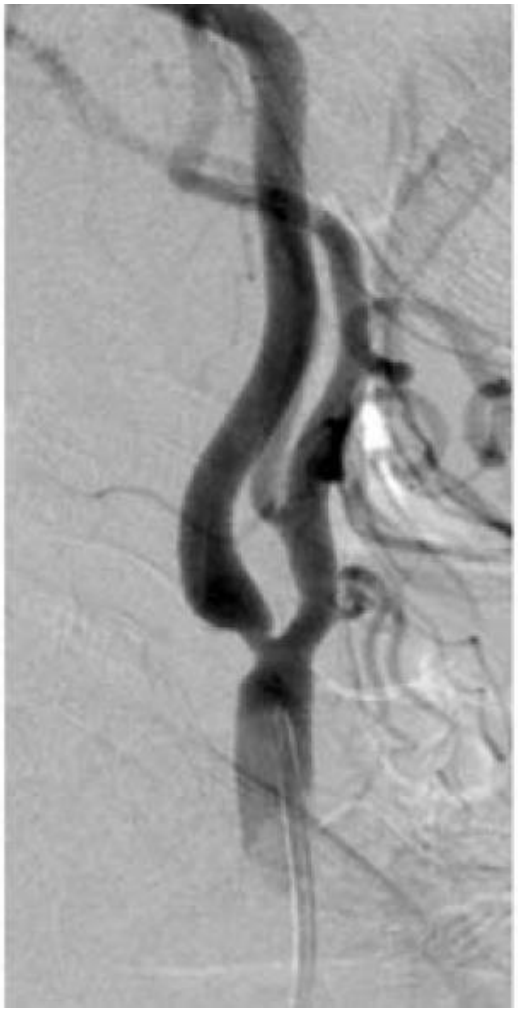
Roadsaver / Casper

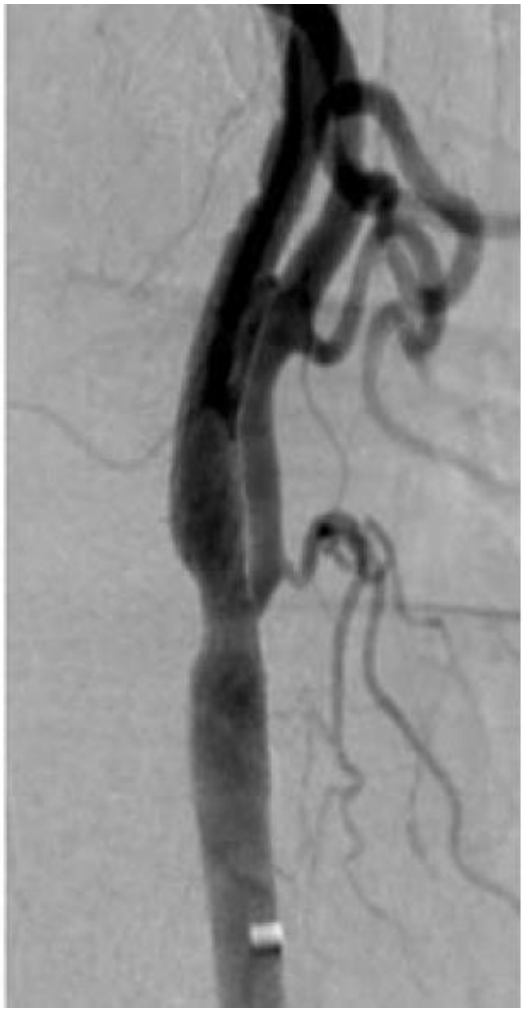


Angio/CAS images courtesy P. Pieniazek / Krakow

Gore Carotid Stent

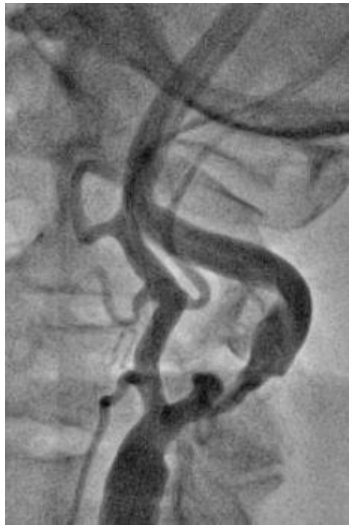


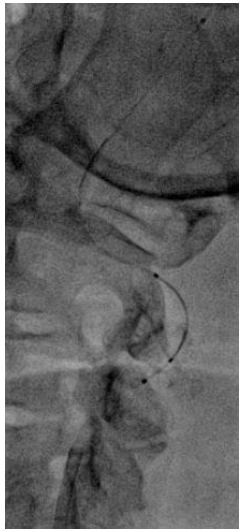


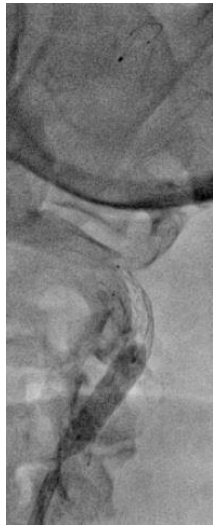


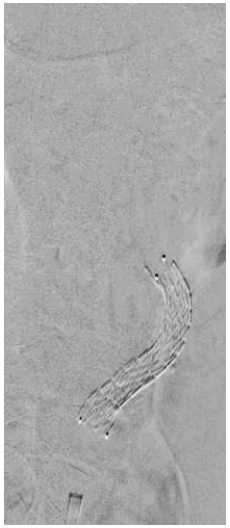
Angio/CAS images courtesy Dr. C. Schönholz

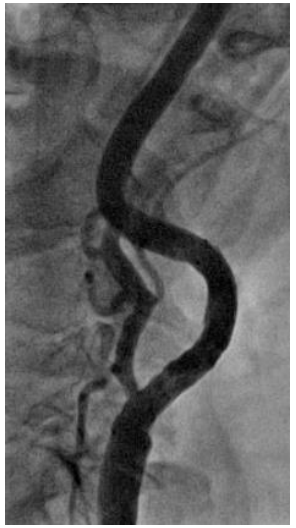
CGuard™ EPS

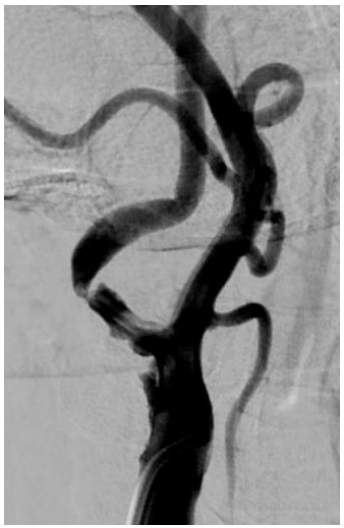


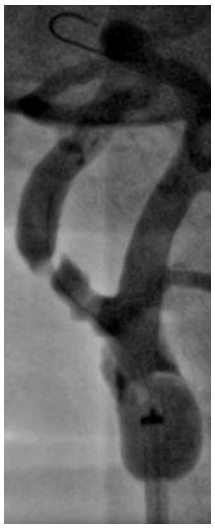


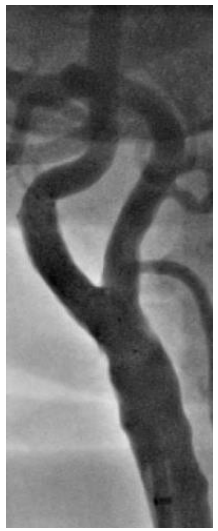


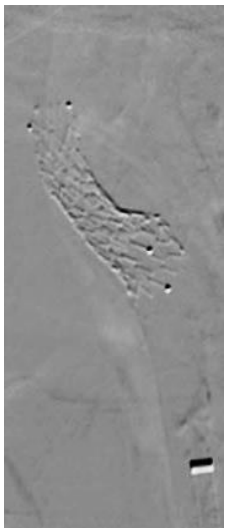


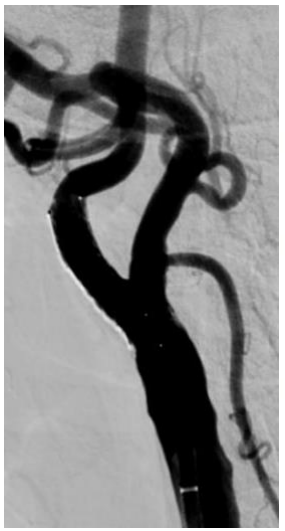


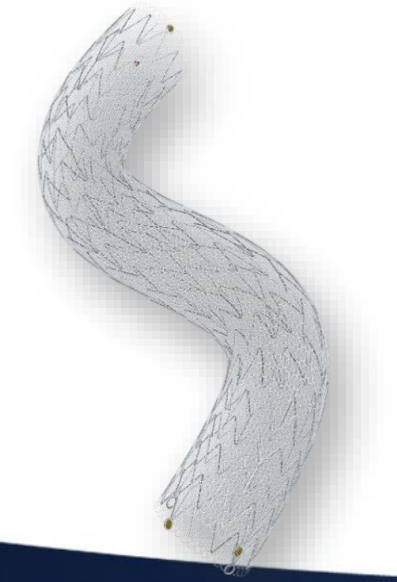










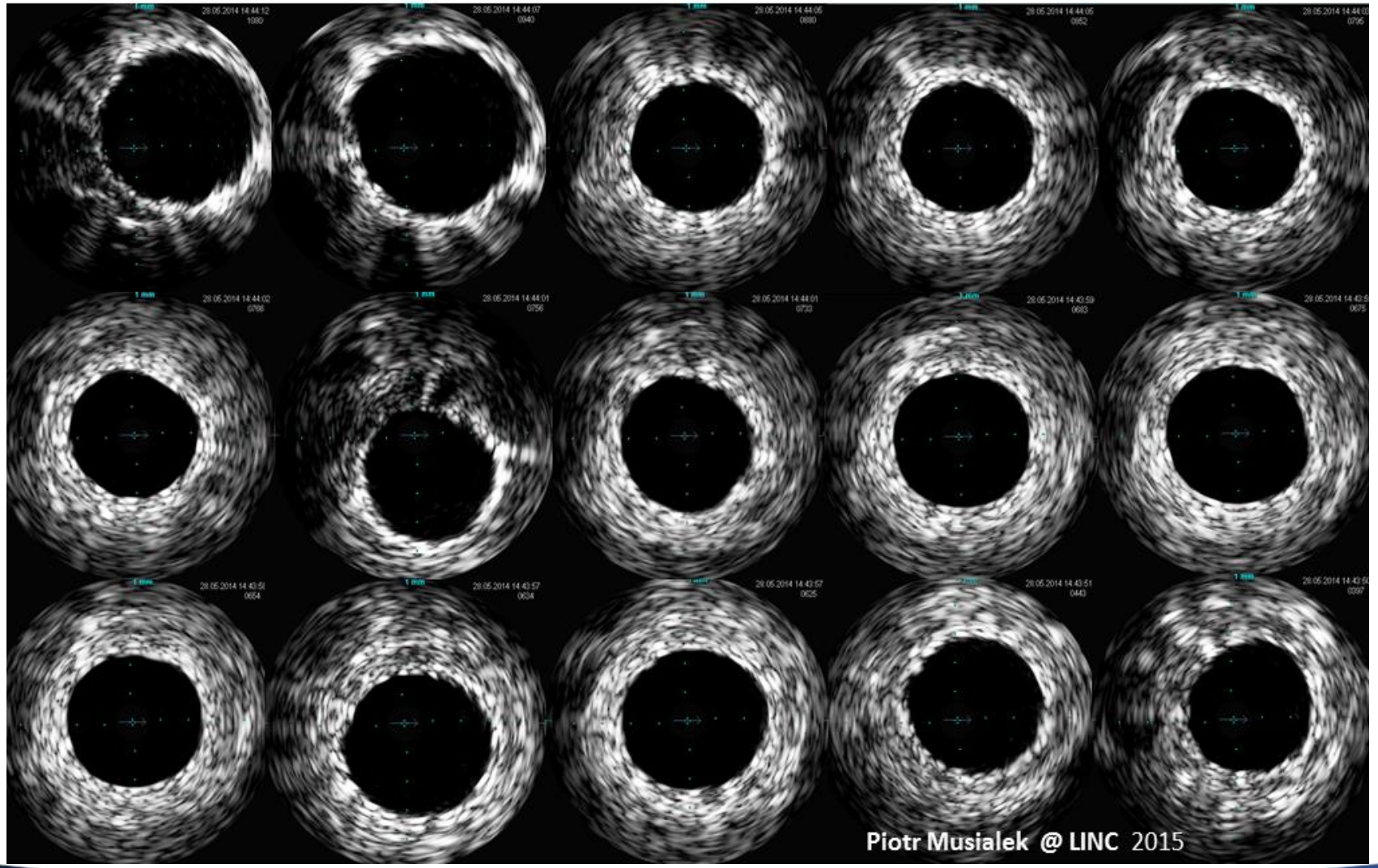


Imaging

IVUS

Initial series of CGuard™ IVUS studies indicates...

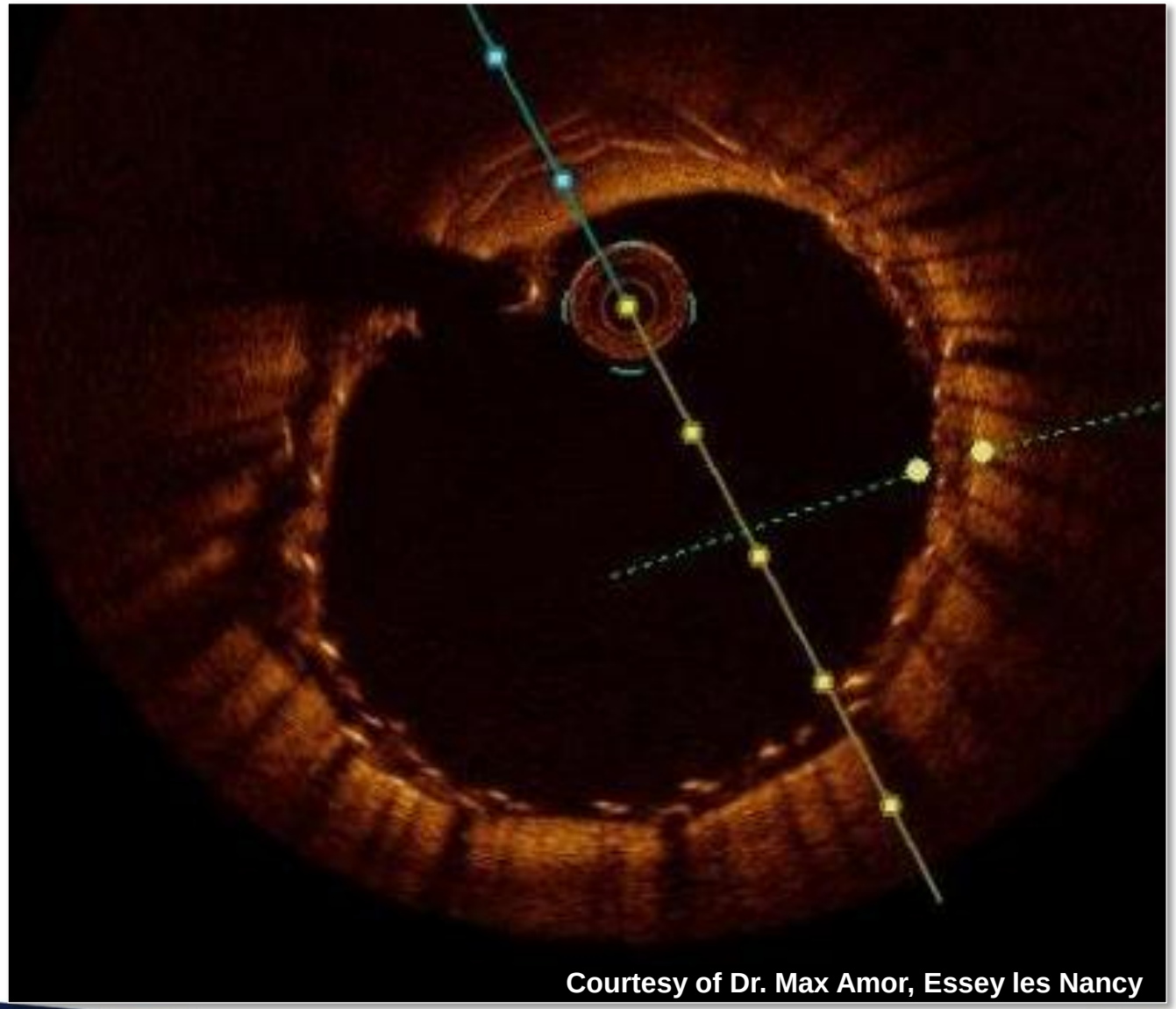
- Excellent stent expansion and apposition √
- ZERO tissue protrusion though mesh-and-struts √

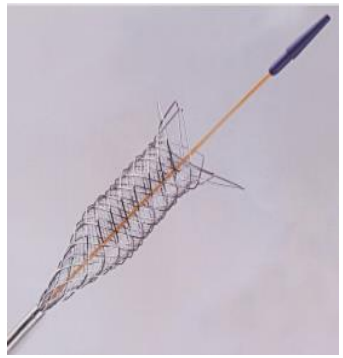


Imaging

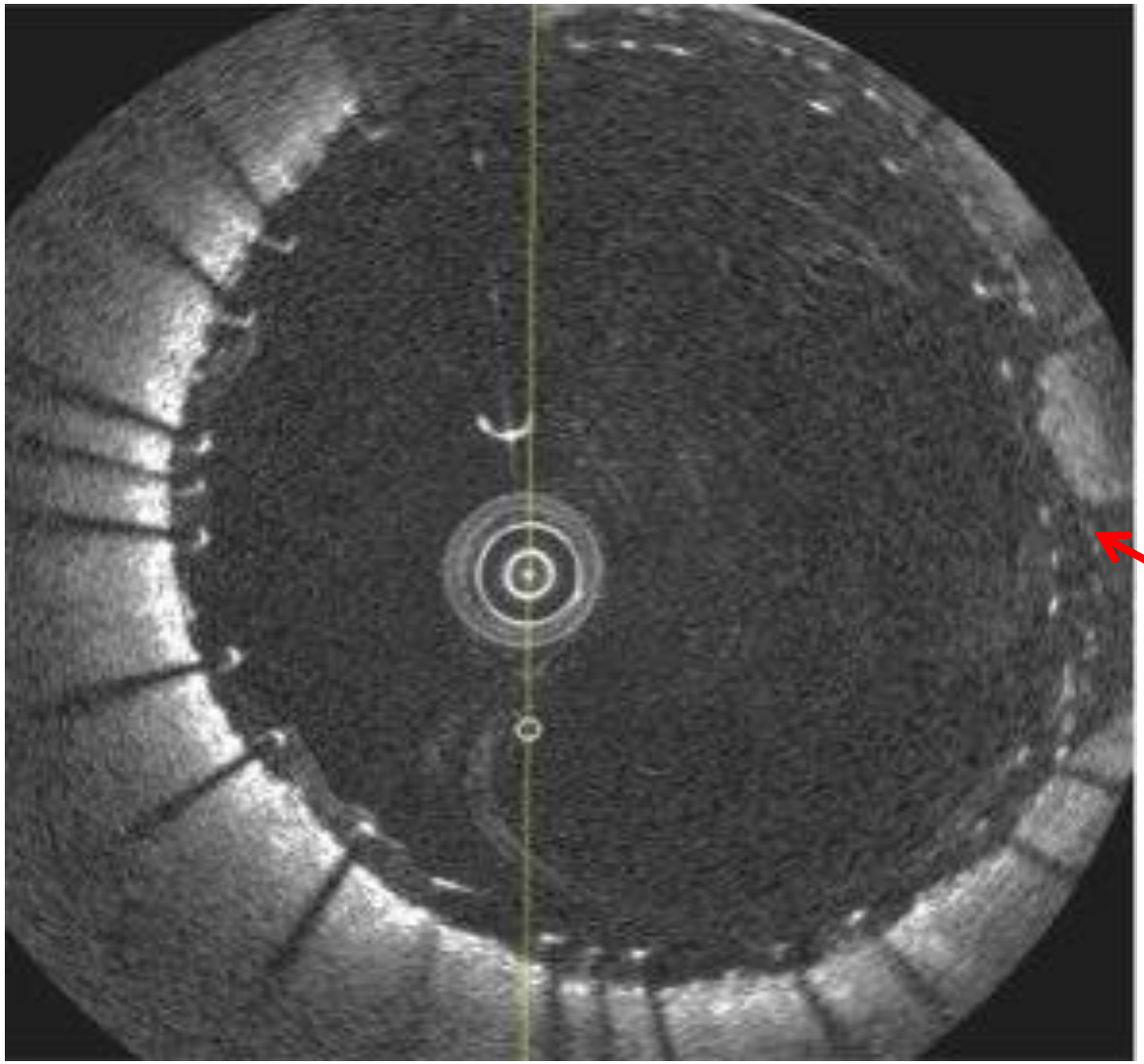
OCT

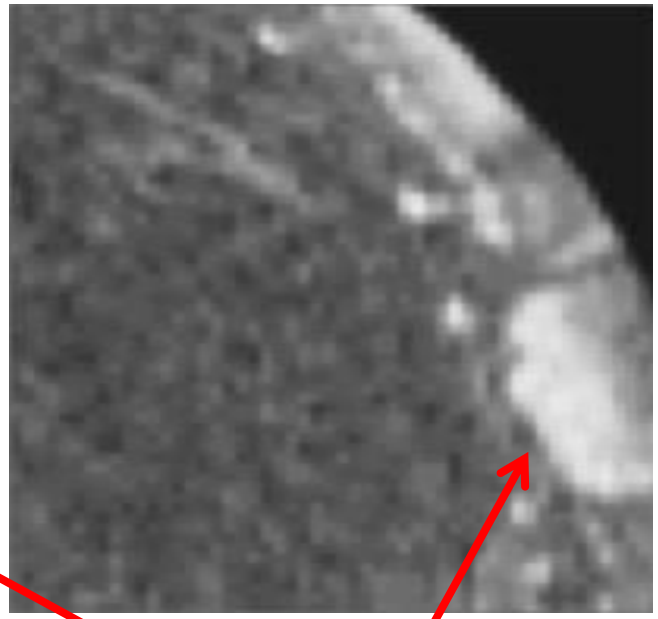
RoadSaver





CGuard™ EPS





Thrombotic material

T R A P P E D

between the stent MicroNET and the vessel wall

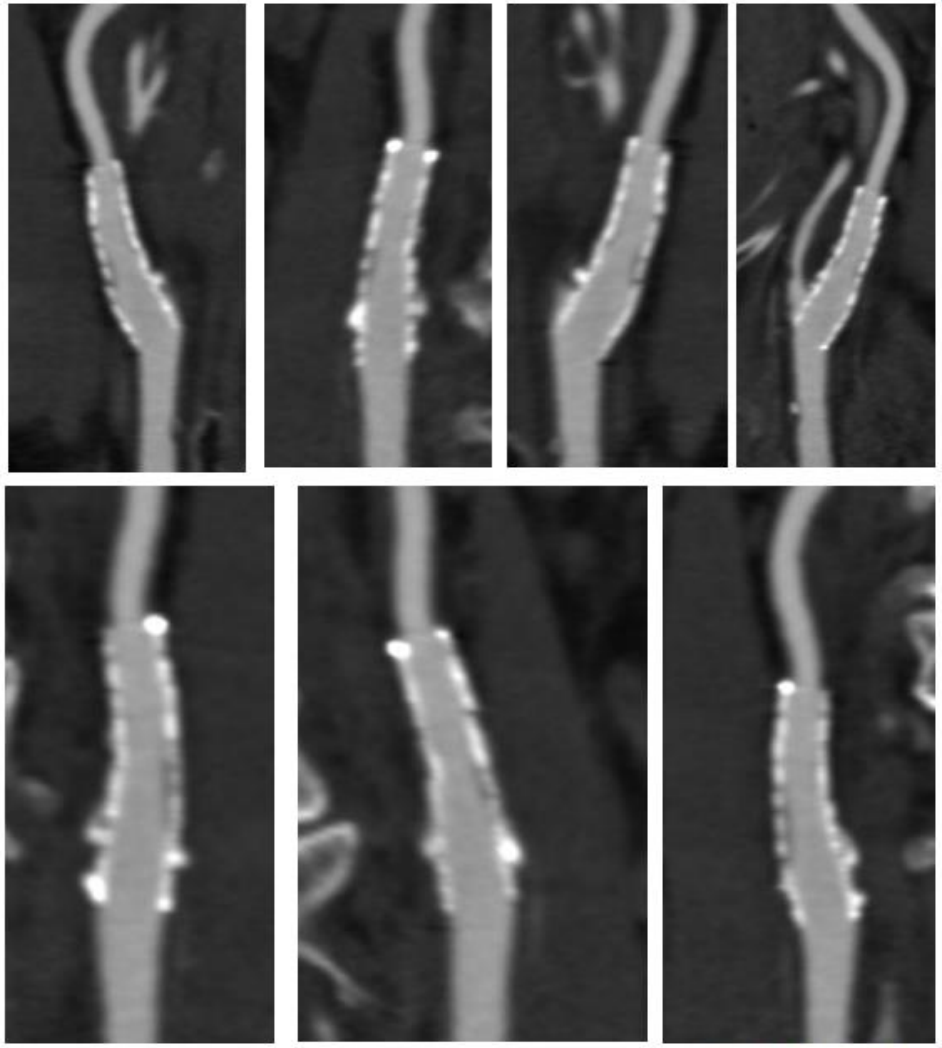
Image Courtesy Dr Juan Rigla, MD PhD
Perceptual Imaging Lab, Univerity of Barcelona

CGuard™ EPS

Imaging

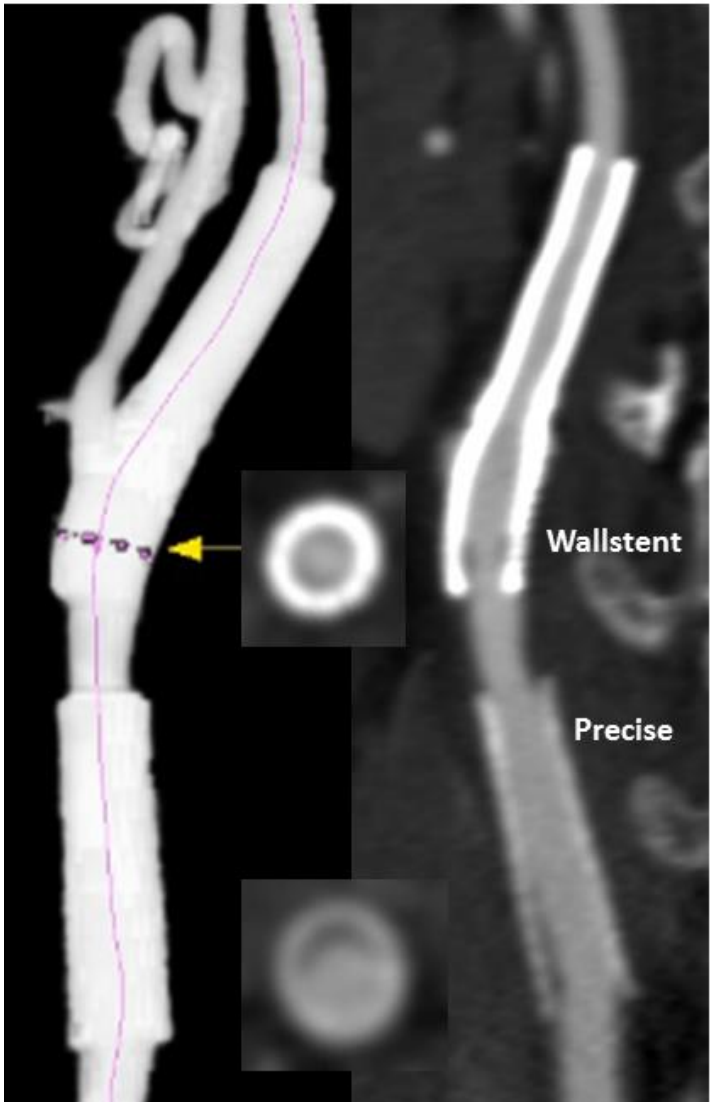
CT

CGuard 5 months follow-up



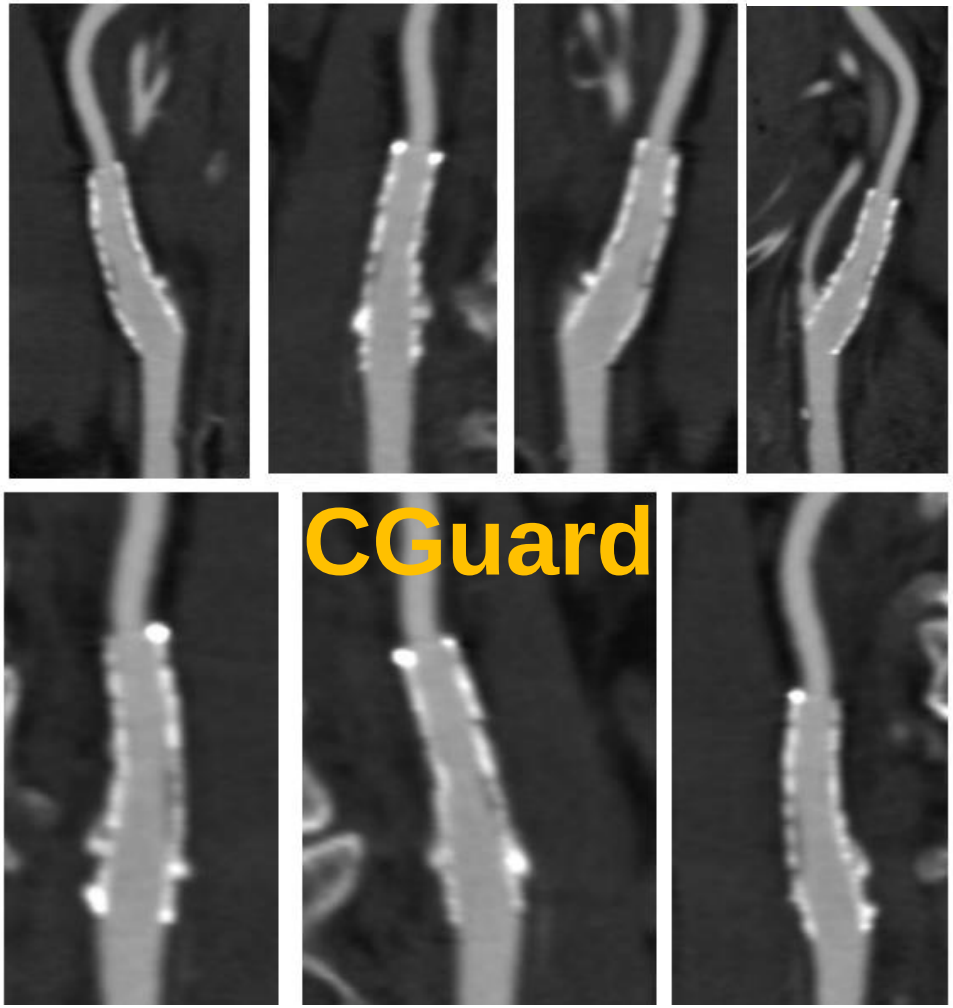
Images M.Urbanczyk / Z.Moczulski / M.Irzyk / P.Banyś
JP2 Hospital, Krakow, Poland

RCCA & RICA



LICA CGuard

5 months follow-up



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

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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.

Evaluation of PET Mesh Covered Stent in Patients with Carotid Artery Disease

The CARENET-Trial

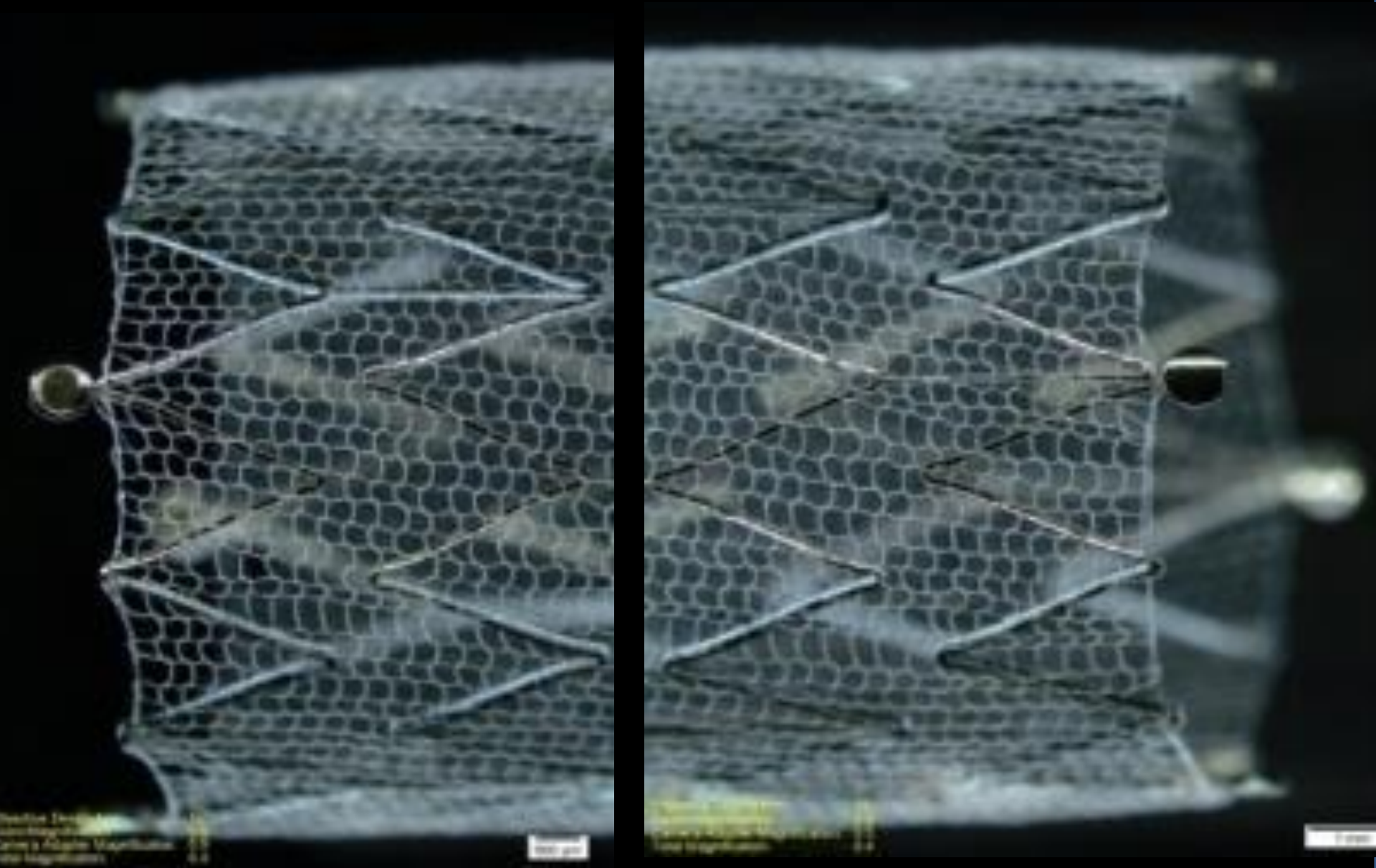
(CARotid Embolic protection using microNET)

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

Joachim Schofer, MD,PhD, Hamburg University CardiovascularCenter, 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

tct2014 In Partnership with the ACC
Columbia University Medical Center
NewYork-Presbyterian

CGuard ™ embolic prevention stent



P. Musialek @ TCT 2015

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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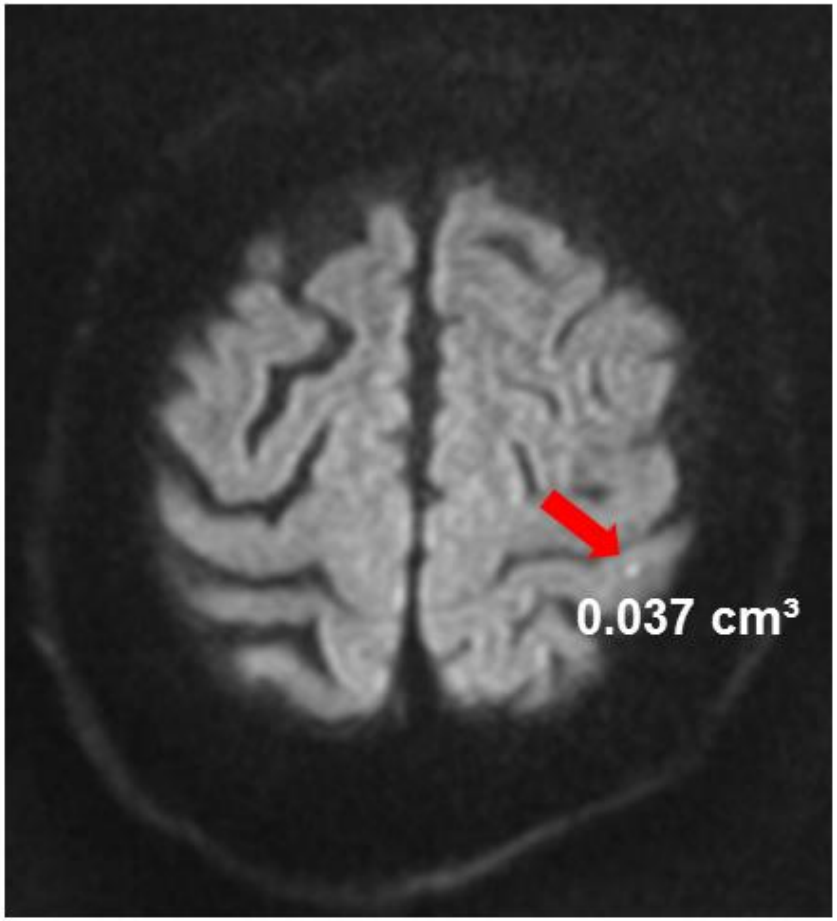
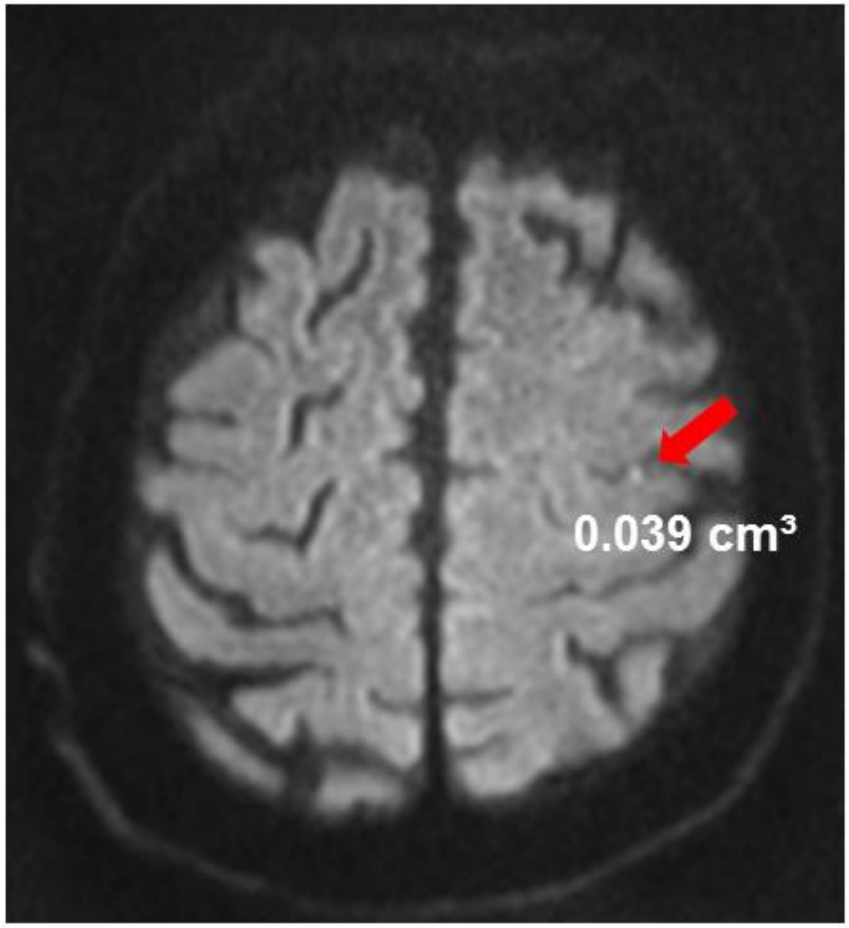
DW-MRI:

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*

DW-MRI analysis @ 48 h	
	CARENET (n=27)
Incidence of new ipsilateral lesions	**37.0%**
Average lesion volume (cm^3)	0.039 ± 0.08
Maximum lesion volume (cm^3)	0.445

see patient fluxogram

***External Core Lab analysis (US)**

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

† bilateral lesions

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

CARENET DW-MRI analysis*

DW-MRI analysis @ 48 hours			
	CARENET (n=27)	**PROFI (all)** (n=62)	**ICSS†** (n=56)
Incidence of new ipsilateral lesions	**37.0%**	**66.2%**	68.0%
Average lesion volume (cm^3)	0.039 ± 0.08	.375	-
Maximum lesion volume (cm^3)	0.445		

≈50% reduction

in new ipsilateral lesion **incidence**

see patient fluxogram

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Incidence of new ipsilateral lesions	37.0%	66.2%	68.0%
Average lesion volume (cm^3)	**0.039**	**0.375**	-
Maximum lesion volume (cm^3)	0.4[illegible]5		

>10-fold reduction

in cerebral lesion **volume**

see patient fluxogram

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

† bilateral lesions

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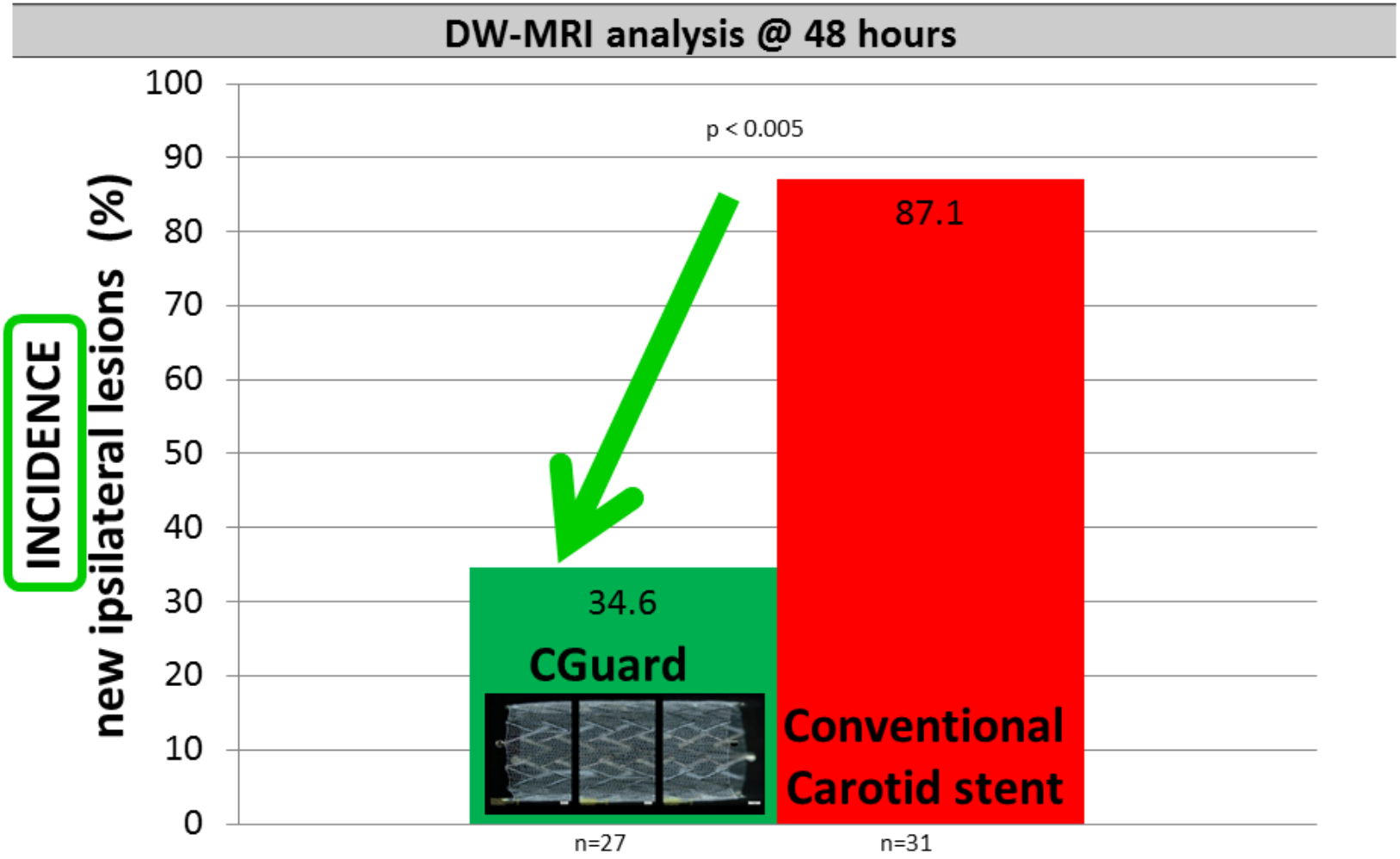
Filter-protected CAS procedures

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

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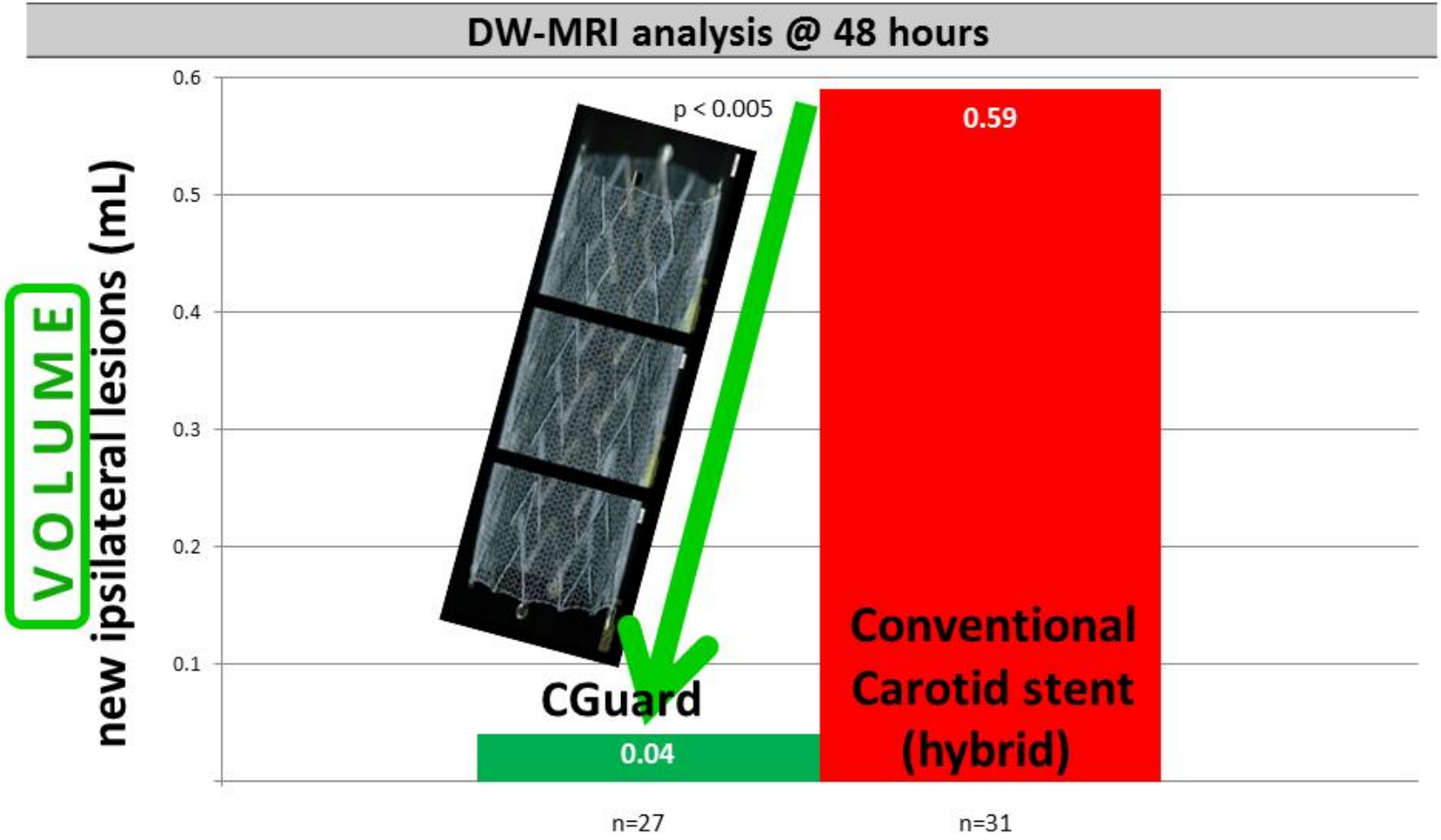

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CARENET DW-MRI analysis*

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

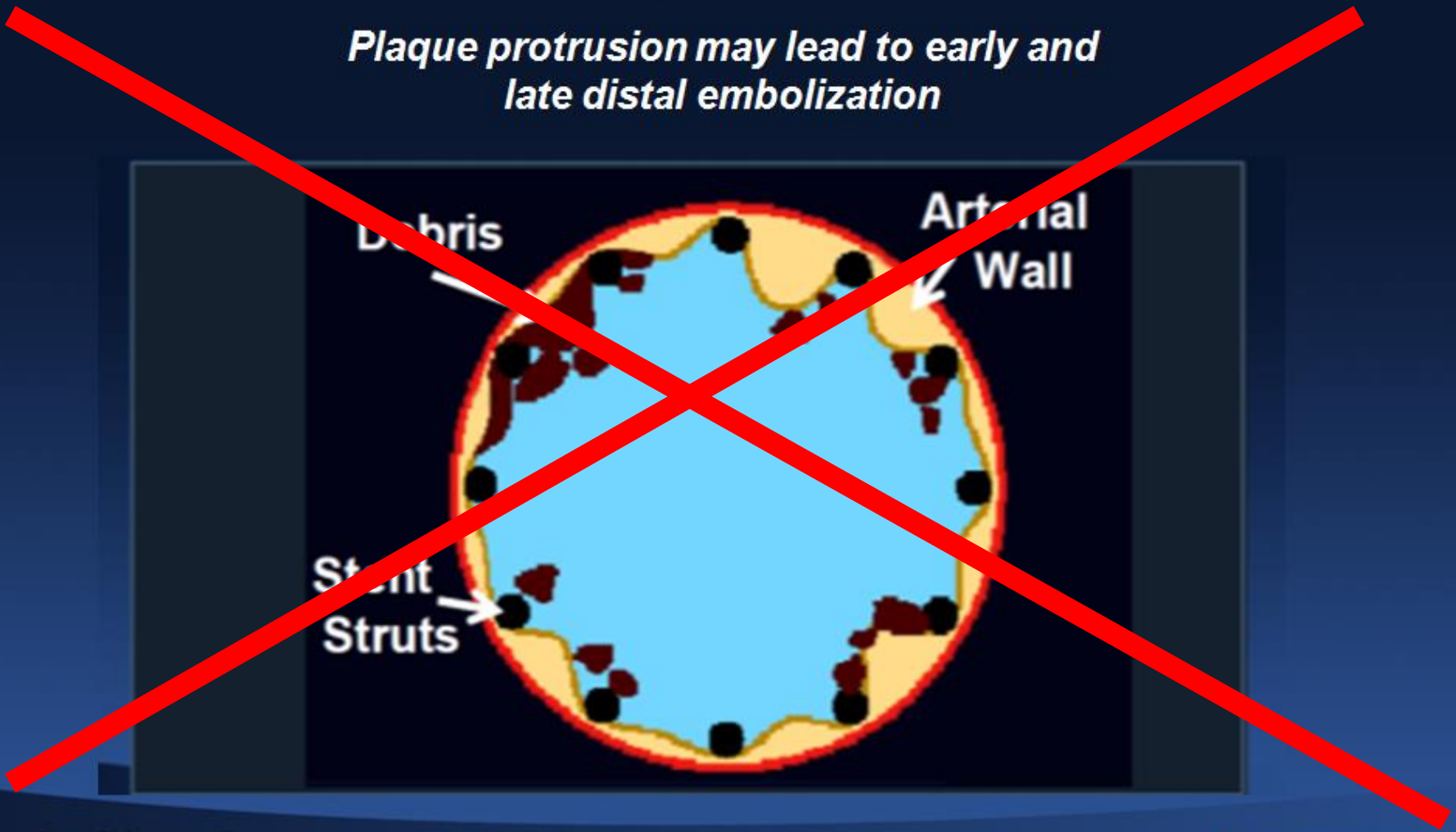
RESOLVED

DW-MRI analysis @ 30 days*	
Incidence of new ipsilateral lesions	1 √
Average lesion volume (cm^3)	0.08 ± 0.00
Permanent lesions at 30 days	1

*External Core Lab analysis (US)

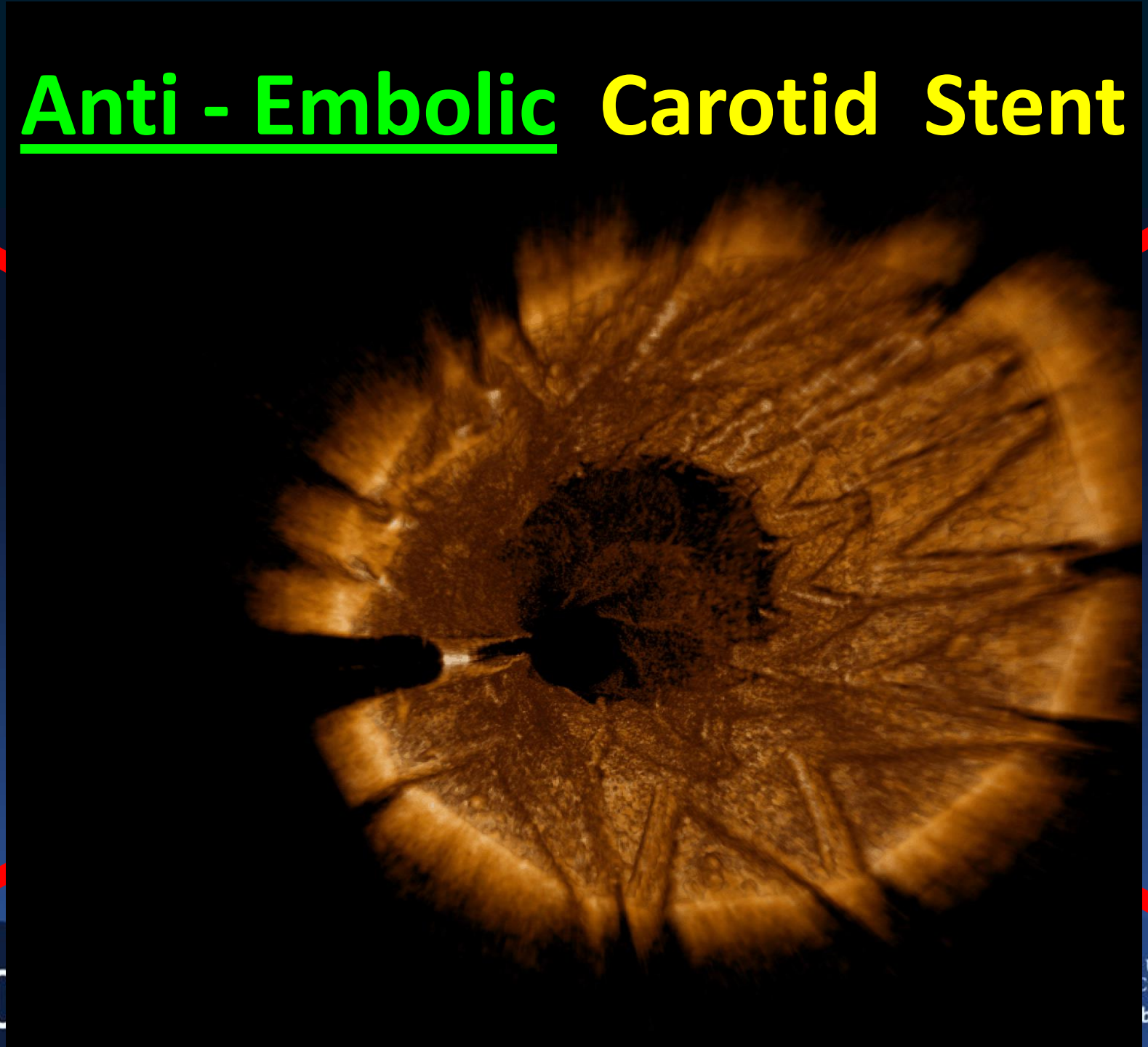
J. Schofer, P. Musialek et al. ***JACC** Intv* 2015;8:1229-34

Anti - Embolic Carotid Stent



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

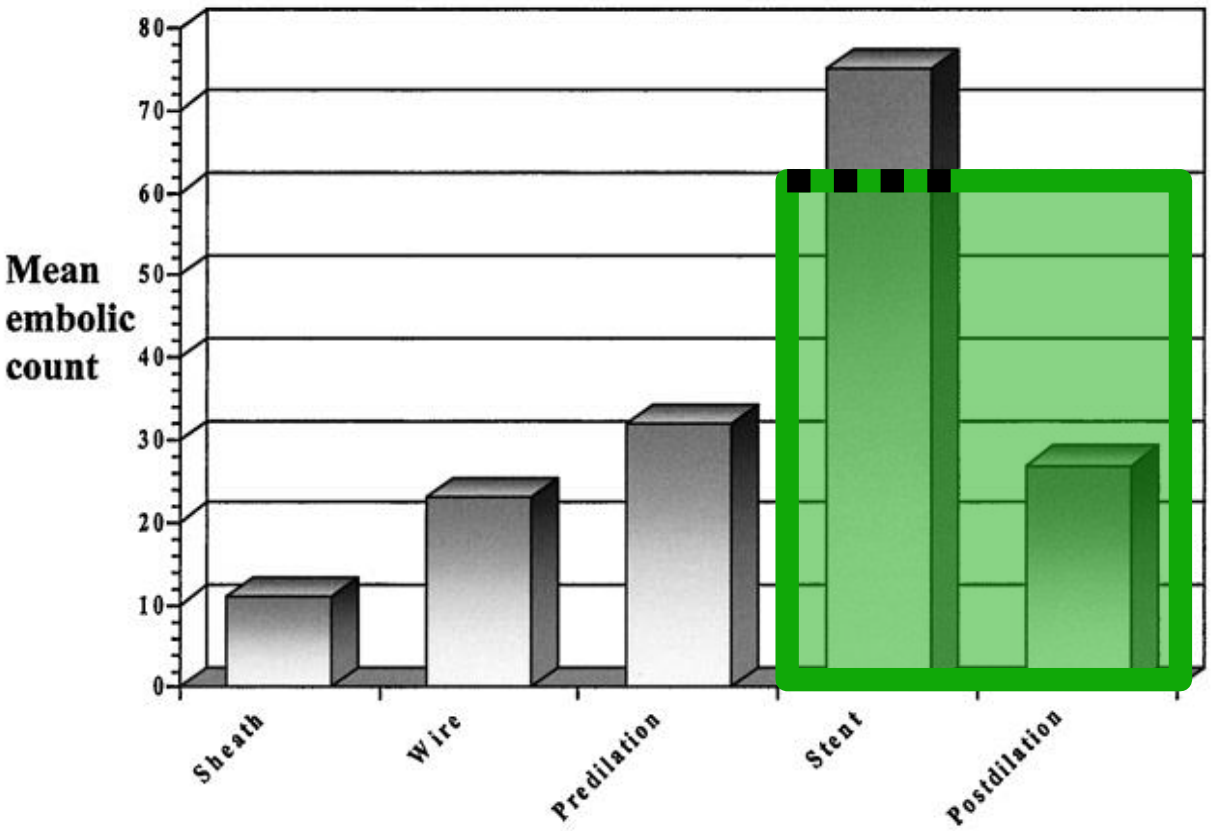
Anti - Embolic Carotid Stent



CAS (and CEA) *are* –and *will remain*– emboli-generating procedures

Effect of the Distal-Balloon Protection System on Microembolization During Carotid Stenting

Nadim Al-Mubarak, MD; Gary S. Roubin, MD, PhD; Jiri J. Vitek, MD, PhD; Sriram S. Iyer, MD; Gishel New, MD; Martin B. Leon, MD



amenable to elimination with mesh

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

Circulation. 2001;104:1999-2002

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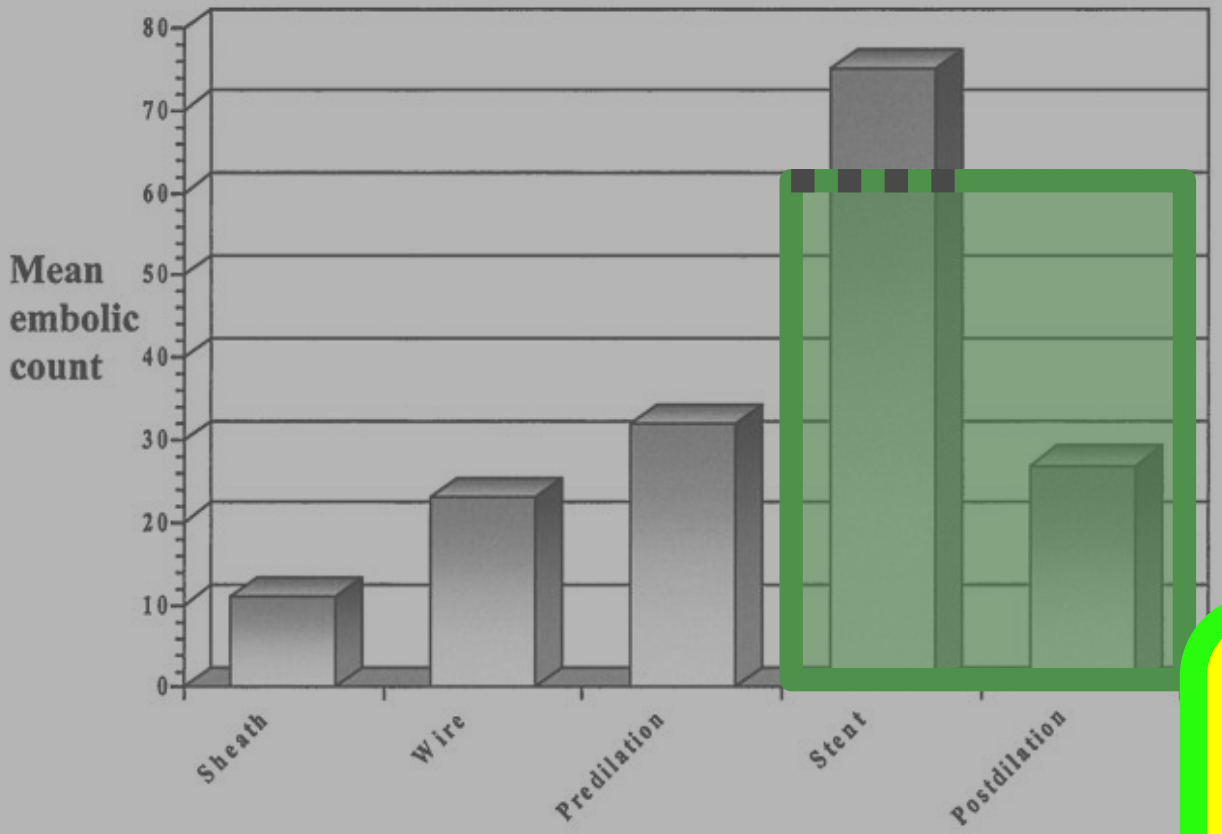


Figure 1. Microembolic profile during unprotected CAS. The mean MES counts during various phases of the procedure are displayed.

Circulation. 2001;104:1999-2002

amenable to elimination with MicroNet

+

MicroNet *protection* during *stent healing*!

Prospective evaluation of All-comer peR-cutaneous cArotiD revascularization In sympto-matic and increased-risk asymptomatic carotid artery stenosis using CGuard™ Micronet-covered embolic prevention stent system:

The PARADIGM Study

CAROTID PARADIGM REVASCULARIZATION

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

Van Laanen J et al. *J Cardiovasc Surg* 2008
Cosottini M et al. *Stroke Res* 2010
Musialek P et al. *J Endovasc Ther* 2010
Wasser K et al. *J Neurol* 2012

* Pieniazek P, Musialek P et al. *J Endovasc Ther* 2008;15:249-62.
Cremonesi A et al. *EuroInervention* 2009;5:589-98.
Pieniazek P, Musialek P et al. *J Endovasc Ther* 2009;16:744-51.

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) — **- 24-48h**
- **in-stent velocities** (Duplex) — **- 30 days**, **- 12 months**, **- up to 5y**

PARADIGM

- **ASYMPTOMATIC patients treated interventionally only if at ↗ stroke risk**
- **established lesion-level increased-risk crieria used:**
  - **thrombus-containing**
  - **tight, near-occlusive**
  - **documented progressive**
  - **irregular and/or ulcerated**
  - **contralteral ICA occlusion/stroke**
  - **asymptomatic ipsilateral brain infarct**

AbuRahma A et al. *Ann Surg.* 2003;238:551-562.
Ballotta E et al. *J Vasc Surg* 2007;45:516-522.
Kakkos SK et al. (ACSRS) *J Vasc Surg.* 2009;49:902-909.
Lovett JK et al. *Circulation* 2004;110:2190-97
Nicolaides AN et al. *J Vasc Surg* 2010;52:1486-96.
Taussky P et al. *Neurosurg Focus* 2011;31:6-17.

Methods (cont'd)

PARADIGM: investigator – independent

- external study data verification
- external angiographic analysis
- external statistical analysis

Krakow Cardiovascular Research Institute

Core Imaging Analysis Laboratory

Krakow Cardiovascular Research Institute

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 occlded + h/o prior ipsil. large infarct with hemorrhagic transformation
n=1: severe haemodynamic instability (ICA stenosis asympt.)

*Dept. of Cardiac & Vascular Dieases, 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 eGRF 14 => no contrast
- n=1 extreme access tortuousity
- n=1 severe aortic valve disease + calcific LICA (AVR + CEA)
- n=1 floating thrombus in CCA
- n=1 ICA diameter <2.0 mm + contralat. occlusion

71 ICAs treated endovascularly in 68 patients

Clinical characteristics of study patients (n=68)

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

PARADIGM: Results (1)

- Percutaneous treatment **100%** 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)

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

* verified on imaging

CoreLab-Quantified

- **ICA reference diameter** **4.99 ± 0.36mm** (from 4.27 to 6.02mm)
- **Lesion length** **19.9 ± 5.8mm** (from 8.19 to 30.25mm)

PARADIGM: Results (3)

Index lesion quantitative characteristics (n=71 lesions)

	All (n=71 lesions)	Symptomatic n=37	Asymptomatic n=34	p
Before CAS				
PSV, m/s	3.8 ± 1.3	3.7 ± 1.1	3.8 ± 1.5	0.862
EDV, m/s	1.3 ± 0.7	1.4 ± 0.6	1.3 ± 0.8	0.687
Diameter stenosis % (QA)	82 ± 9	79 ± 9	84 ± 9	0.021
CAS				
EPD type				0.092
Proximal*	35% (25)	44% (16)	26% (9)	
Distal**	65% (46)	56% (21)	74% (25)	
post-dilat balloon# peak pressure, mmHg	18.4 ± 3.4	17.5 ± 3.6	19.2 ± 2.9	0.037
After CAS				
Stent length (QA)§				NA
Nominal 30 mm	29.66 ± 0.30	29.66 ± 0.28	29.65 ± 0.32	
(min-max)	(28.73-30.07)	(29.02-30.07)	(28.73-30.02)	
Nominal 40 mm	39.73 ± 0.34	39.69 ± 0.41	39.77 ± 0.28	
(min-max)	(38.88-40.22)	(38.88-40.22)	(39.14-40.04)	
Residual diam. stenosis	7 ± 4%	5 ± 4%	7 ± 5%	0.257
in-stent PSV, m/s	0.70 ± 0.28	0.66 ± 0.29	0.74 ± 0.27	0.266
in-stent EDV, m/s	0.17 ± 0.07	0.17 ± 0.07	0.18 ± 0.07	0.457

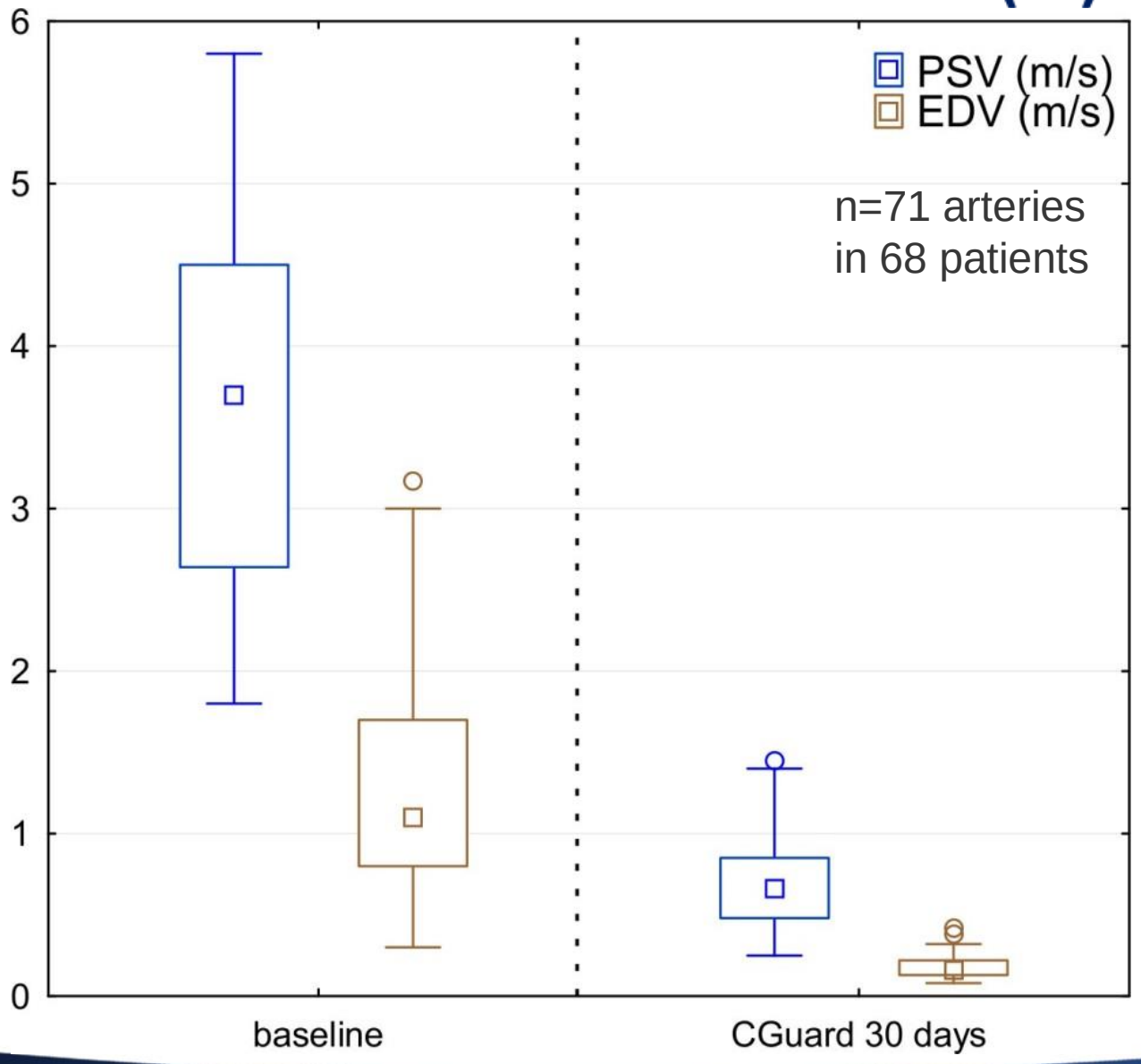
* Emboshield (n=7); FilterWire (n=14); Spider (n=25)
** Gore FlowReversal (n=4) or flow reversal with MoMa (n=21)

(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)

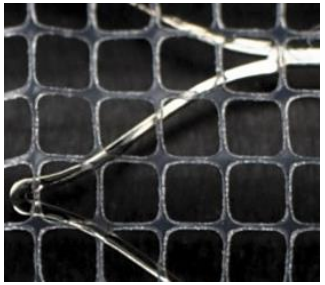
PARADIGM: Results (4)

- Death/stroke/MI @ 48h 0%
- Death/stroke/MI @ 30d 0%

PARADIGM: Results (5)



Procedure - Relevant Information

Name	 RoadSaver *aka* Casper	 Gore® Carotid Stent	 CGuard™ Embolic Prevention Stent
Re-sheathable ?	yes*	no	no
Crossing profile	5F	**5F** (smaller diam) **6F** (larger diam)	6F
Foreshortening	yes	unknown**	no #
Stent placement accuracy	–	N/D	++ #
Ability to eliminate residual stenosis	N/D	N/D	yes #
Externally-analysed systematic DW MRI study data	unknown	unknown	yes ##

*up to 50% released length # PARADIGM PCR2015 and TCT-73
**probably not substantial ## CARENET *JACC Intv* 2015;8:1229
N/D = not determined

on-going
Studies

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

Sponsors and Collaborators
Flanders Medical Research Program

Investigators
Principal Investigator: Marc Bosiers, MD

Roadsaver

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

ClinicalTrials.gov Identifier:
NCT02529345

First received: April 27, 2015
Last updated: August 19, 2015
Last verified: August 2015
History of Changes

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)

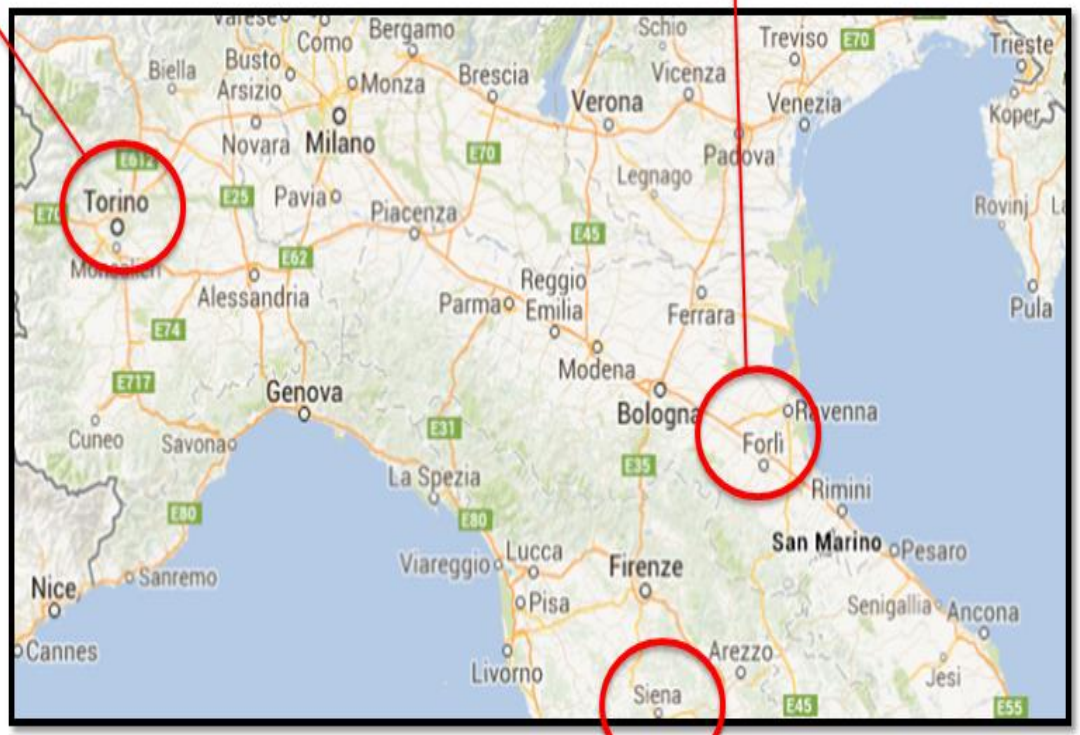
Estimated Enrollment: 100
Study Start Date: April 2015
Estimated Study Completion Date: May 2017
Estimated Primary Completion Date: April 2016 (Final data collection date for primary outcome measure)

50% patient cohort recruitment threshold crossed √

Italian registry - Roadsaver

Torino: Dr. C. Rabbia
Radiologist

Cotignola: Dr. A. Cremonesi
Cardiologist



3 Italian Vascular Centers

Siena: Prof. C. Setacci
Vascular Surgeon

RoadSaver Italian registry - Preliminary results

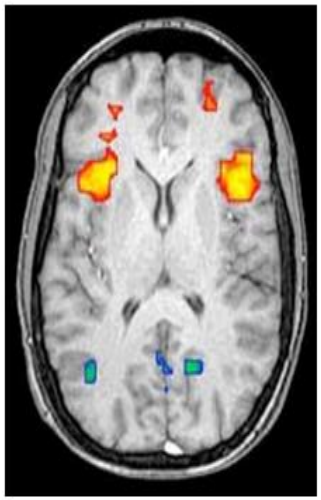
3 Centers

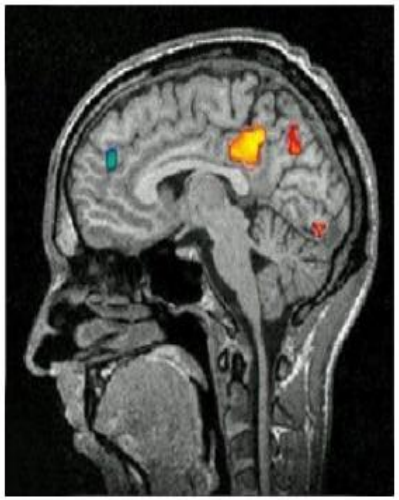
Cotignola, Siena, Torino

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 controlateral 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)

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

NCT # 01901874

- **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** √
- **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

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*

Planned enrollment: n = 200 patients

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

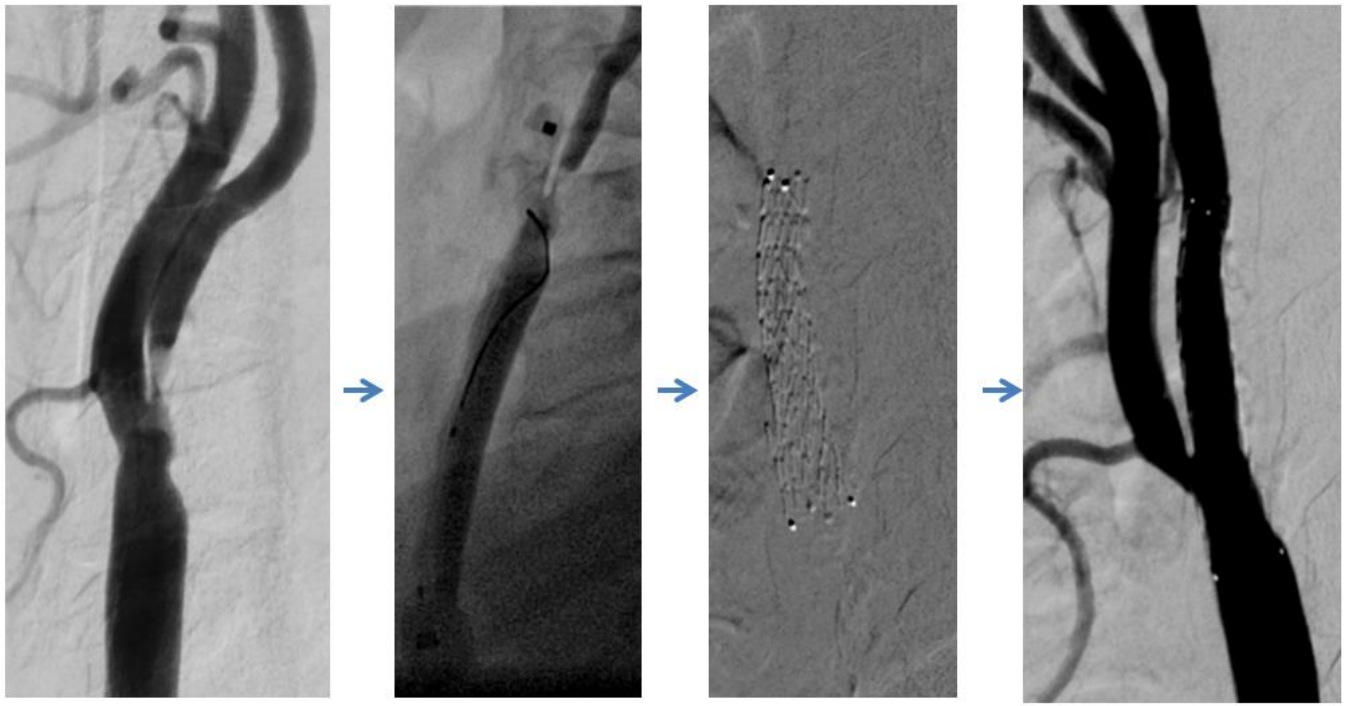
PARADIGM – Extend (aka PARADIGM-101)

Cardiovascular and Interventional Radiological Society of Europe

Lisbon, Portugal
September 26-30
CIRSE 2015

24.09.2015

PARADIGM – 101 recruitment completed



√

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

remaining
Unknowns

Remaining Unknowns (1)

- Is there a **product/design-specific ”gradient”** in the embolic prevention efficacy?

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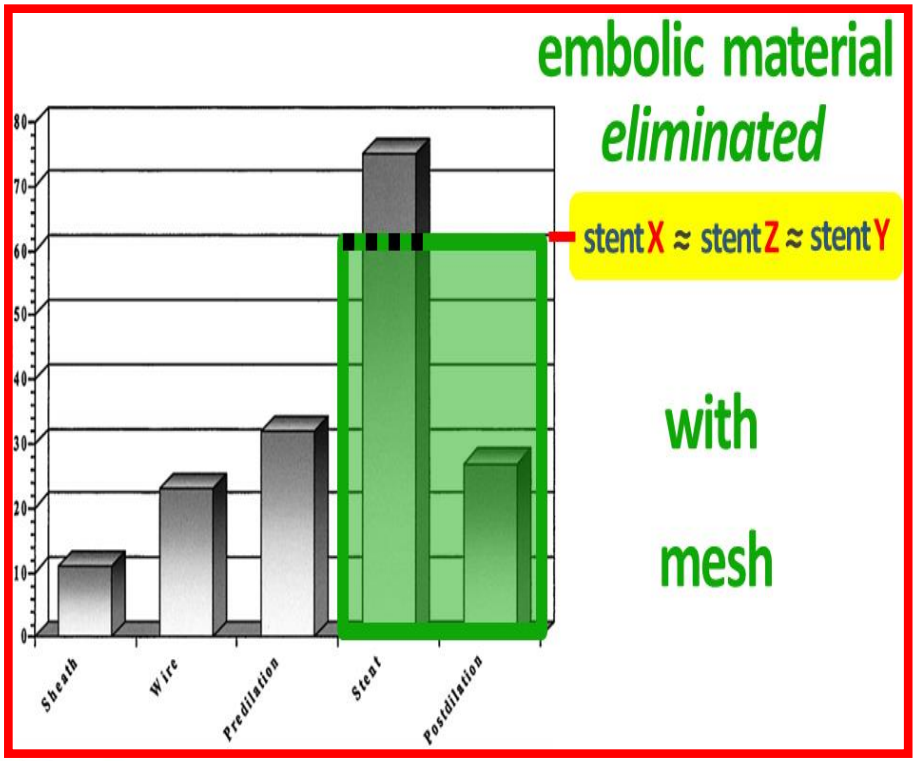

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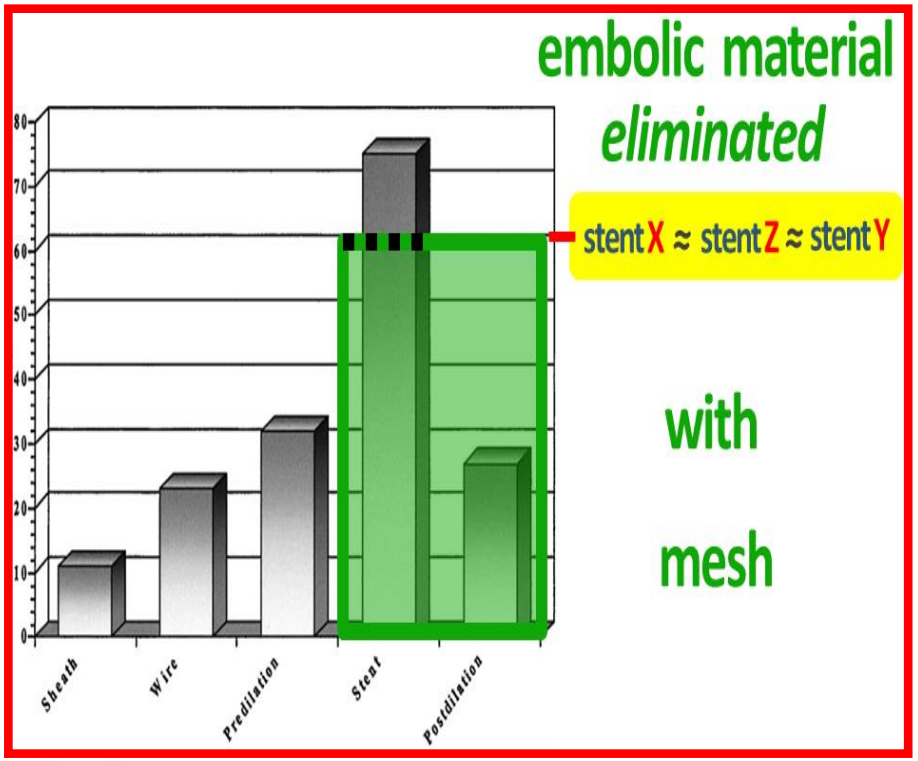

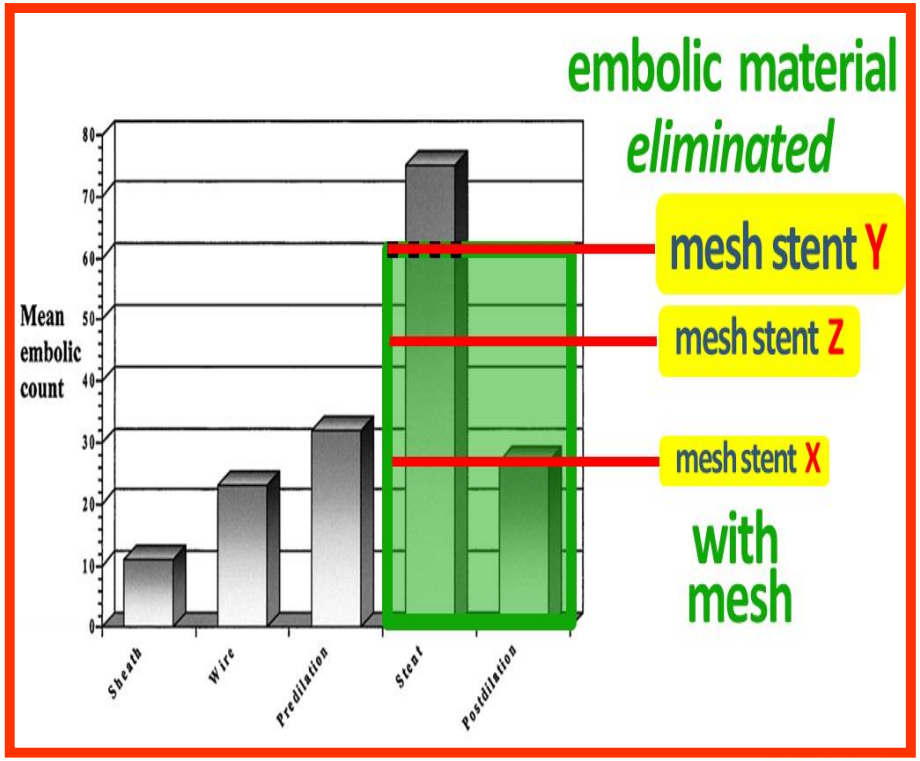

Remaining Unknowns (2)

- **Large-scale** (muli-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)**

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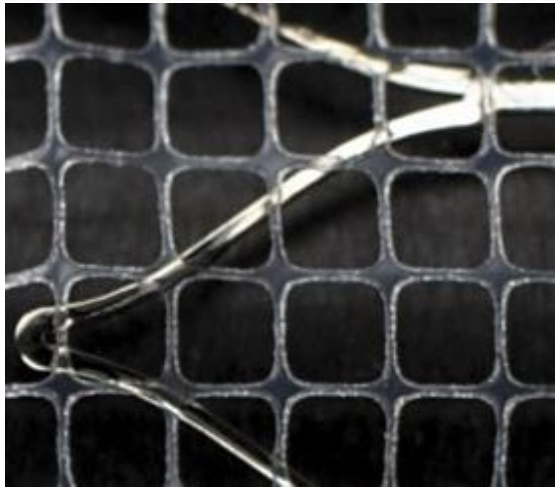
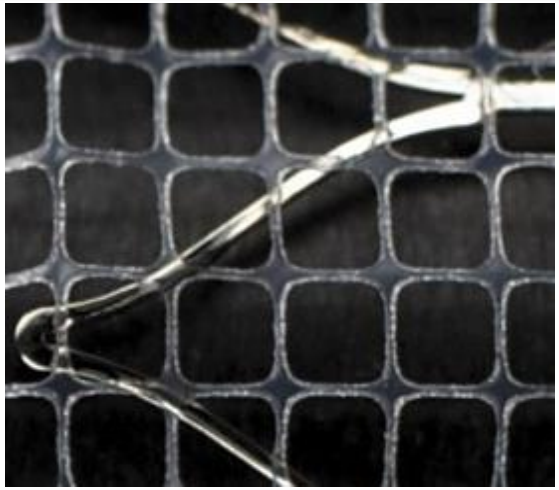



This concept has been desired.

And it works.

This is the future

of Carotid Artery Stenting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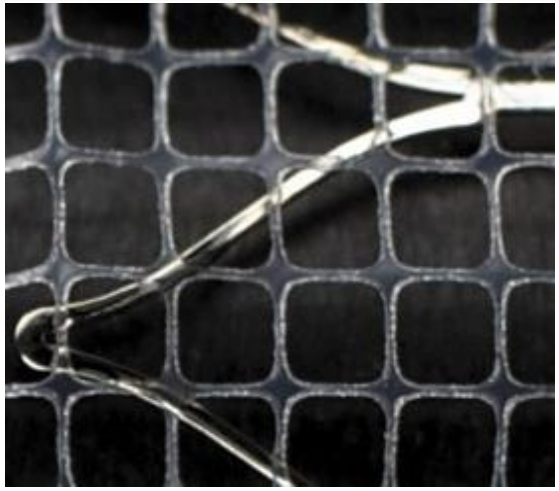


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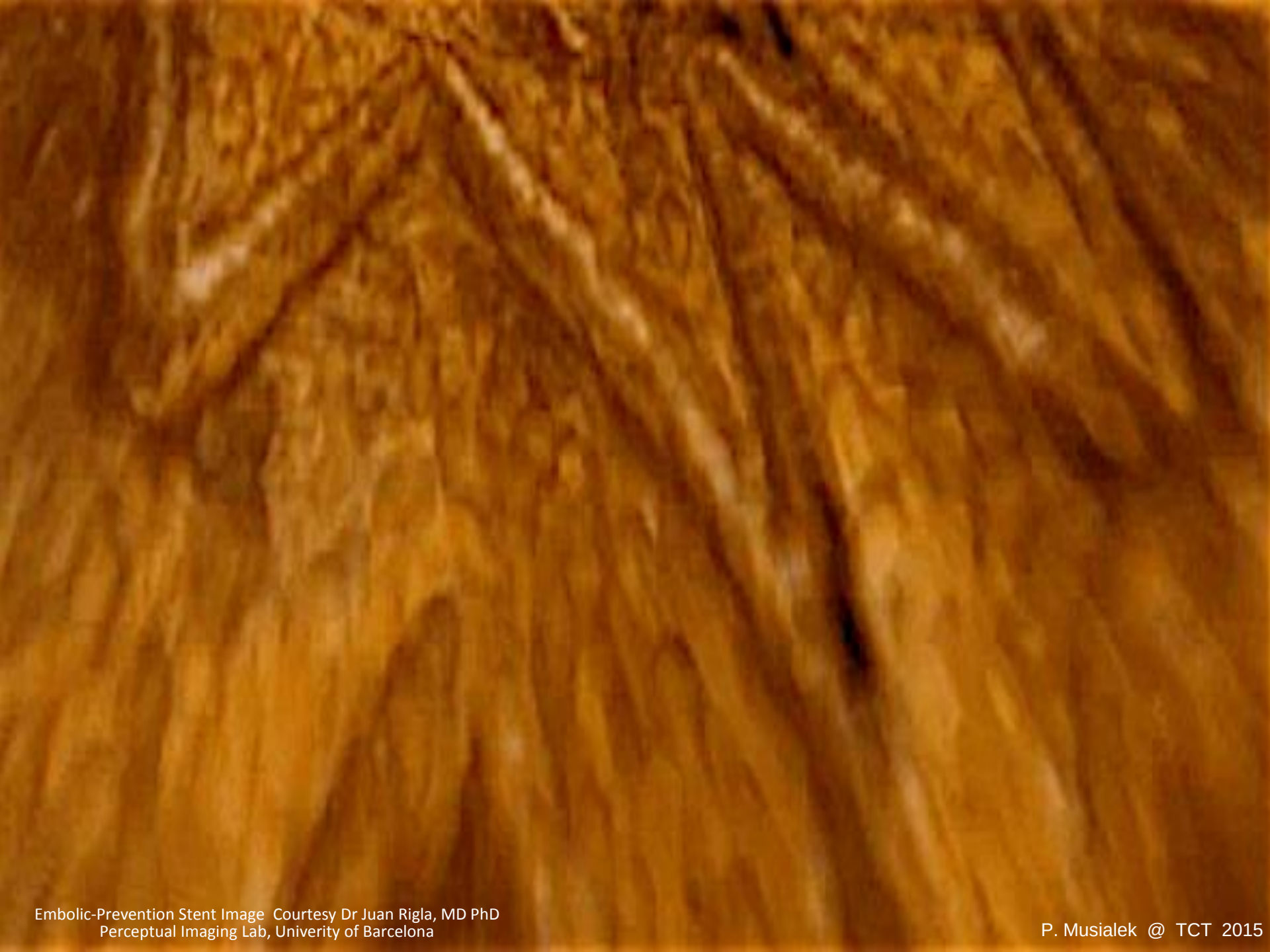
of Carotid Artery St[illegible]

revascularization ?


NEW
PARADIGM
AHEAD



Embolic-Prevention Stent Image Courtesy Dr Juan Rigla, MD PhD
Perceptual Imaging Lab, Univerity of Barcelona

Carotid Revascularization 2015+ REALITY

CAS 2010 VISION

Kosmas I. Paraskevas, MD,[a] Dimitri P. Mikhailidis, MD, FFPM, FRCPath, FRCP,[b] and Frank J. Veith, MD, FACS,[c,d] *Athens, Greece; London, United Kingdom; Cleveland, Ohio; and New York, NY*

Improved technology for CAS — better EPDs (flow reversal and proximal occlusion) and better stents (membrane-covered, ultra-closed cell, and biodegragable). 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.[69]

JOURNAL OF VASCULAR SURGERY
November 2010

Embolic-Prevention Stent Image Courtesy Dr Juan Rigla, MD PhD
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