euro PCR 2016 LATE BREAKING TRIALS

EAPCI | EUROPEAN SOCIETY OF CARDIOLOGY | EACTS

2016 euro PCR

CAROTID PARADIGM REVASCULARIZATION

Novel PARADIGM in carotid revascularization:

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

P. MUSIALEK [1], A. MAZUREK [1], M. TRYSTULA [2], A. BORRATYNSKA [3], A. LESNIAK-SOBELGA [1], M. URBANCZYK [4], RP. BANYS [4], A. KOZANECKI [1], P. WILKOLEK [1], A. BRZYCHCZY [2], L. PARTYKA[5], W. ZAJDEL [6], K. ZMUDKA [6], P. PODOLEC [1]

(1) Jagiellonian University Dept. Cardiac & Vascular Diseases, John Paul II Hospital, (2) Dept Vascular Surgery, John Paul II Hospital; (3) Neurology Outpatient Dept., John Paul II Hospital, Krakow; (4) Dept. Radiology, John Paul II Hospital; (5) KCRI, Krakow, (6) Jagiellonian University Dept. Interventional Cardiology, John Paul II Hospital, Krakow, POLAND

Jagiellonian University Dept. of Cardiac & Vascular Diseases

John Paul II Hospital, Krakow, Poland

euro PCR 2016 LATE BREAKING TRIALS

EAPCI | EUROPEAN SOCIETY OF CARDIOLOGY | EACTS

2016 euro PCR

CAROTID PARADIGM REVASCULARIZATION

Novel PARADIGM in carotid revascularization

P. MUSIALEK [1], A. MAZUREK [1], M. TRYSTULA [2], A. BORRATYNSKA [3], A. LESNIAK-SOBELGA [1], M. URBANCZYK [4], RP. BANYS [4], A. KOZANECKI [1], P. WILKOLEK [1], A. BRZYCHCZY [2], L. PARTYKA[5], W. ZAJDEL [6], K. ZMUDKA [6], P. PODOLEC [1]

(1) Jagiellonian University Dept. Cardiac & Vascular Diseases, John Paul II Hospital, (2) Dept Vascular Surgery, John Paul II Hospital; (3) Neurology Outpatient Dept., John Paul II Hospital, Krakow; (4) Dept. Radiology, John Paul II Hospital; (5) KCRI, Krakow, (6) Jagiellonian University Dept. Interventional Cardiology, John Paul II Hospital, Krakow, POLAND

Jagiellonian University Dept. of Cardiac & Vascular Diseases

John Paul II Hospital, Krakow, Poland

Potential conflicts of interest

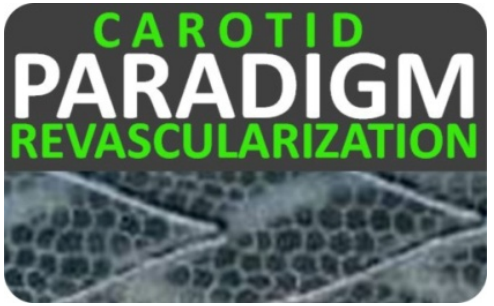
Speaker's name: Piotr Musialek

☑ I have the following potential conflicts of interest to report:

Advisory Board participation: InspireMD, PENUMBRA
Training / Educational Activities for MEDTRONIC
Research support and KoL travel support from ABBOTT

N.B. **PARADIGM** study has been Invesigator-Initiated and Investigator-Executed **(no industry support)**

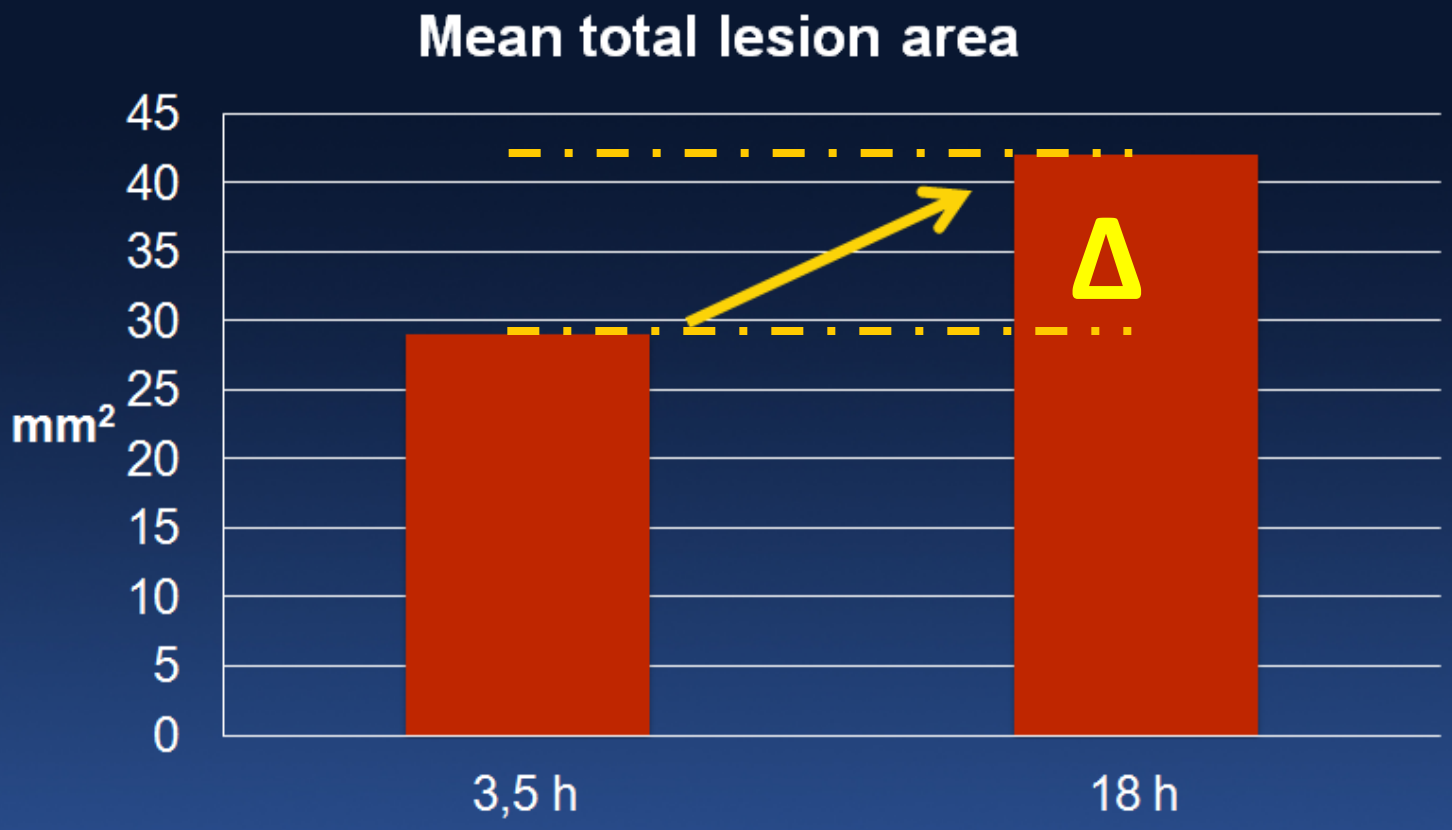
MicroNet EPS



The NEED

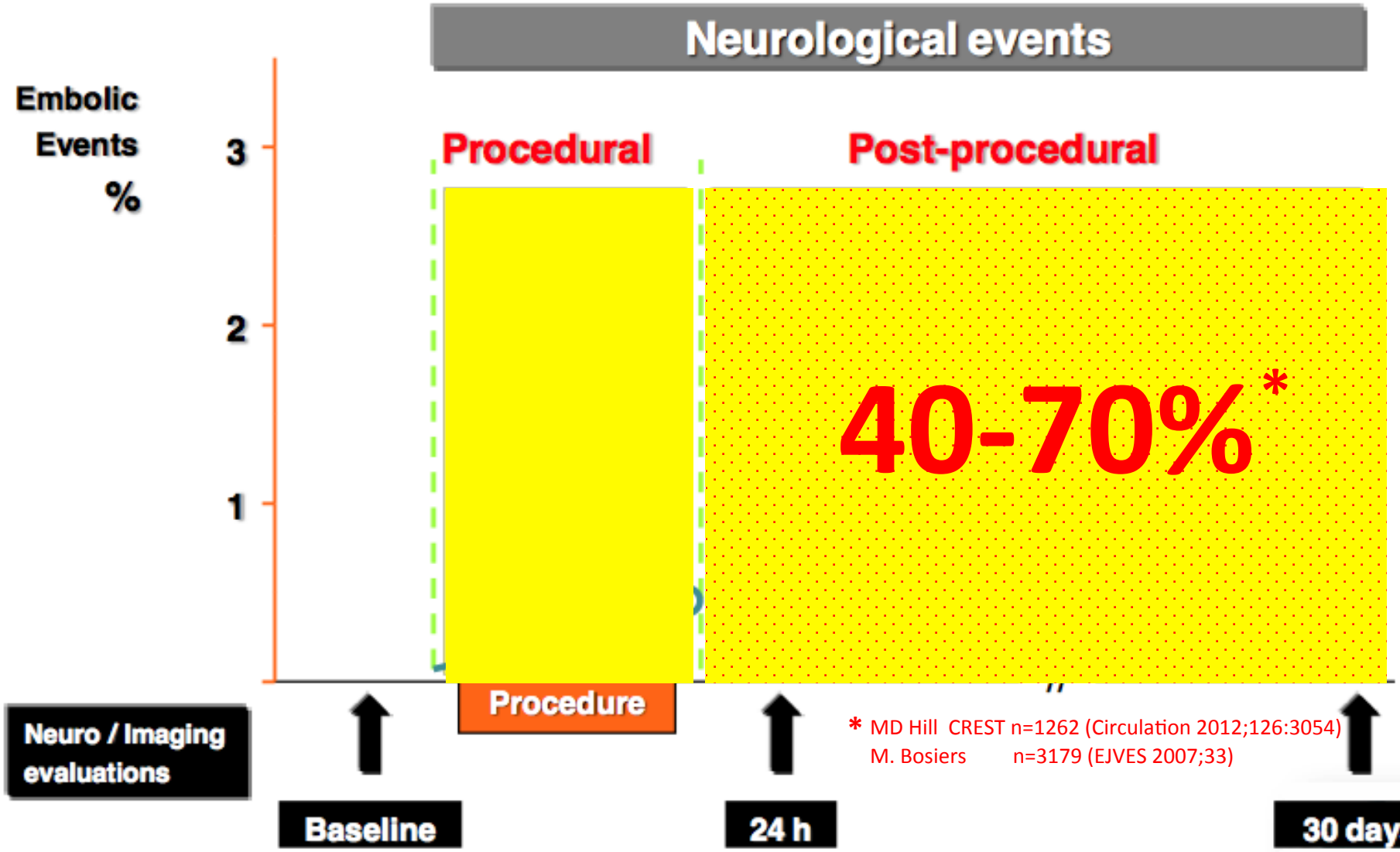
Post-procedural Embolization with conventional carotid stents

DW-MRI post CAS



Schofer J et al, JACC Cardiovasc interv 2008

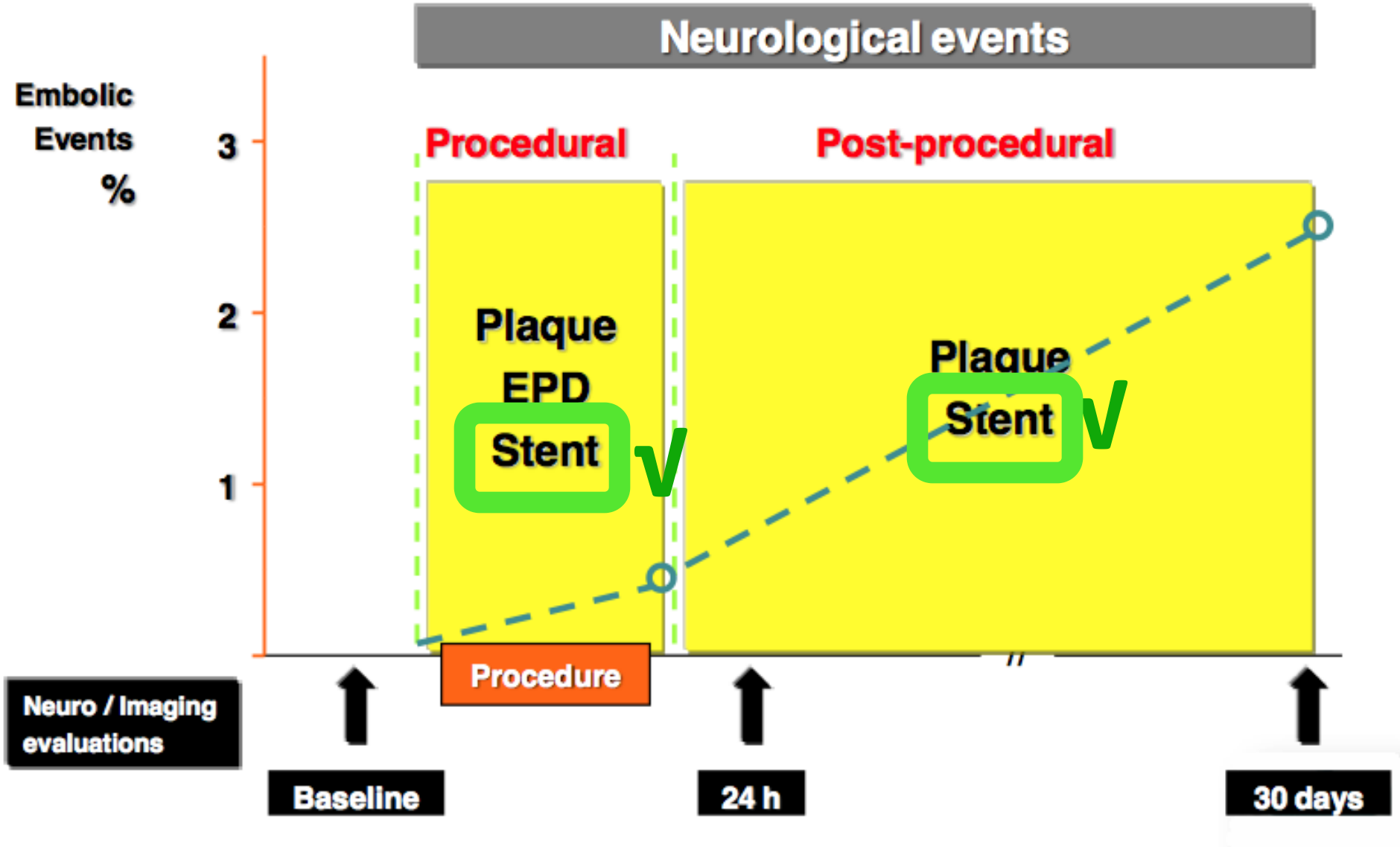
Timing of neuro-embolic events after CAS



D. McCormick TCT 2012, modified

P. Musialek @ ePCR 2016

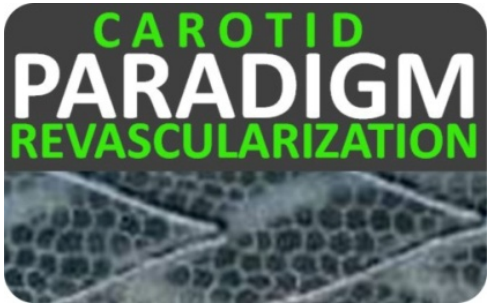
Timing of neuro-embolic events after CAS



D. McCormick TCT 2012, modified

P. Musialek @ ePCR 2016

MicroNet EPS

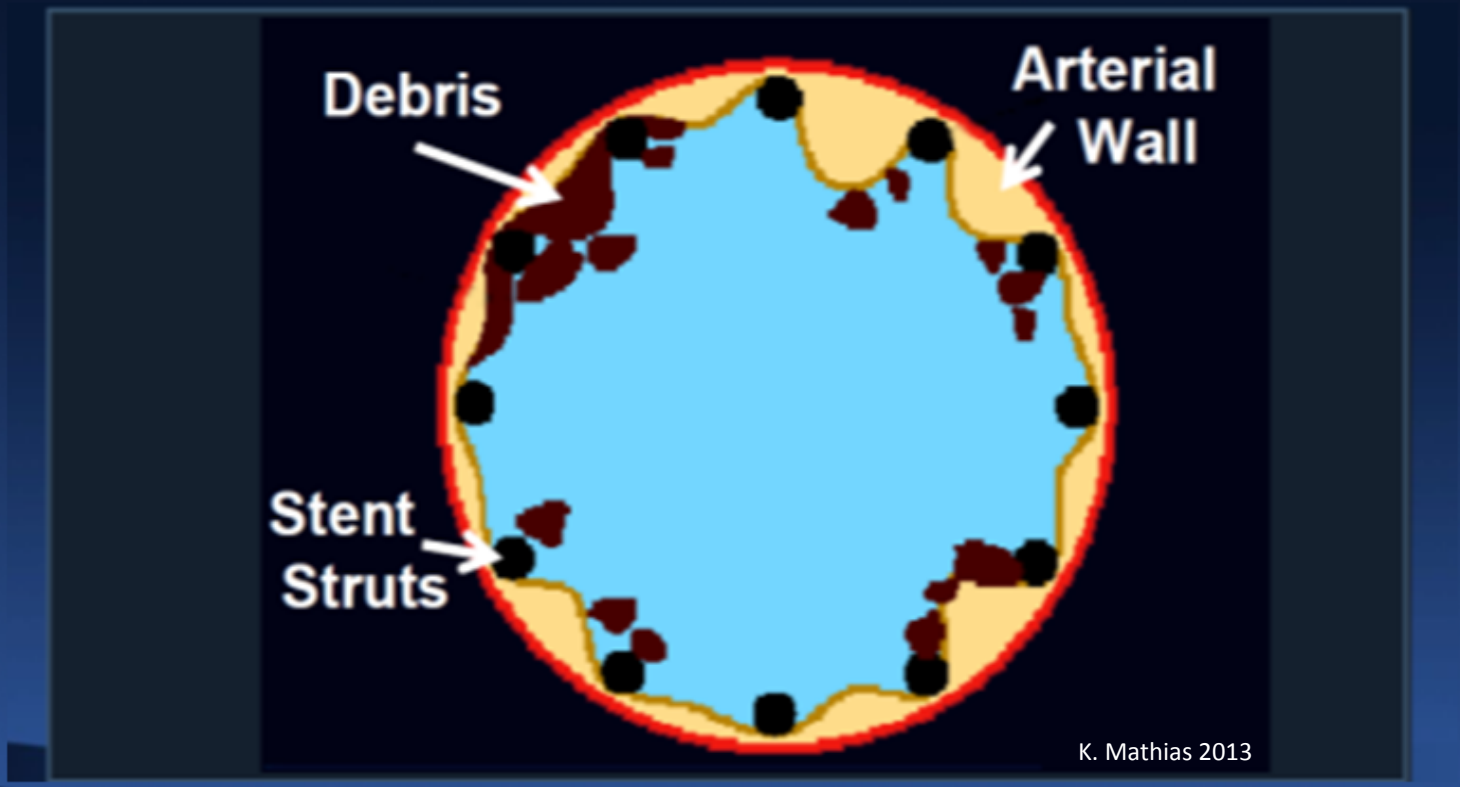


The NEED

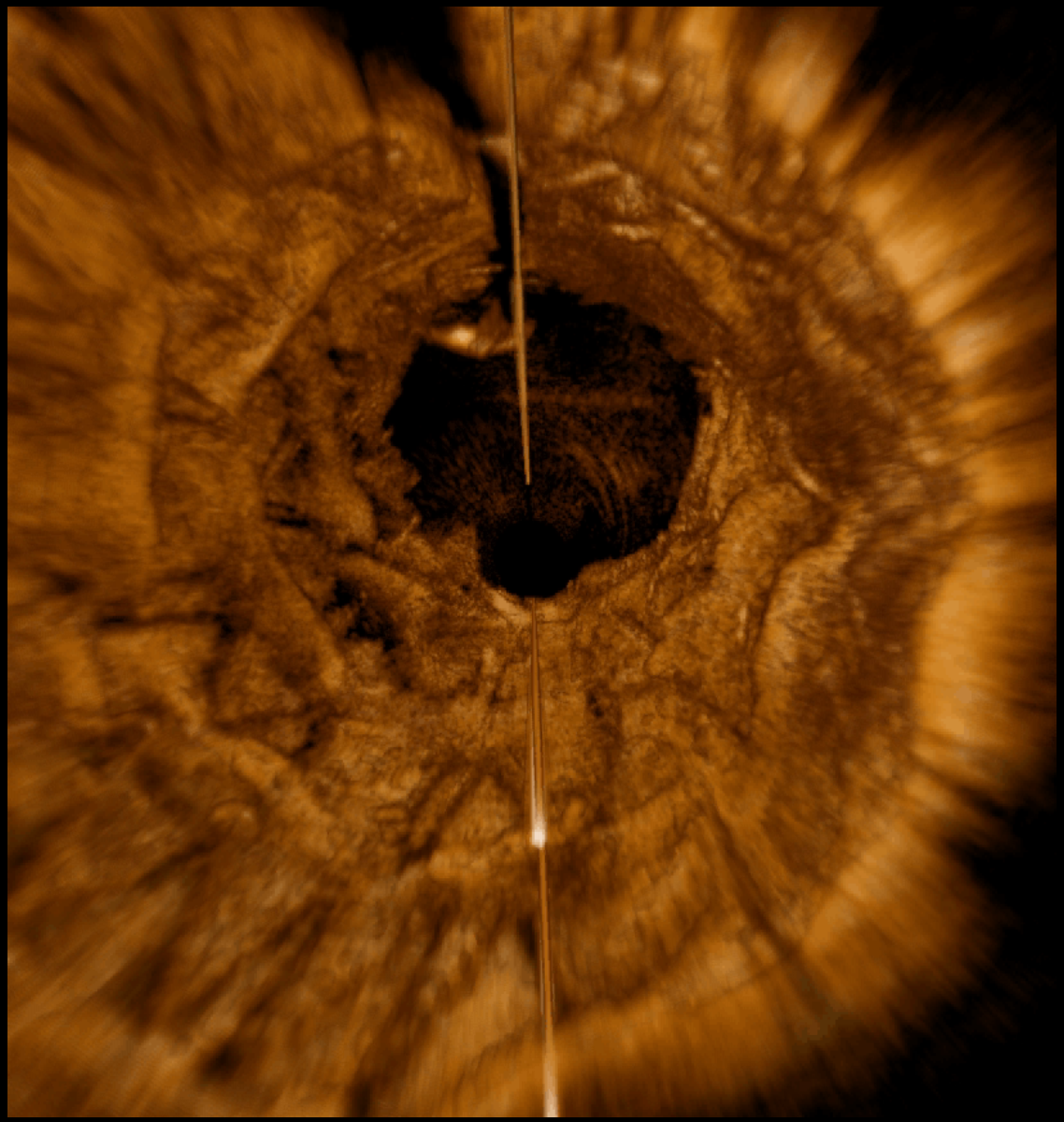
- CEA excludes the plaque
- In CAS, the stent should exclude the plaque too

Conventional Carotid Stent

Plaque protrusion may lead to early and late distal embolization

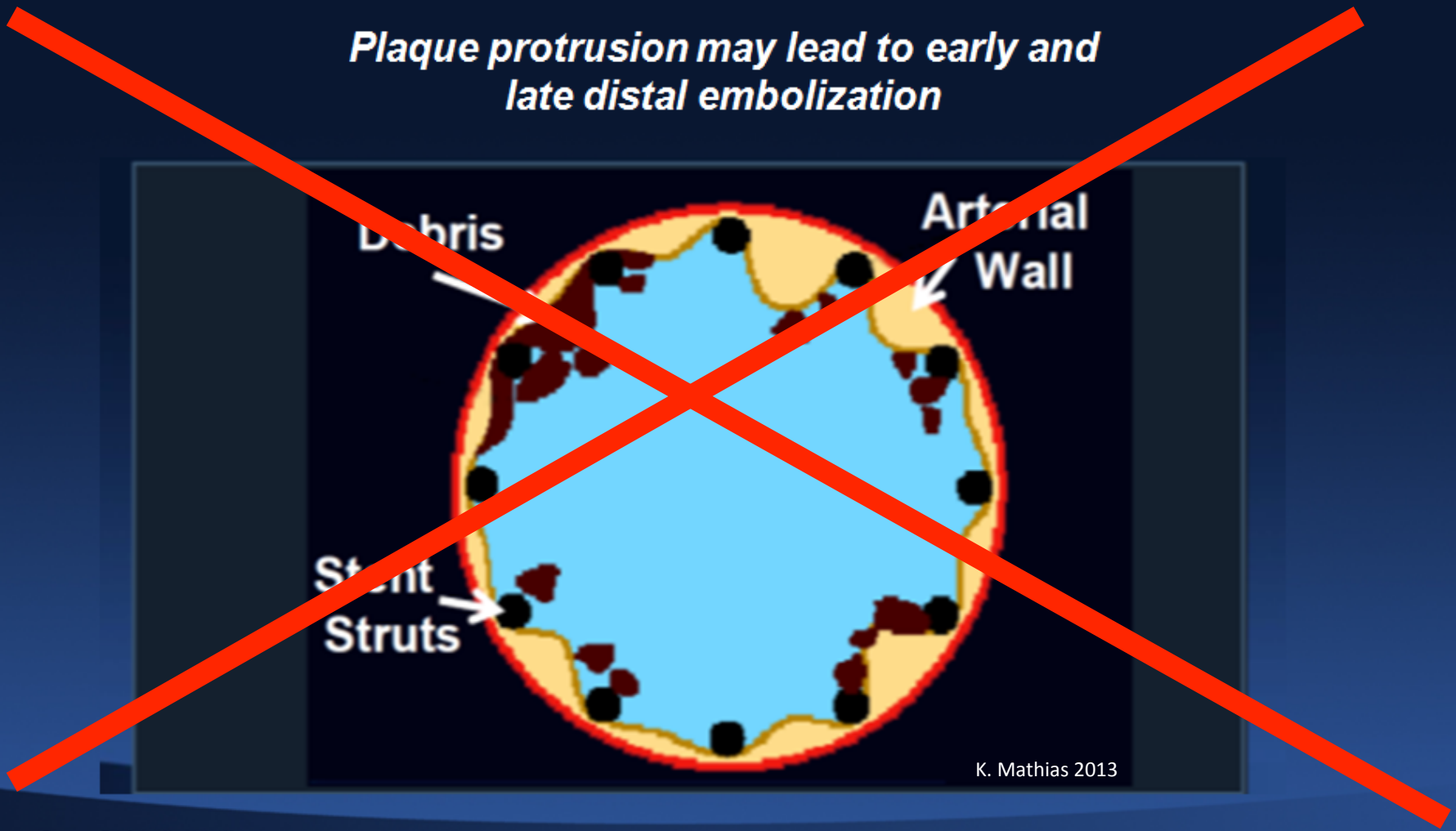


Conventional Carotid Stent

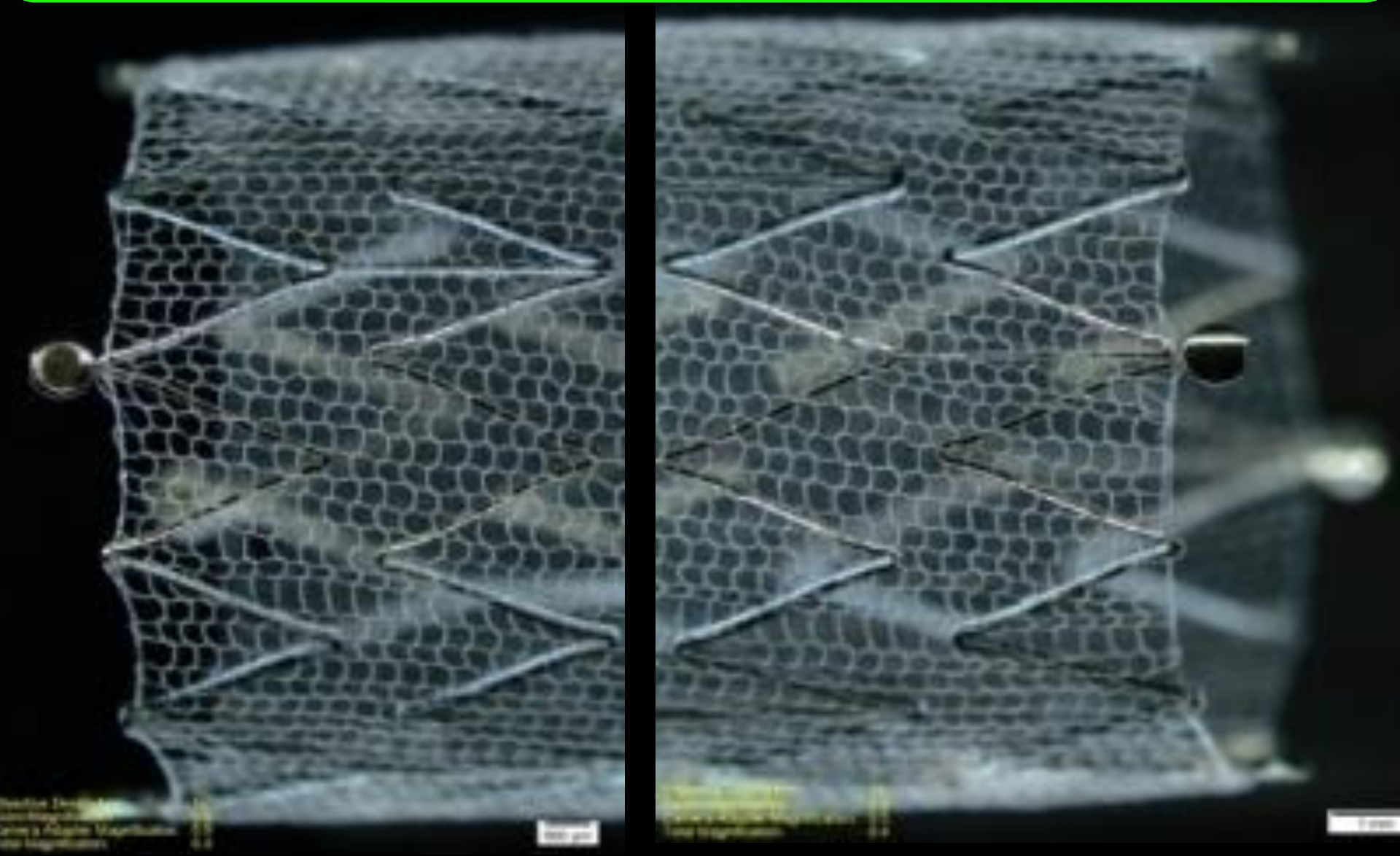


Human Carotid OCT Image Courtesy Dr Juan Rigla, MD PhD
Perceptual Imaging Lab, Univerity of Barcelona

Anti - Embolic Carotid Stent

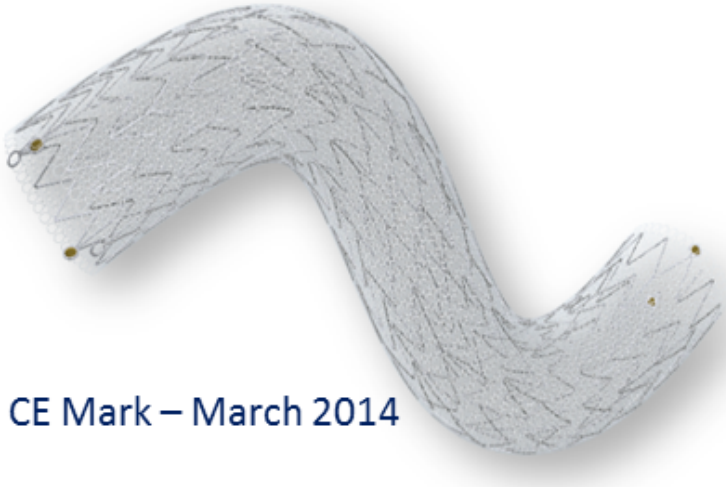


CGuard™ embolic prevention system

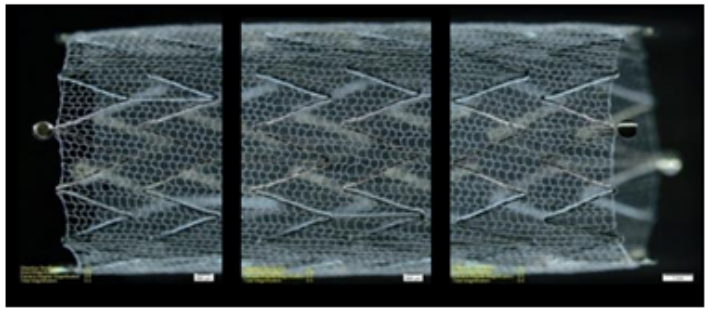


CGuard™– Carotid Embolic Prevention System

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



CE Mark – March 2014

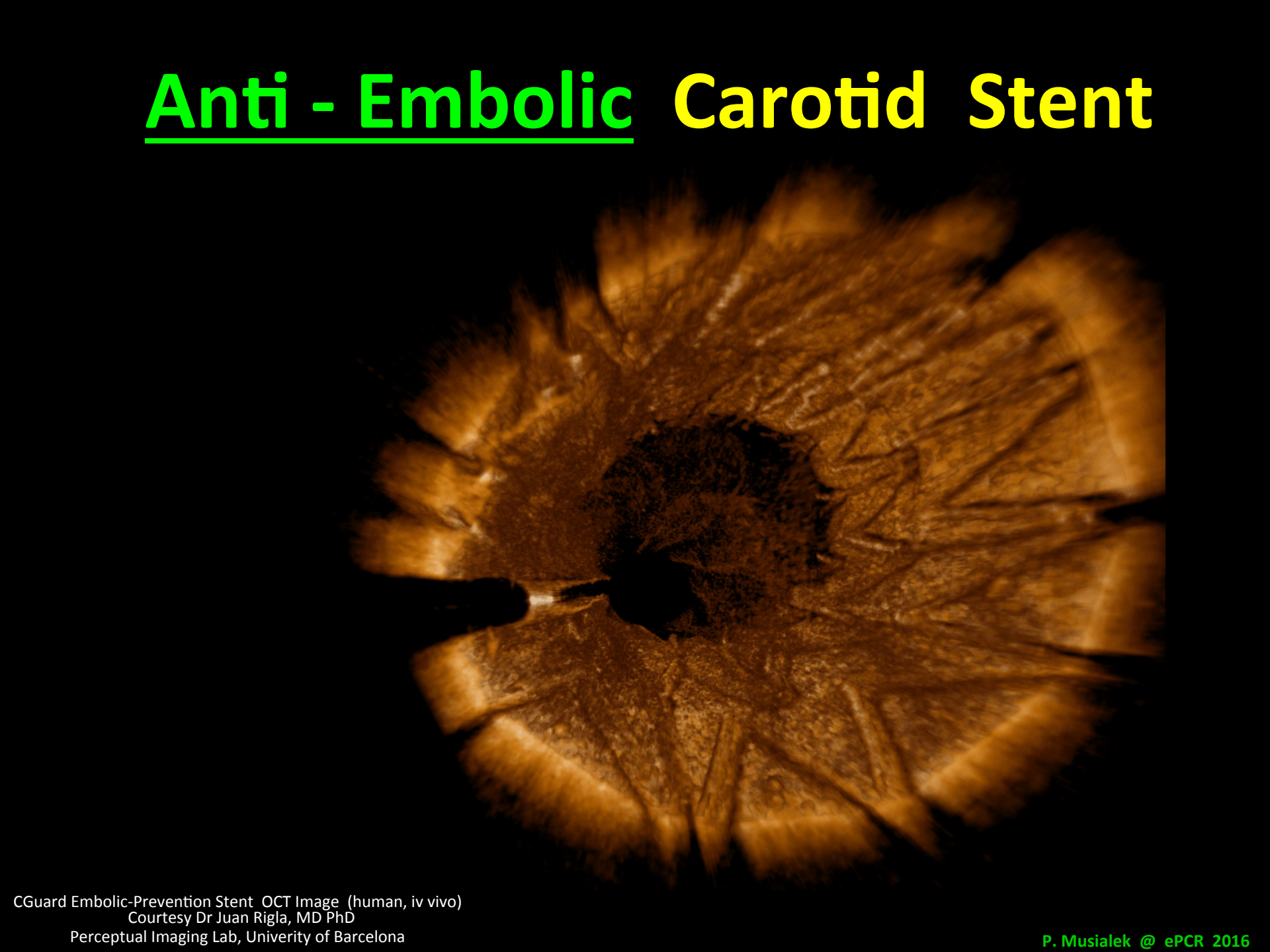


Specific, carotid-dedicated design √

Nitinol frame open cell area = 21.7mm^2
MicroNet cell area ≈ 0.3mm^2

LARGEST SMALLEST

Anti - Embolic Carotid Stent



CGuard Embolic-Prevention Stent OCT Image (human, iv vivo)
Courtesy Dr Juan Rigla, MD PhD
Perceptual Imaging Lab, Univerity of Barcelona

CGuard™ – Carotid Embolic Prevention System

Safety & Efficacy EVIDENCE:

- CARENET DW-MRI & pilot clinical
- PARADIGM larger-scale clinical

JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 8, NO. 9, 2015
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2015.04.016

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‖

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

ABSTRACT

OBJECTIVES This study sought to evaluate the feasibility of the CGuard Carotid Embolic Protective Stent system—a novel thin strut nitinol stent combined with a polyethylene terephthalate mesh covering designed to prevent embolic events from the target lesion in the treatment of carotid artery lesions in consecutive patients suitable for carotid artery stenting.

BACKGROUND The risk of cerebral embolization persists throughout the carotid artery stenting procedure and remains during the stent healing period.

METHODS A total of 30 consecutive patients (age 71.6 ± 7.6 years, 63% male) meeting the conventional carotid artery stenting inclusion criteria were enrolled in 4 centers in Germany and Poland.

P. Musialek @ ePCR 2016

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**	**0.375**	-
Maximum lesion volume (cm^3)	0.4[illegible]5		

>10-fold reduction

in cerebral lesion **volume**

***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*

All but one peri-procedural ipsilateral lesions

RESOLVED

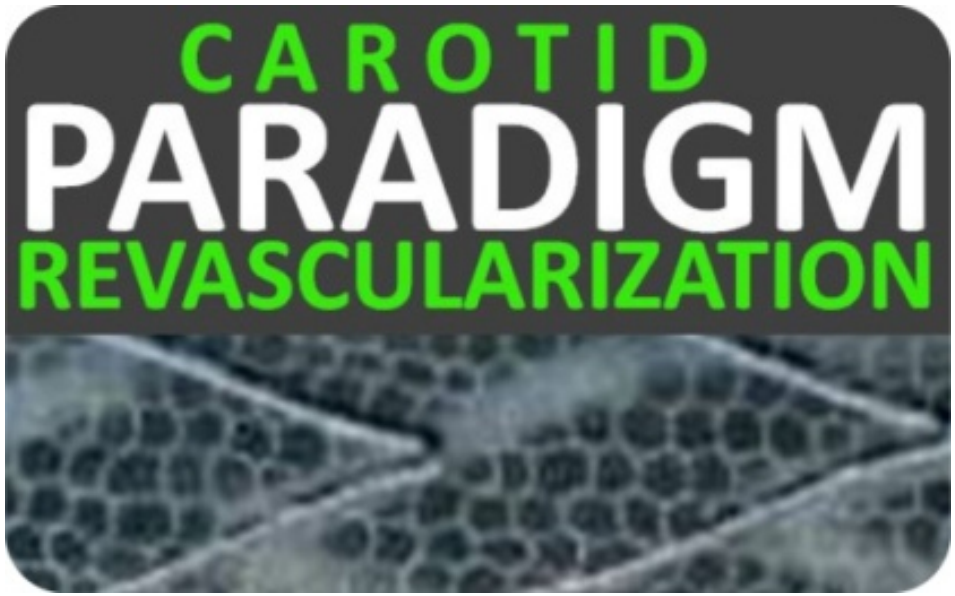
DW-MRI analysis @ 30 days*	
Incidence of new ipsilateral lesions	1
Average lesion volume (cm^3)	0.08 ± 0.00
Permanent lesions at 30 days	1

*External Core Lab analysis (US)

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

Prospective evaluation of All-comer peRcutaneous cArotiD revascularization in sympto-matic and Increased-risk asymptomatic carotid artery stenosis using the CGuard™ Micronet-covered embolic prevention stent system

The PARADIGM Study



euro 2016 PCR

CAROTID PARADIGM REVASCULARIZATION

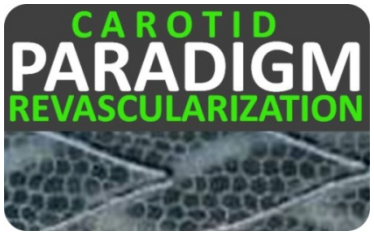
Objective

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

euro 2016 PCR

euro PCR 2016 LATE BREAKING TRIALS

PARADIGM



Study questions:

(1) feasibility of routine use of CGuard MN-EPS in an all-comer carotid stenosis requiring revasc. ?

(2) CGuard EPS device/procedure acute success rate ?

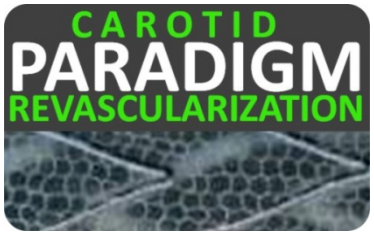
(3) safety and 30-day clinical efficacy ?

(4) proportion of all-comer carotid stenosis patients that can be treated through the endovascular route ?

(5) feasibility of MN-EPS post-dilatation optimization (”CEA-like” effect of CAS) ?

euro PCR 2016 LATE BREAKING TRIALS

PARADIGM

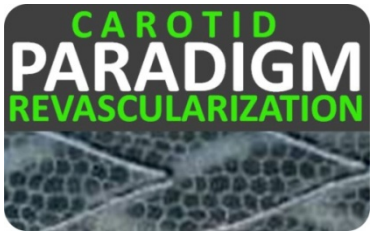


Methods:

- academic cardio-vascular centre
- investigator-initiated study
- not industry-funded
- all-comer inclusion (target = 101 consecutive patients)
- all referrals tracked
- routine consultation and management pathways
- qualitative and quantitative lesion & stent evaluation
- ***investigator-independent*** **neurological and angiographic evaluation, and external study data verification**

euro PCR 2016 LATE BREAKING TRIALS

PARADIGM



Methods (cont'd):

- **ASYMPTOMATIC patients treated interventionally only if at ↗ stroke risk**
- **established lesion-level increased-risk crieria used:**
  - **thrombus-containing**
  - **documented progressive**
  - **irregular and/or ulcerated**
  - **contralateral 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.

euro PCR 2016 LATE BREAKING TRIALS

PARADIGM

CAROTID PARADIGM REVASCULARIZATION

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.

euro PCR 2016 LATE BREAKING TRIALS

PARADIGM

CAROTID PARADIGM REVASCULARIZATION

PARADIGM: investigator – independent

- **external source data verification**

KCRI
Excellence in clinical research

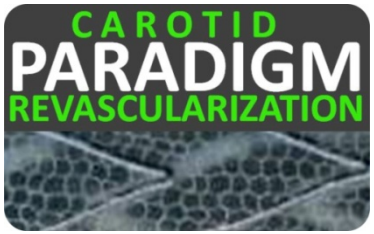
- **external angiographic analysis**

Core Imaging Analysis
KCRI
Laboratory

- **external statistical analysis**

euro PCR 2016 LATE BREAKING TRIALS

PARADIGM



Study endpoints:

- **PRIMARY** a composite of **death, stroke (major/minor) and MI** in the peri-procedural period and at 30 days

- **SECONDARY**

(1) **acute study device success** defined as ability to treat the index carotid lesion using the study device (CGuard MN-EPS) successfully delivered and deployed at the lesion site, obtaining residual diameter stenosis <30% by QA
(2) **procedural success** defined as device success in absence of any vascular complication that would require interventional management
(3) **in-stent velocities/patency** (Duplex) — **- 30 days**
(4) **long-term clinical efficacy**: stroke and stroke-related death — **- every 12 months up to 5y**

euro PCR 2016 LATE BREAKING TRIALS

PARADIGM study: referrals flow chart

139 carotid stenosis patient referrals

CAROTID PARADIGM REVASCULARIZATION

Neuro Vascular Team

- Neurologist
- Interventional angiologist
- Vascular surgeon
- Cardiologist

for carotid revascularisation
108 patients

NOT for carotid revascularisation
31 patients

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

PARADIGM study: revascularisation flow chart

108 patients for carotid revascularisation

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

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

(6%) → **CEA** in n=7 patients

- 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

euro PCR 2016 LATE BREAKING TRIALS

PARADIGM

CAROTID PARADIGM REVASCULARIZATION

Table 1. Clinical characteristics of the study patients (n=101).

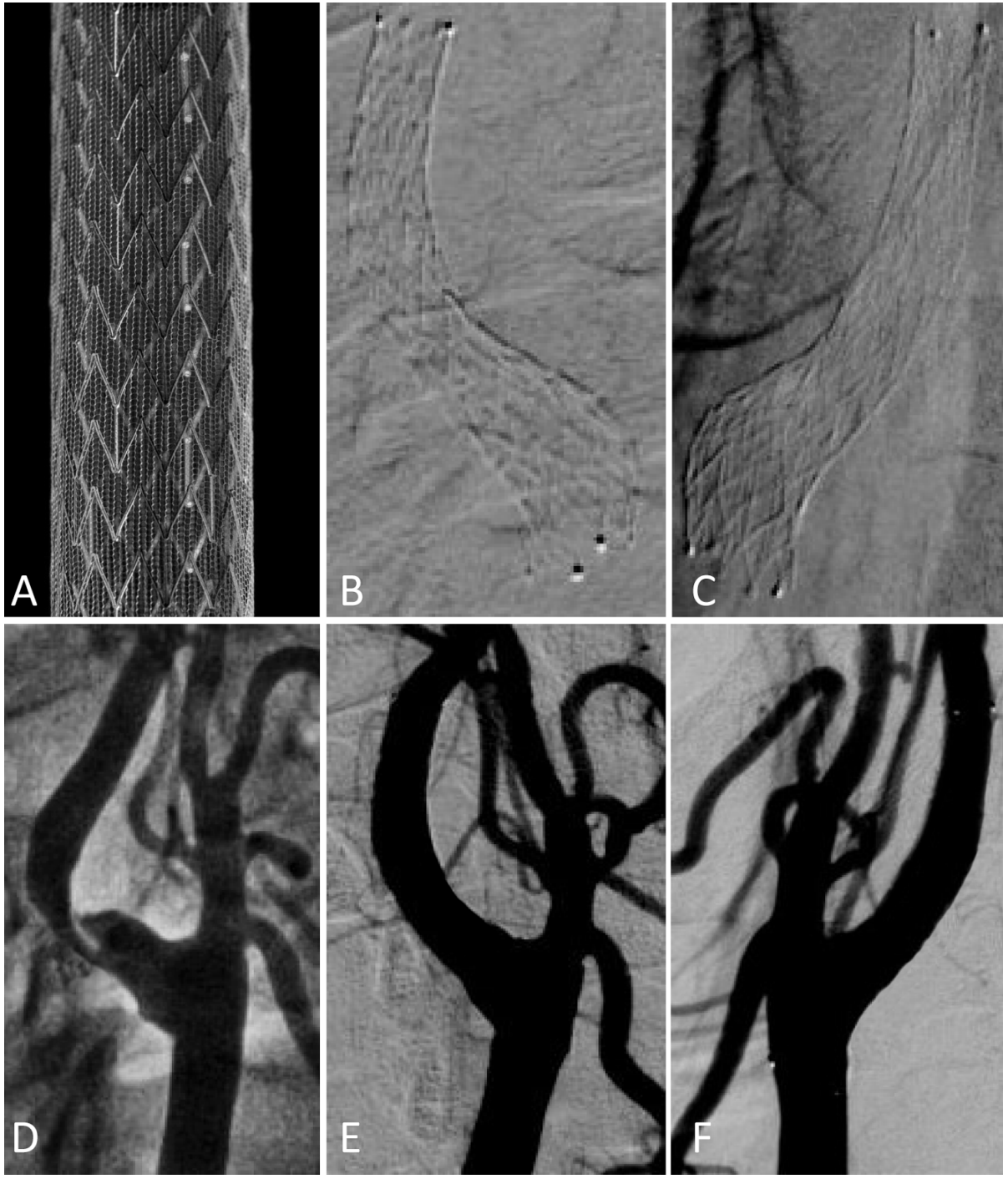
Age, mean±SD (min-max)	69±7 (51-86)
Male, % (n)	70% (71)
Symptomatic, % (n)	55% (55)
Symptomatic ≤14 days, % (n)	22%* (12)
Acutely symptomatic (emergent CAS), % (n)	14%* (9)
Index lesion (CAS), % (n)	
RICA	51% (52)
LICA	49% (49)
RICA+LICA	5% (5)
CAD, % (n)	63% (64)
h/o MI, % (n)	32% (32)
CABG or PCI in the past, % (n)	40% (40)
PCI as bridge to CAS, % (n)	18% (18**)
AFib (h/o or chronic), % (n)	9% (9)
Diabetes, % (n)	41% (41)
h/o neck or chest radiotherapy, % (n)	6% (6)

*proportion of symptomatic patients; **simultaneous (one-stage) PCI+CAS in 4 patients; h/o: history of

PCR EAPCI EUROPEAN SOCIETY OF CARDIOLOGY EACTS

euro PCR 2016 LATE BREAKING TRIALS

PARADIGM



CAROTID PARADIGM REVASCULARIZATION

PCR EAPCI EUROPEAN SOCIETY OF CARDIOLOGY EACTS

euro PCR 2016 LATE BREAKING TRIALS

PARADIGM

CAROTID PARADIGM REVASCULARIZATION

Table 2. Quantitative lesion characteristics (n=106), NPD type, and CGuard MN-EPS in situ characteristics.

	All (n=106 lesions)	Symptomatic n=55	Asymptomatic n=51	*p*-value
Before CAS				
PSV, m/s	3.7±1.2	3.7±1.1	3.7±1.2	0.964
EDV, m/s	1.2±0.5	1.1±0.5	1.2±0.5	0.268
Diameter stenosis % (QA)	83±9	80±9	86±9	0.002
CAS				
EPD type				
Proximal #	46% (49)	56% (31)	35% (18)	0.030
Distal *	54% (57)	44% (24)	65% (33)	

ICA reference diameter
4.99 ± 0.36mm (from 4.27 to 6.02 mm)

Lesion length
19.9 ± 5.8mm (from 8.19 to 30.25 mm)

* **Emboshield** (n=11); **FilterWire** (n=15); **Spider** (n=31)
\# **Gore FlowReversal** (n=6) or flow reversal with **MoMa** (n=43);
(mean flow reversal time was 6min 35s, from 3min 51s to 11min 2s)

Direct (primary) stenting in 9 (8.5%); predilatation in 97 (91.5%) lesions
Postdil. balloon: ø 4.5mm (n=9); ø 5.0mm (n=55); ø 5.5mm (n=37); ø 6.0mm (n=5)

PARADIGM

Table 2. (cont'd) **CGuard MN-EPS in situ characteristics.**

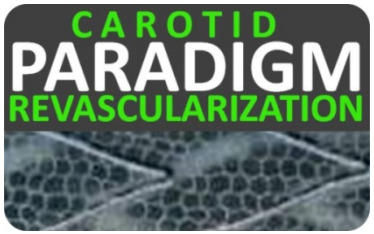
	All (n=106 lesions)	Symptomatic n=55	Asymptomatic n=51	*p*-value
After CAS				
Stent length (QA, CoreLab)[§]				N/A
Nominal 30 mm	29.82±0.68	29.83±0.76	29.80±0.59	
(min-max)	(27.83-32.62)	(27.83-32.62)	(28.83-31.89)	
Nominal 40 mm	39.89±0.59	39.80±0.70	39.97±0.51	
(min-max)	(38.88-41.43)	(38.88-41.43)	(39.14-41.01)	
Residual diameter stenosis	6.7±5%	6.1±5%	7.8±5%	0.262
In-stent PSV, m/s	0.68±0.29	0.64±0.26	0.72±0.31	0.121
in-stent EDV, m/s	0.18±0.08	0.16±0.07	0.19±0.08	0.087

[§]In three cases two overlapping stents were used to cover the whole lesion length; these are not included in the in situ stent length evaluation. N/A: not applicable

=> no foreshortening, no elongation, placement precision

euro PCR 2016 LATE BREAKING TRIALS

PARADIGM



- **CAS feasibility using the study-tested MicroNet-covered embolic prevention stent system** **100% CAS** (n= 106)

(ie, no cross-over to other stents or other carotid stent use during the whole study period)

- **Device success** **99.1%** (n=105)*
- **Procedure success** **99.1%** (n=105)*
- **Transient dopamine infusion** **15.1%** (n = 16)
- **Debris in EPD** **17.9%** (n = 19)
- **Vascular plug closure** **53.8%** (n = 57)
- **Access site complications** **0%** (n = 0)

* in 1 case no stent post-dilatation was performed due to profound bradycardia-asystole, and 46% residual diameter stenosis was left (ie, above the Protocol-defined threshold <30% DS for "device success")

ECA patency data

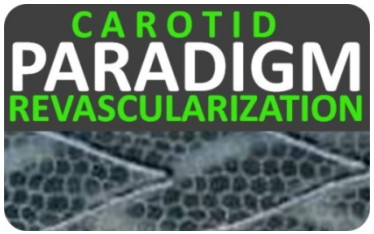
6/106 (5.6%) ECAs were occluded on the index side prior to CAS
3/100 (3.0%), with severe stenosis prior to CAS, occluded at CAS
NO ECA occlusion occurred between CAS and 30 days

=> no concern

30-day neurological, duplex, and cardiologic follow up was executed in 100% patients (101) and arteries (106)

euro PCR 2016 LATE BREAKING TRIALS

PARADIGM



Clinical Results (MACNE)

- 0 peri-procedural death/major stroke/MI 0%
- 1 peri-procedural minor stroke* 0.9%
- 0 new clinical events by 30 days 0%

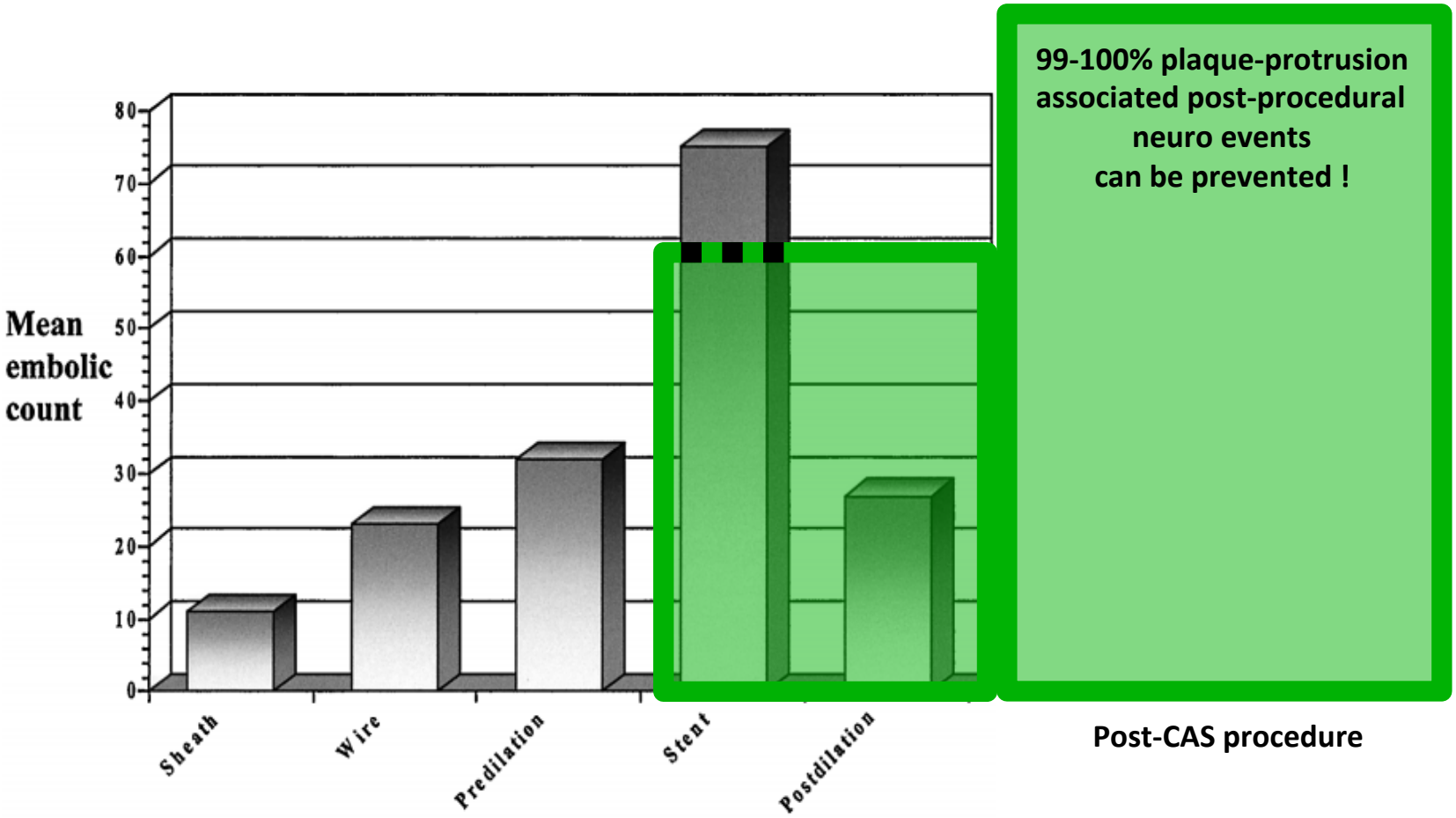
(100% follow-up, independent neuro evaluation)

*One patient, with symptomatic RICA stenosis (minor right-hemispheric stroke 2 months prior to CAS), had **hypotonia** and transient, fluctuating cognitive dysfunction at 24-48h after CAS. The patient had additional neurologic evaluation on discharge (day 7) that showed **no change in NIH-SS [3] and no change in modified Rankin scale [1] against 48h (and baseline) evaluation**.
CT scan on day 2 showed no new cerebral lesions but day 6 CT indicated **an extension of the prior lesion in the right hemisphere**.
The event, in **absence of right haemispheric symptoms and in absence of any clinical sequelae**, was CEC–adjudicated as 'minor stroke in relation to CAS'.

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

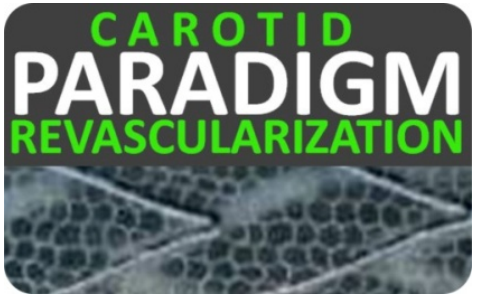


Circulation. 2001;104:1999-2002

amenable to elimination with MicroNet

euro PCR 2016 LATE BREAKING TRIALS

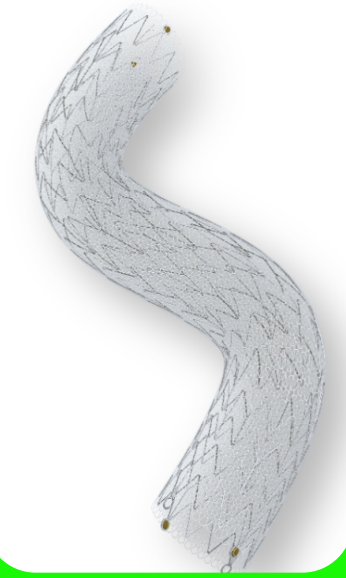
PARADIGM Strengths

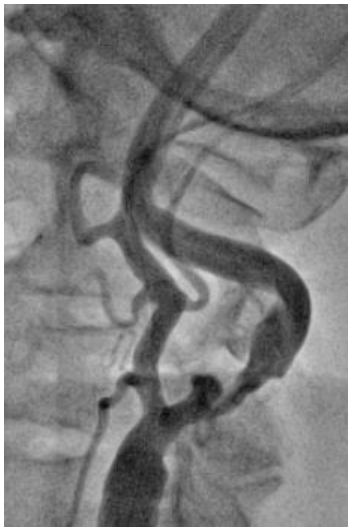


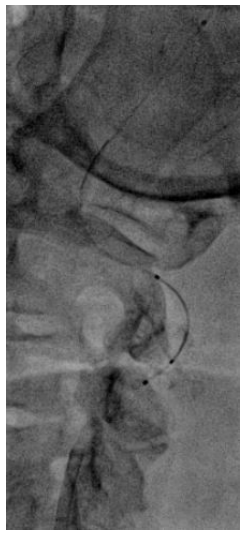
- No exclusion criteria (all-comer, consecutive, incl. stroke-inevolution)
- Asymptomatics revascularised only if at stroke risk
- NeuroVascular Team decision-making
- Independent neurologist evaluation
- 100% follow-up
- Independent source data verification (SDV) / monitoring
- Independent angiographic analysis
- Independent statistical analysis
- External adjudication of clinical events (CEC)

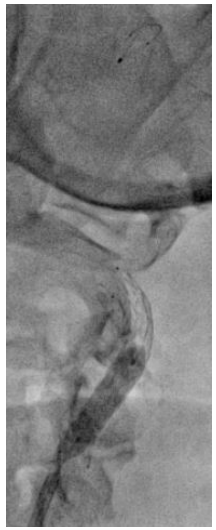
• Real-life study • Controlled study

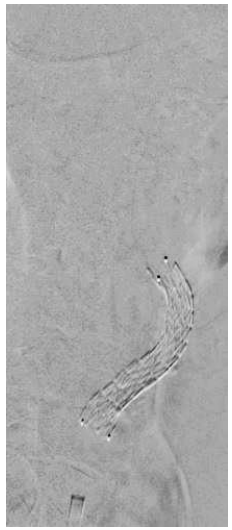
Endovascular Solution for All-Comers

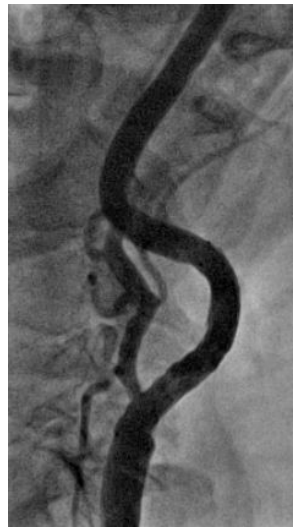


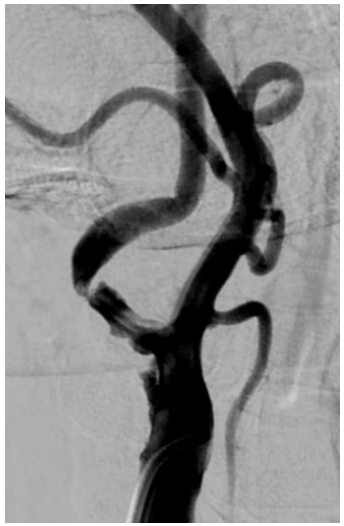


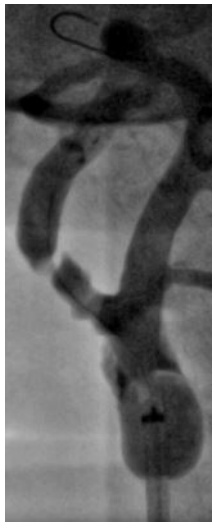


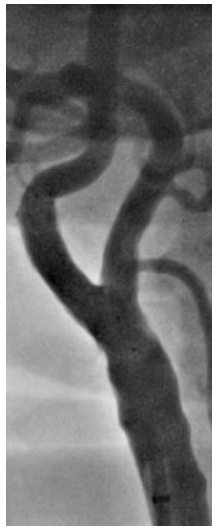


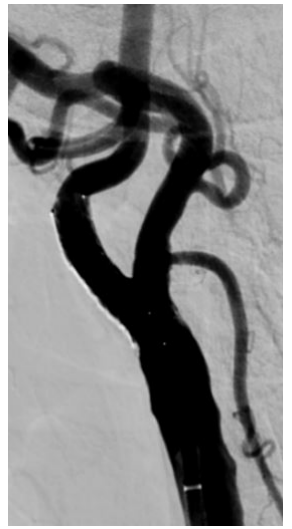












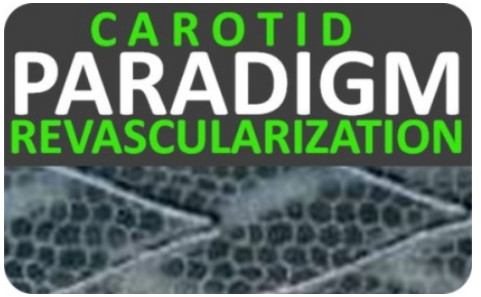
Endovascular Reconstruction of the Carotid Bifurcation

Prevention of embolism, High radial force, Conformability

P. Musialek @ ePCR 2016

euro PCR 2016 LATE BREAKING TRIALS

PARADIGM Conclusion

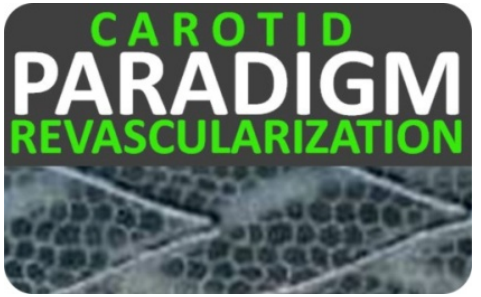


Using the MicroNet-covered carotid stent technology, **ROUTINE ENDOVASCULAR** carotid stenosis revascularization is

- **safe**
- **fully compatible with routine CAS**, including all NPD types
- **effective**
- can be used to treat >90% **all-comers: symptomatics** (incl. stroke-in-evolution) **and** revascularization-requiring **asymptomatics**
- **CEA-like effect**: endovascular reconstruction of diseased carotid segment

euro PCR 2016 LATE BREAKING TRIALS

Impact on clinical practice



Using the **MicroNet-covered CGuard stent system** technology,

ENDOVASCULAR carotid stenosis management in **PRIMARY and SECONDARY Stroke Prevention** is

- **Viable** √
- **Safe and effective** √
- Applicable to **>90%** of all-comer patients √
- Applicable to **routine clinical practice of CAS** √

CGuard Embolic-Prevention human OCT Stent Image in situ / in vivo
Courtesy Dr Juan Rigla, MD PhD Perceptual Imaging Lab, Univerity of Barcelona

P. Musialek @ ePCR 2016

EuroIntervention 2016;12-online publish-ahead-of-print May 2016

euro PCR 2016 LATE BREAKING TRIALS

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

Piotr Musialek[1]*, MD, DPhil; Adam Mazurek[1], MD; Mariusz Trystula[2], MD, PhD; Anna Borratynska[3], MD, PhD; Agata Lesniak-Sobelga[1], MD, PhD; Malgorzata Urbanczyk[4], MD; R. Pawel Banys[4], MSc; Andrzej Brzychczy[2], MD, PhD; Wojciech Zajdel[5], MD, PhD; Lukasz Partyka[6], MD, PhD; Krzysztof Zmudka[5], MD, PhD; Piotr Podolec[1], MD, PhD

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