ESC 2019 ***Rapid Fire Session***

New data in carotid disease: From understanding the pathology to management

PARADIGM-Extend Prospective Academic Trial:

Accumulating long-term evidence for MicroNet-covered stent safety and stroke prevention efficacy

P. Musialek, A. Mazurek, M. Trystuła, A. Borratynska, T. Tomaszewski, A. Lesniak-Sobelga, M. Brozda, U. Gancarczyk, E. Sobieraj, N. Dluzniewska, M. Urbanczyk, P. Banys, J. Miszczuk, P. Judzialo, G. Stankiewicz, T. Drazkiewicz, P. Podolec

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Supported K/ZDS/007819 (Jagiellonian University Medical College)

Disclosures

Proctoring/Speaker Bureau/Advisory Boards - Abbott, InspireMD, Medtronic

Research Support - Abbott (IIS)

Research work in this presentation is supported by the Jagiellonian University Medical College (K/ZDS/007819)

PARADIGM-Extend = **P**rospective evaluation of **A**ll-comer pe**R**cutaneous c**A**roti**D** revascularization in symptomatic and **I**ncreased-stroke-risk asymptomatic carotid artery stenosis using C**G**uard™ **M**icronet-covered embolic prevention stent system – clinical trial multi-centre extension

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

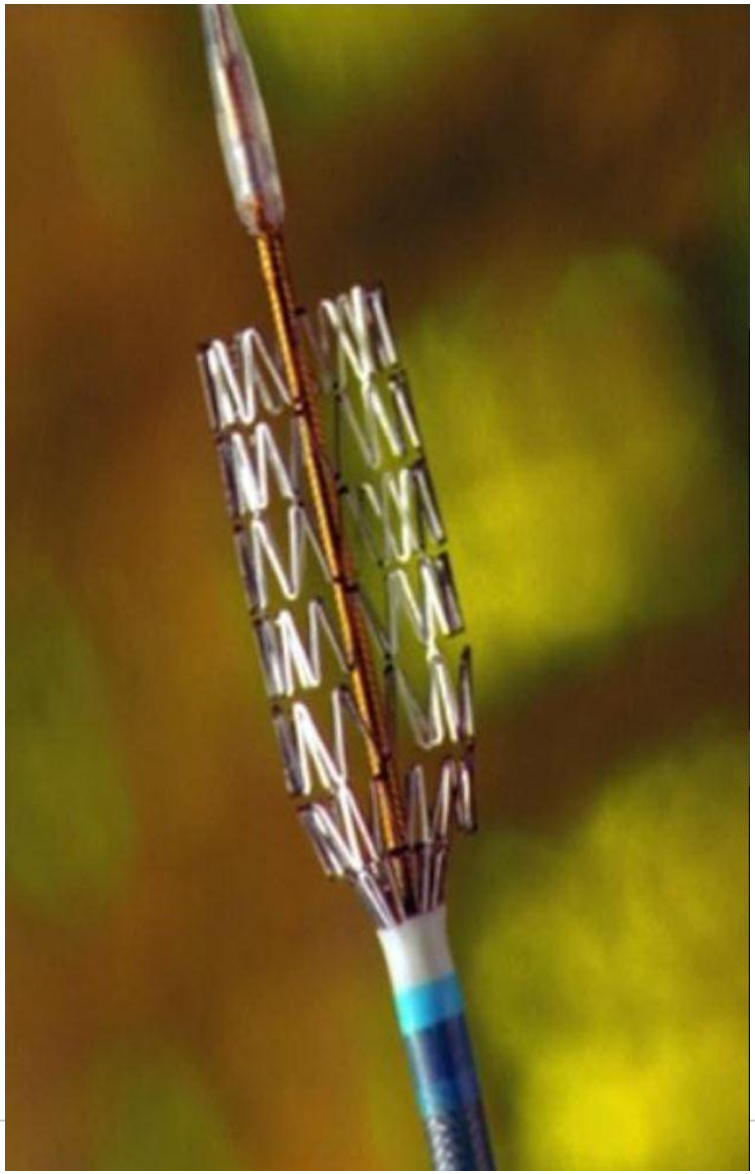
CLINICAL RESEARCH

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

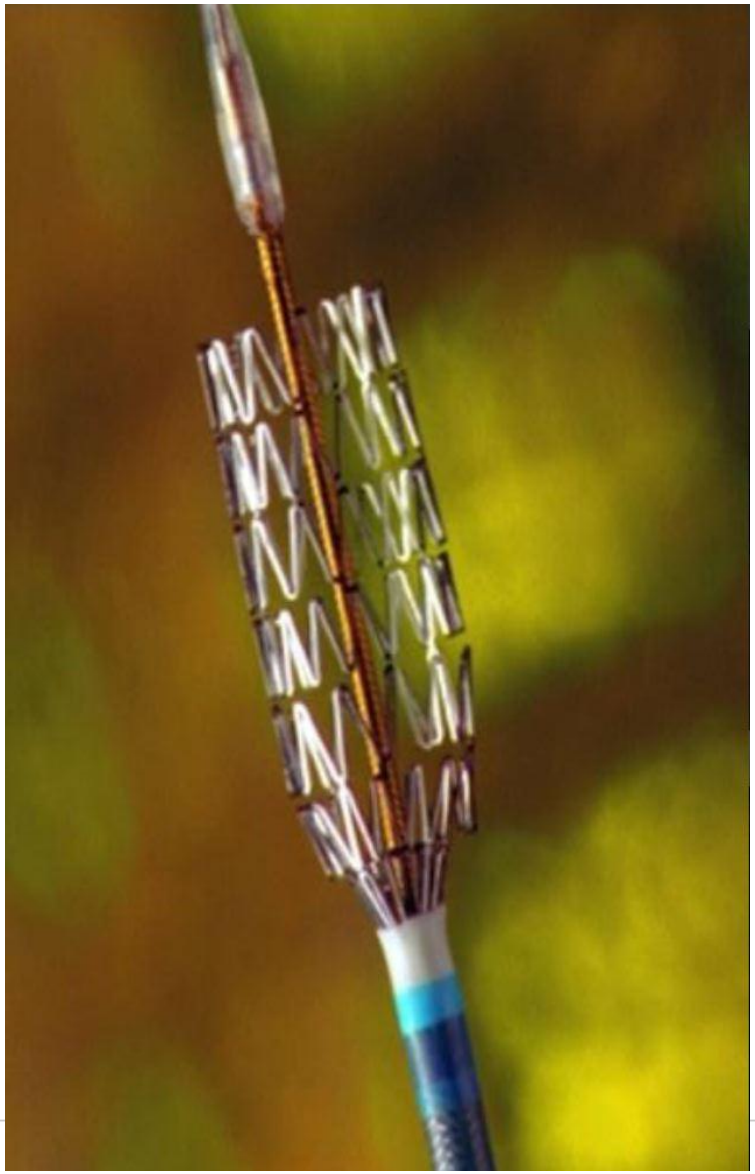
Piotr Musialek[1]*, MD, DPhil; Adam Mazurek[1], MD; Mariusz Trystula[2], MD, PhD; Anna Borratynska[3], MD, PhD; Agata Lesniak-Sobelga[1], MD, PhD; Malgorzata Urbanczyk[4], MD; R. Pawel Banys[4], MSc; Andrzej Brzychczy[2], MD, PhD; Wojciech Zajdel[5], MD, PhD; Lukasz Partyka[6], MD, PhD; Krzysztof Zmudka[5],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

Conventional Carotid Stents



Conventional Carotid Stents

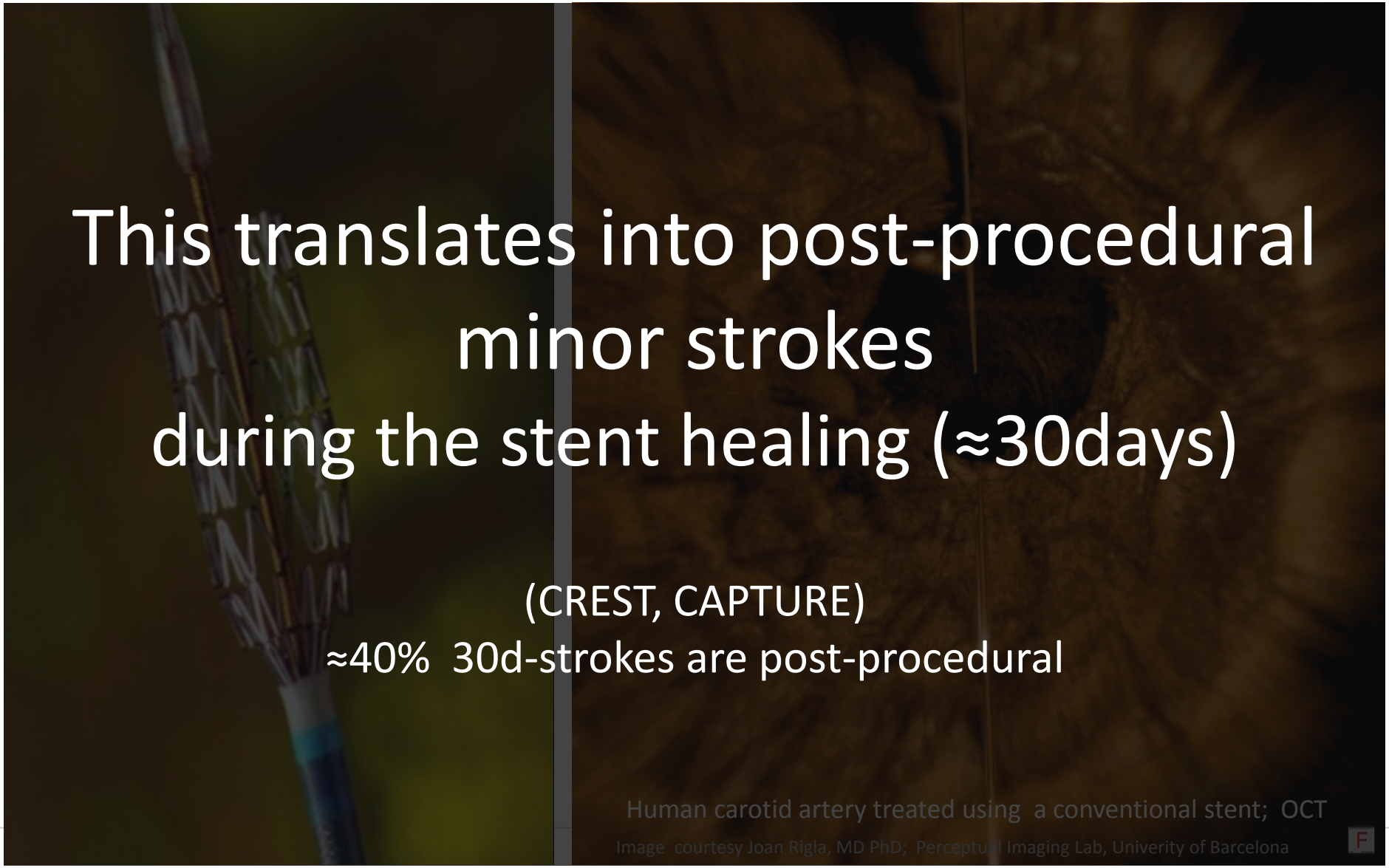
Do Have A Problem



Human carotid artery treated using a conventional stent; OCT

Image courtesy Joan Rigla, MD PhD; Perceptual Imaging Lab, Univerity of Barcelona

Conventional Carotid Stents
Do Have A Problem



This translates into post-procedural minor strokes during the stent healing (≈30days)

(CREST, CAPTURE)
≈40% 30d-strokes are post-procedural

Human carotid artery treated using a conventional stent; OCT

Image courtesy Joan Rigla, MD PhD; Perceptual Imaging Lab, Univerity of Barcelona

FUNDAMENTAL

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- CEA, by excluding the plaque, excludes the post-procedural problem of the plaque

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- In CAS, the stent needs to exclude the plaque too

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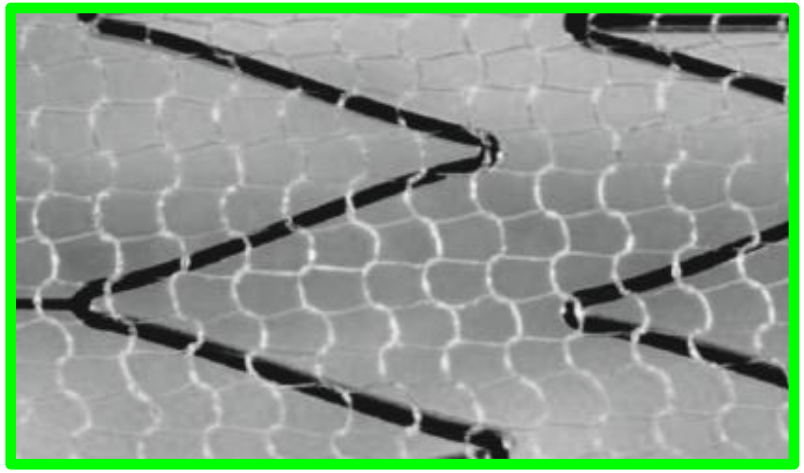
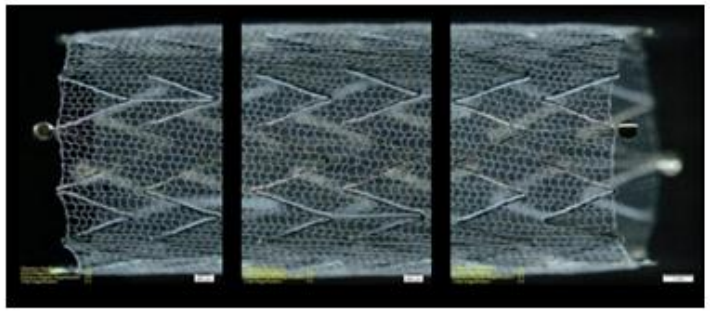


CGuard™– Carotid Embolic Prevention System

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

carotid-dedicated design

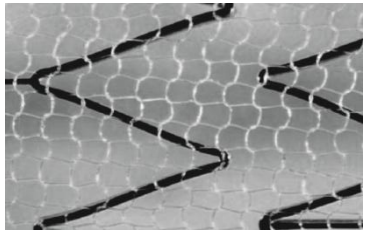


Nitinol frame open-cell area ≈ 21 mm^2

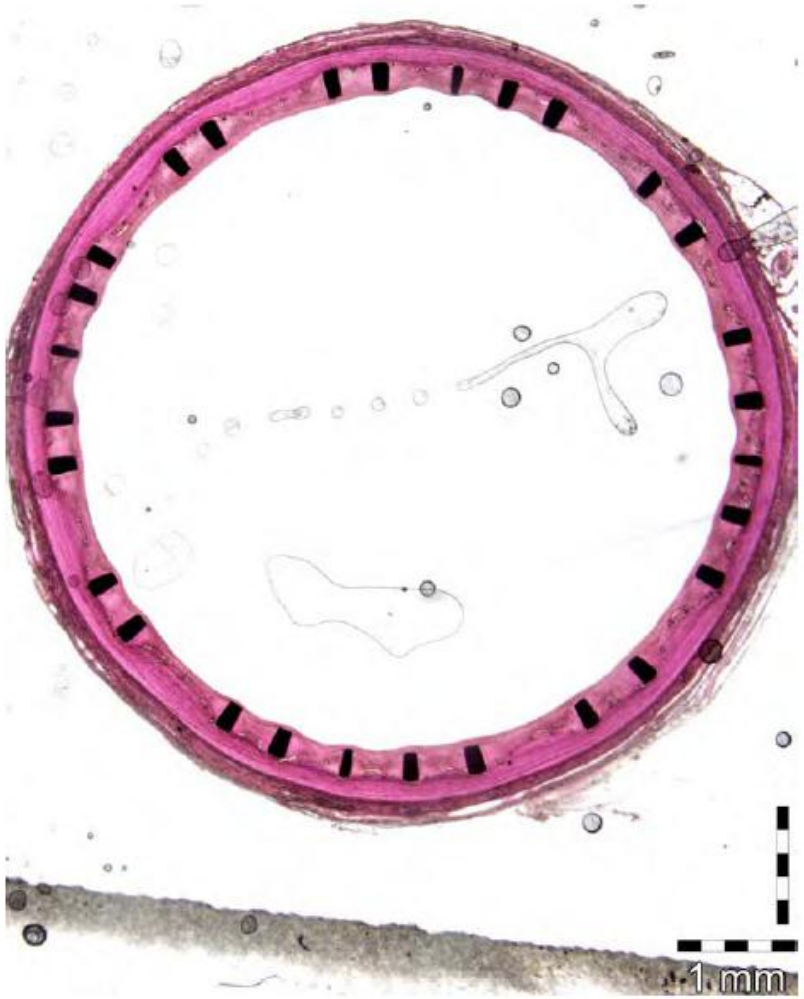
MicroNet closed-cell area ≈ 0.3mm^2

LARGEST √

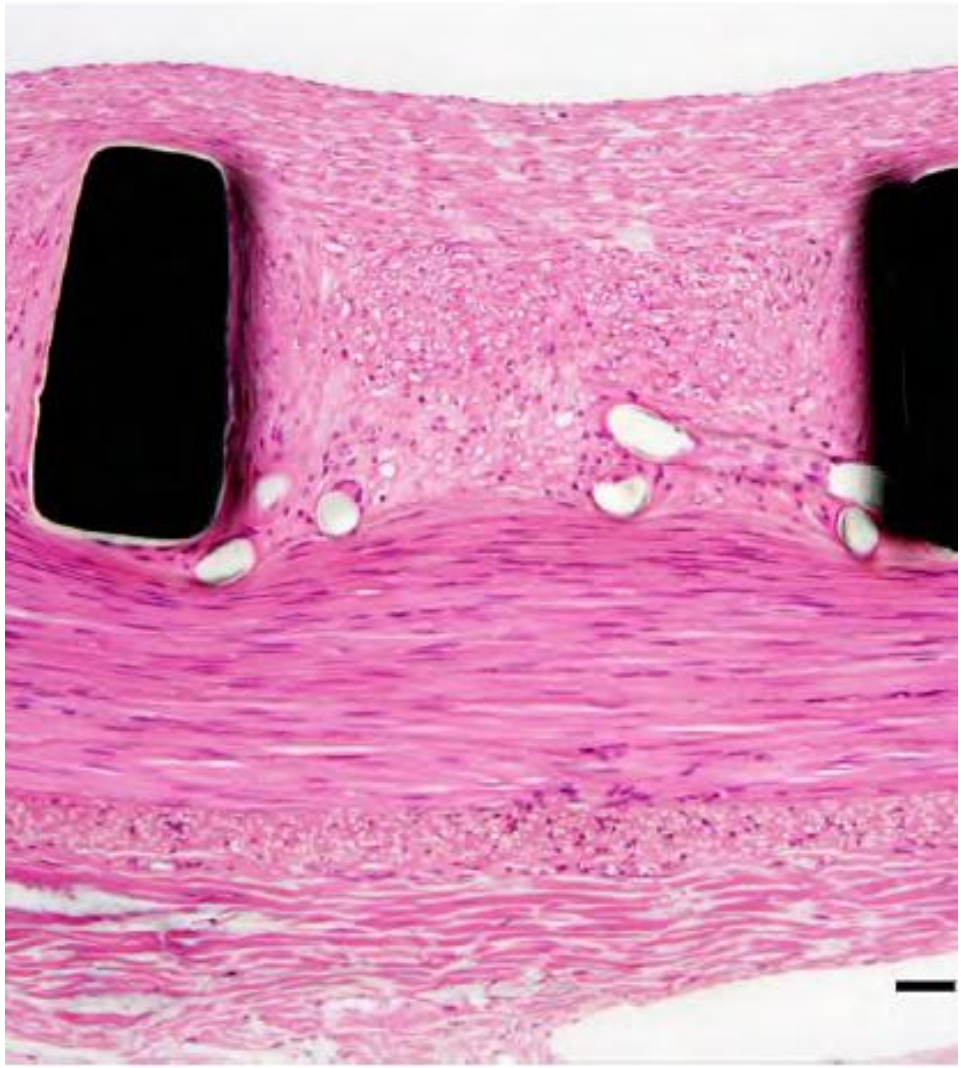
SMALEST √



CGuard EPS 90 days/pig



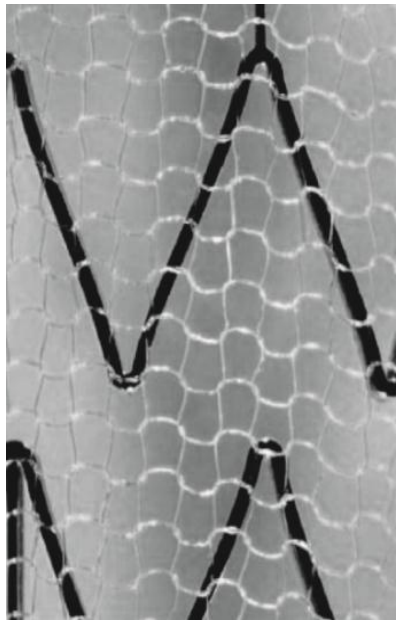
12-105 LCCA-S 3 13-1689-3 1.25x H&E.tif

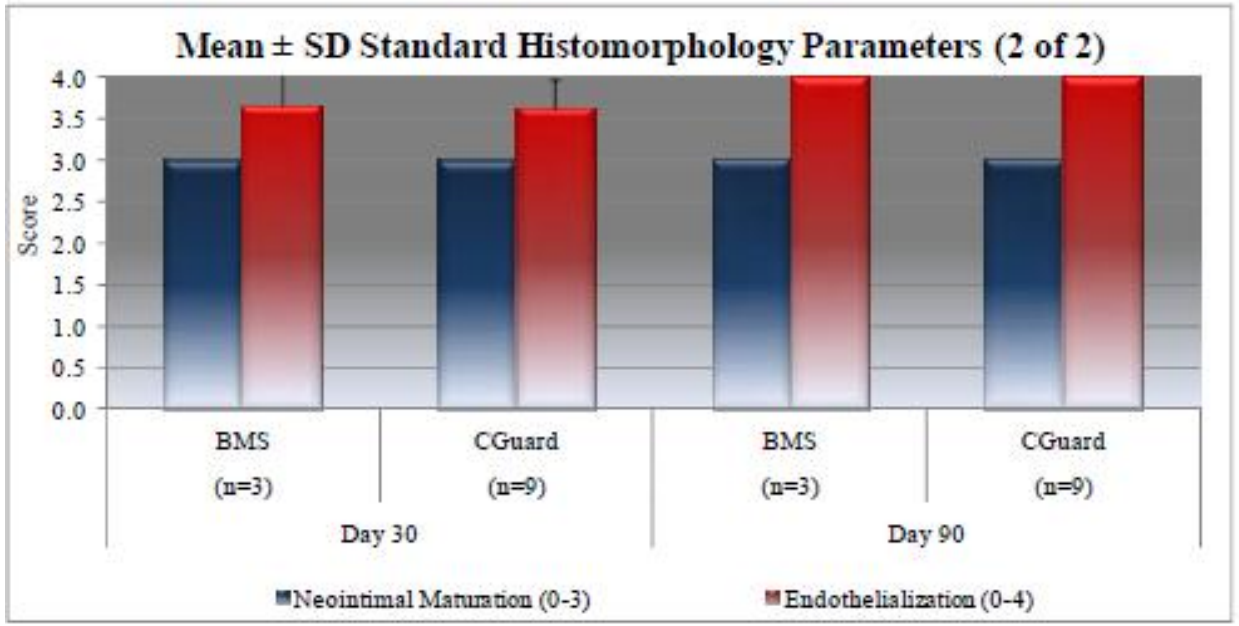


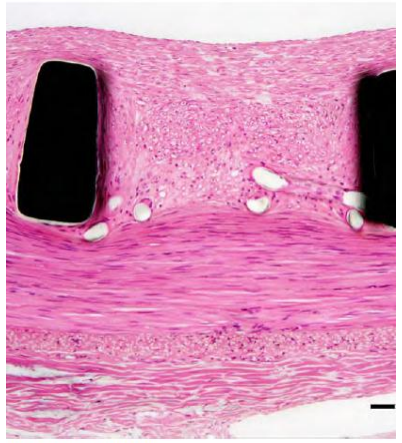
CA-S 3 13-1689-3 10x H&E.tif

InspireMD data / by permission

CGuard EPS 30 & 90 days / pig



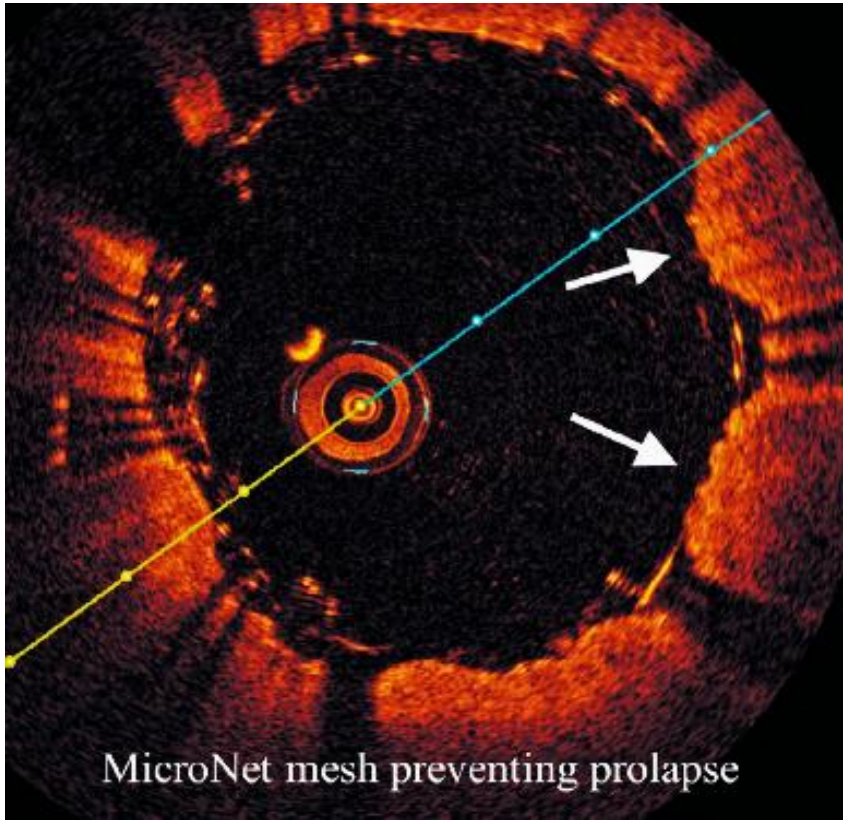




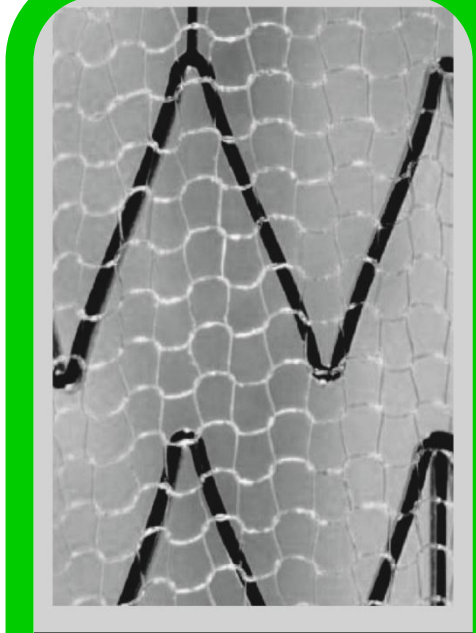
CA-S 3 13-1689-3 10x H&E.tif

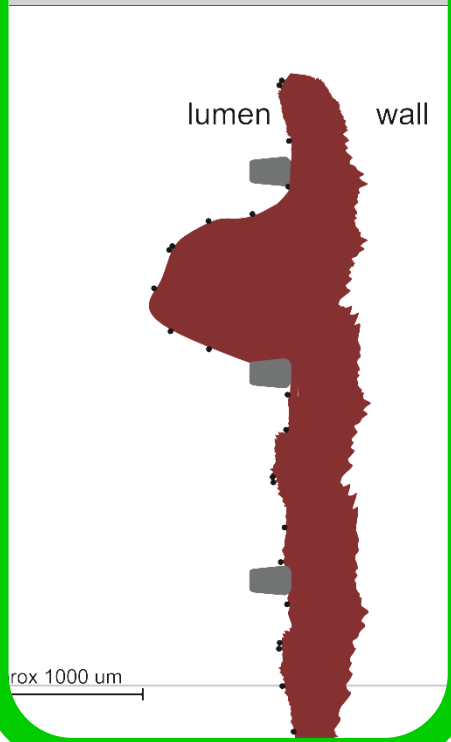
Mean ± SD and Median Standard Histomorphology Parameters								
Parameter	Day 30				Day 90			
	BMS (n=3)		CGuard (n=9)		BMS (n=3)		CGuard (n=9)	
Injury (0-3)	0.00 ± 0.01	0.00	0.00 ± 0.01	0.00	0.01 ± 0.02	0.00	0.00 ± 0.01	0.00
Inflammation (0-3)	0.43 ± 0.23	0.51	0.41 ± 0.22	0.36	0.17 ± 0.16	0.11	0.09 ± 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

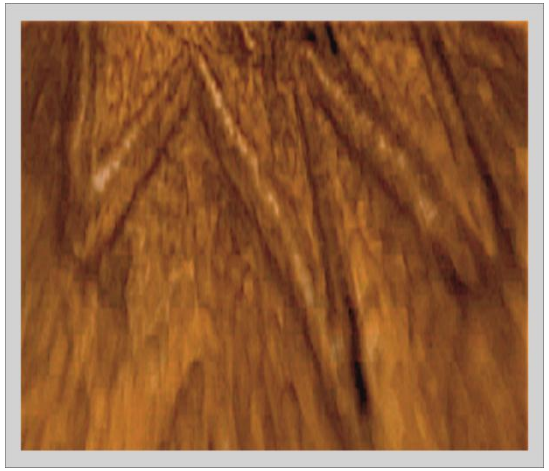
BMS = non mesh-covered CGuard nitynol frame; InspireMD data / used with permission



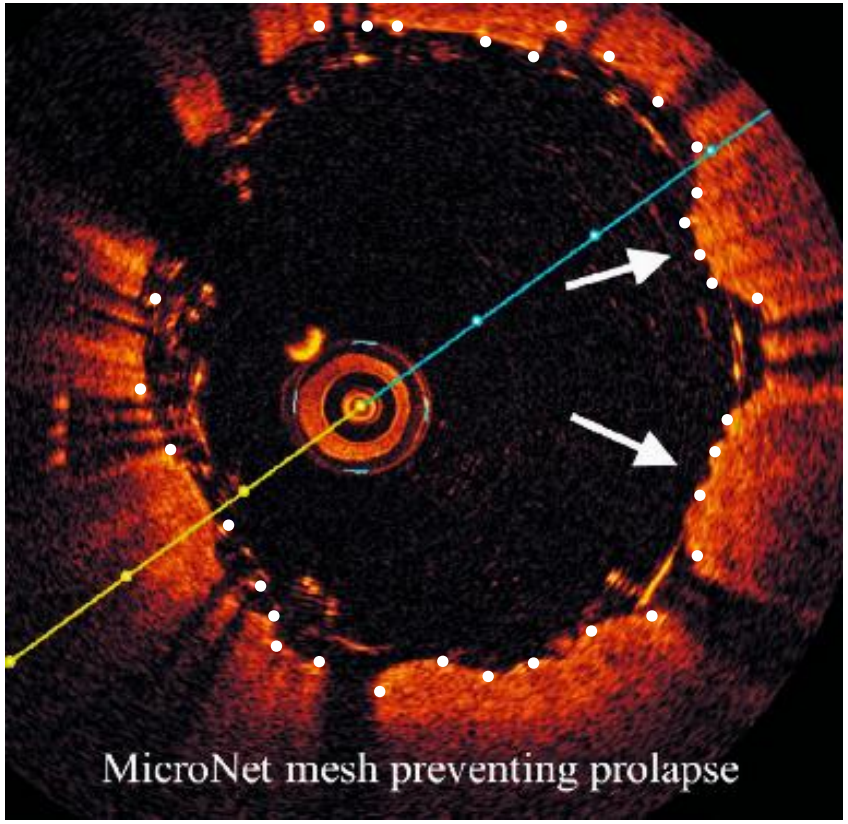
Tomyuki Umemoto et al.
EuroIntervention 2017







Musialek & Stabile
EuroIntervention 2017



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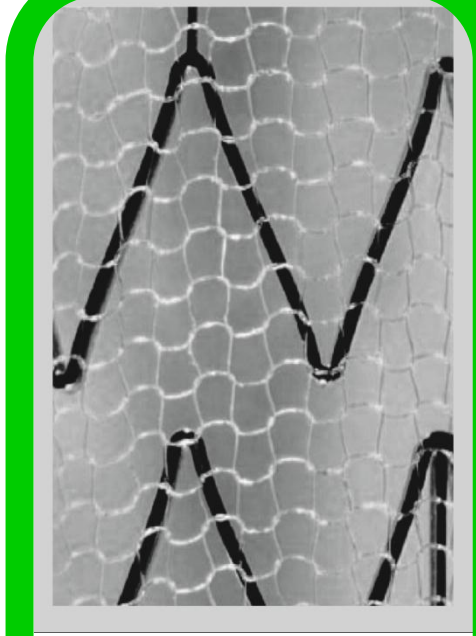
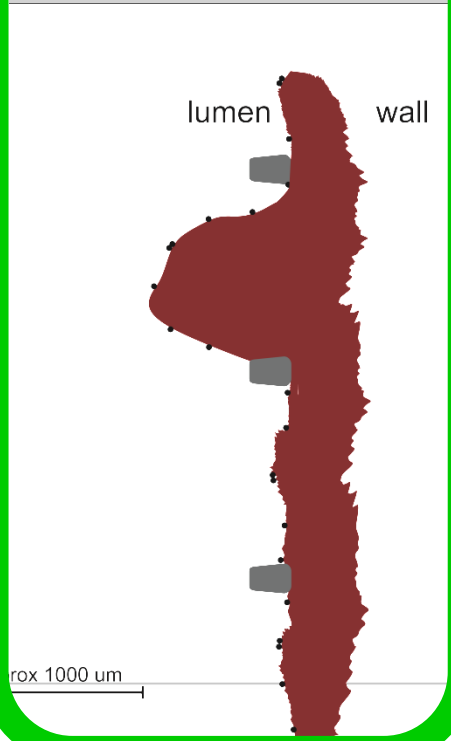
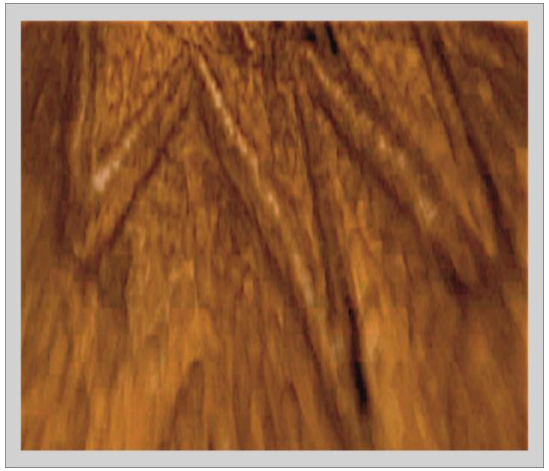






Musialek & Stabile
EuroIntervention 2017

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)

Prospective evaluation of **A**ll-comer pe**R**cutaneous c**A**roti**D** revascularization in sympto-matic and **I**ncreased-risk asymptomatic carotid artery stenosis using the C**G**uard™ **M**icronet-covered embolic prevention stent system

The PARADIGM Study

euro PCR 2016 LATE BREAKING TRIALS

PARADIGM study: referrals flow chart

139 carotid stenosis patient referrals

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.)

P. Musialek, A. Mazurek et al. *EuroIntervention* 2016;12:e658-70

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

euro PCR 2016 LATE BREAKING TRIALS

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.

P. Musialek, A. Mazurek et al. EuroIntervention 2016;12:e658-70
(PARADIGM design and 30-day outcome data)

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

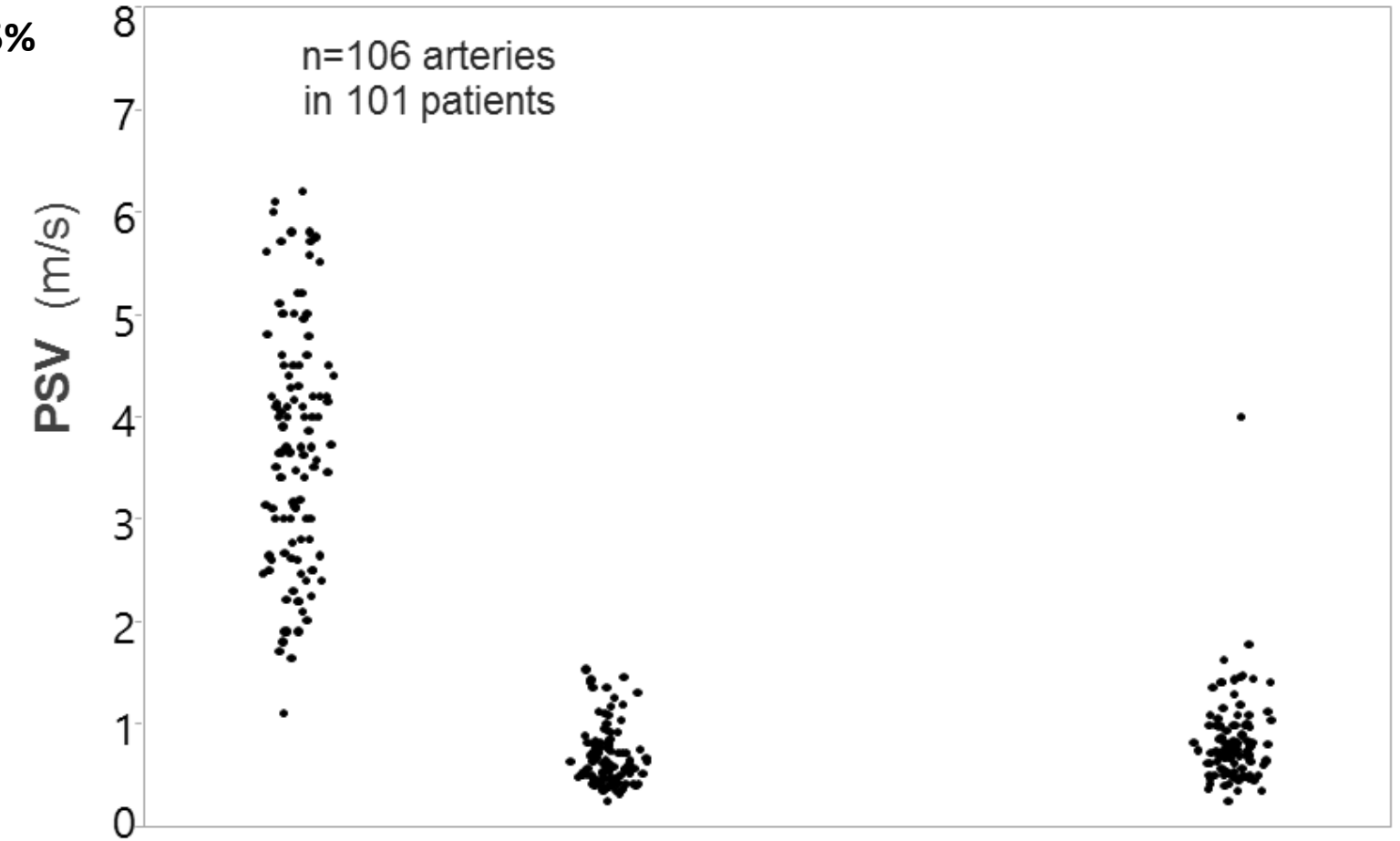
P. Musialek, A. Mazurek et al. *EuroIntervention* 2016;12:e658-70

CGuard™ EPS Carotid **PARADIGM** Study
12mo Duplex Ultrasound Data

CAROTID PARADIGM REVASCULARIZATION

12month data

Symptomatic – 54.5%



ECA* patency

ECA

100/106 ECAs were patent prior to CAS

baseline	30 days	12 months
97.0% 3 ECAs occluded at CAS	**97.0%** 97/100 ECAs patent	**96.9%** 93/96 ECAs patent

PARADIGM – Extend

continues as an ALL-Comer Multi-Centre Study

No exclusion criteria

other than absence of carotid stenosis that requires revascularization by NVT reccomendation

PARADIGM – Extend

continues as an ALL-Comer Multi-Centre Study

31 July 2019

- 402 patients / 436 arteries
  NeuroVascular Team decision-making on endovascular revascularization

PARADIGM – Extend

continues as an ALL-Comer Multi-Centre Study

31 July 2019

- 402 patients / 436 arteries
  NeuroVascular Team decision-making on endovascular revascularization
- Age 48-87 years, 56.4% symptomatic
- Crossed the trial first follow-up window (30d)

PARADIGM – Extend

continues as an ALL-Comer Multi-Centre Study

31 July 2019

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  NeuroVascular Team decision-making on endovascular revascularization
- Age 48-87 years, 56.4% symptomatic
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- 100% CGuardEPS use, Proximal/distal EPD ≈ 50% : 50%

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31 July 2019

- 402 patients / 436 arteries
  NeuroVascular Team decision-making on endovascular revascularization
- Age 48-87 years, 56.4% symptomatic
- Crossed the trial first follow-up window (30d)
- 100% CGuardEPS use, Proximal/distal EPD ≈ 50% : 50%
- Angiographic diameter stenosis was reduced from 84±8% to only 6.9±5% (p<0.001, 'CEA-like' effect of CAS)

PARADIGM – Extend

402 patients / 436 arteries

31 July 2019

- *Peri-procedural outcome*

0 death/major stroke – 0%
1 minor stroke – 0.25%
1 MI (type2) **– 0.25%**

PARADIGM – Extend

402 patients / 436 arteries

31 July 2019

- *Peri-procedural outcome*

  0 death/major stroke – **0%**
  1 minor stroke – 0.25%
  1 MI (type2) **– 0.25%**

- *By 30 days*

  1 haemorrhagic transformation of prior ischaemic cerebral infarct leading to **death – 0.25%**

  1 bleeding-related death – 0.25%

PARADIGM – Extend

402 patients / 436 arteries

31 July 2019

- **Total**

  30-day death/MI/any stroke – **0.995 %** (4/402)

- **no major stroke by 30 days – 0.0 %** (0/402)

PARADIGM – Extend

402 patients / 436 arteries

31 July 2019

- **Total**

  30-day death/MI/any stroke – **0.995 %** (4/402)

- **no major stroke by 30 days – 0.0 %** (0/402)

- *Then clinical (inc. Neurology exam) and Duplex follow-up every 12 months*

PARADIGM – Extend

NB. ALL–Comer, Unselected Population
(eg. AFib 8.9%)

	1-12 mo	13-24 mo	25-36 mo	37-48 mo
	n=311	n=205	n=108	n=61
ipsilateral stroke	0	0	1	1

PARADIGM – Extend

NB. ALL–Comer, Unselected Population
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	1-12 mo	13-24 mo	25-36 mo	37-48 mo
	n=311	n=205	n=108	n=61
ipsilateral stroke	**0**	**0**	**1**	**1**
any stroke	**0**	**2** 1 cerebellal 1 contralat.	**1** brain stem	**2** (1 contralat.)

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	n=311	n=205	n=108	n=61
ipsilateral stroke	0	0	1	1
any stroke	0	2 1 cerebellal 1 contralat.	1 brain stem	2 (1 contralat.)
stroke-related death	0	1	0	1
MI or other non-cerebral VA	3	3	2	2

PARADIGM – Extend

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	n=311	n=205	n=108	n=61
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any stroke	0	2 1 cerebellal 1 contralat.	1 brain stem	2 (1 contralat.)
stroke-related death	0	1	0	1
MI or other non-cerebral VA	3	3	2	2
any death	13 CHF-4, Ca-3, PE-1, MI-2 COPD-1,uroseps -1, surg-1	10 CHF-3, Ca-2, MI-2 surg-2, intrac. bleed-1	6 CHF-2, Ca-2, MI-1 urosepsis -1	4 CHF-2, Ca-2, MI-2

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stroke-related death	**0**	**1**	**0**	**1**
MI or other non-cerebral VA	**3**	**3**	**2**	**2**
any death	**13** CHF-4, Ca-3, PE-1, MI-2 COPD-1,uroseps -1, surg-1	**10** CHF-3, Ca-2, MI-2 surg-2, intrac. bleed-1	**6** CHF-2, Ca-2, MI-1 urosepsis -1	**4** CHF-2, Ca-2, MI-2
in-stent velocities	PSV **0.79**±0.41m/s EDV **0.21**±0.11 m/s	PSV **0.75**±0.36 m/s EDV **0.19**±0.09 m/s	PSV **0.75**±0.36 m/s EDV **0.20**±0.09 m/s	PSV **0.74**±0.28 m/s EDV **0.20**±0.07 m/s

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PARADIGM – Extend

NB. ALL–Comer Unselected Population
(eg. AFib 8.9%)

	1-12 mo	13-24 mo	25-36 mo	37-48 mo
	n=311	n=205	n=108	n=61
ipsilateral stroke	0	0	1	1
any stroke	0	2 1 cerebellum 1 contralat.	1 brainstem	2 (1 contralat.)
stroke-related death	0	1	0	1
MI or other non-cerebral VA	3	3	2	2
any death	15 CHF-4, Ca-3, PE-1, MI-2 COPD-1,uroseps -1, surg-1	10 CHF-3, Ca-2, MI-2 surg-2, intrac. bleed-1	6 CHF-2, Ca-2, MI-1 urosepsis -1	4 CHF-2, Ca-2, MI-2
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By 48 months

Normal healing

No Stent Thrombosis

No abnormal ISR signal

(Per-vessel ISR 0.92% - 4/436; DEB-PTA)

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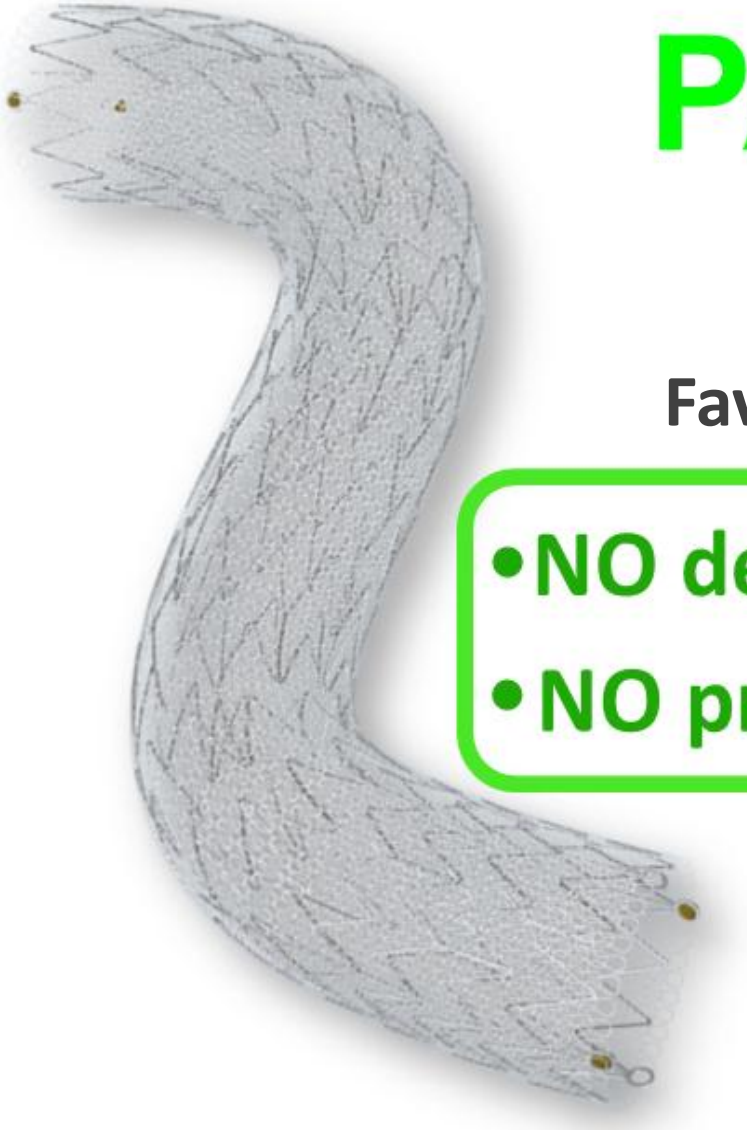
CGUARD™
Carotid Embolic Prevention System



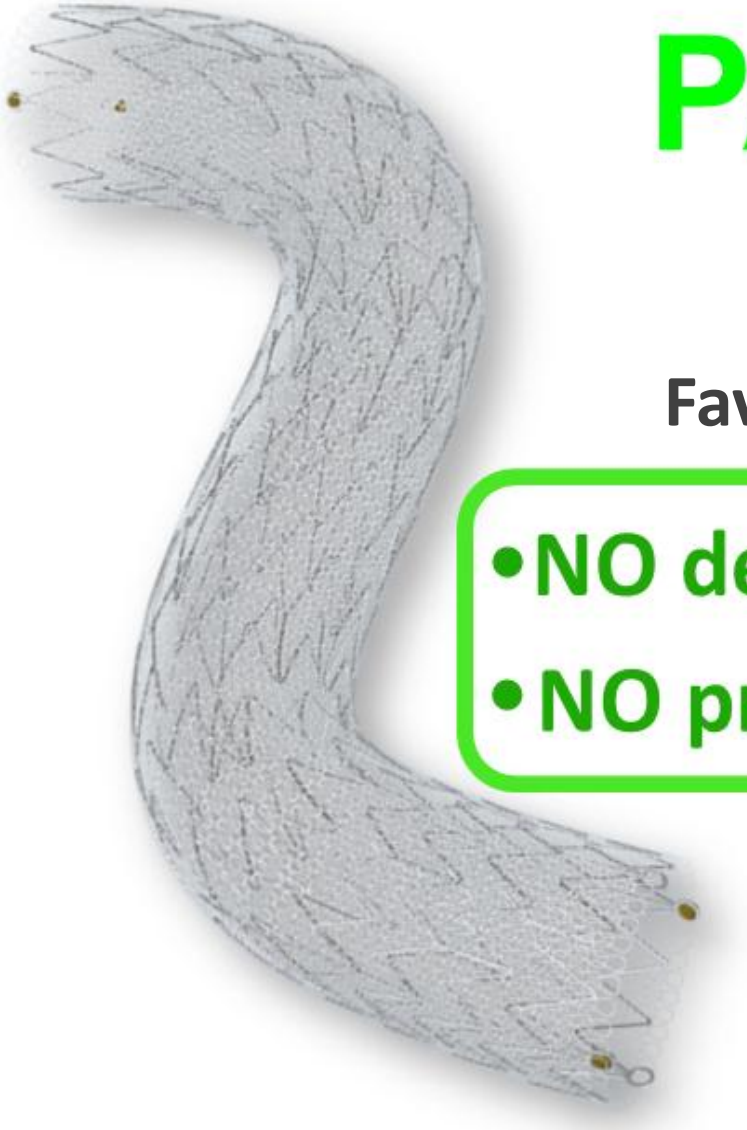
PARADIGM–EXTEND

@ 48 months

Favourable Cerebral Outcome

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

CGUARD™
Carotid Embolic Prevention System



PARADIGM–EXTEND

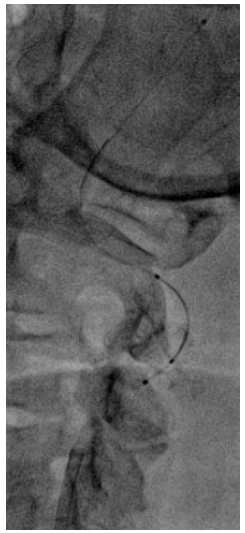
@ 48 months

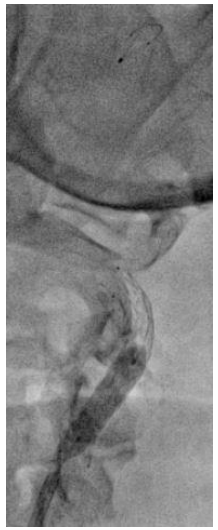
Favourable Cerebral Outcome

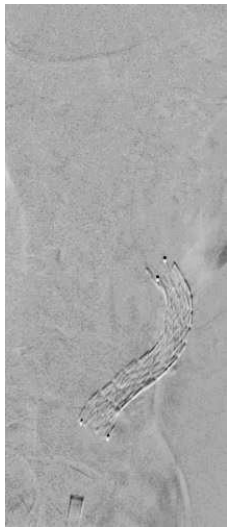
- **NO device-related adverse events**
- **NO procedure-related events**

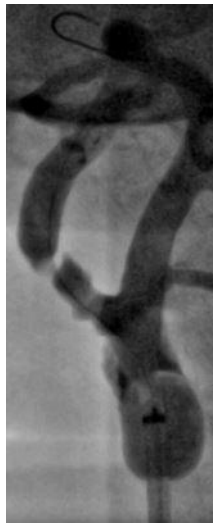
s u s t a i n e d
stroke prevention

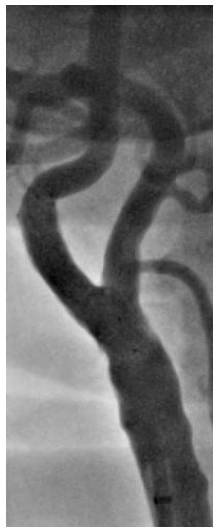
Endovascular Solution for All-Comers







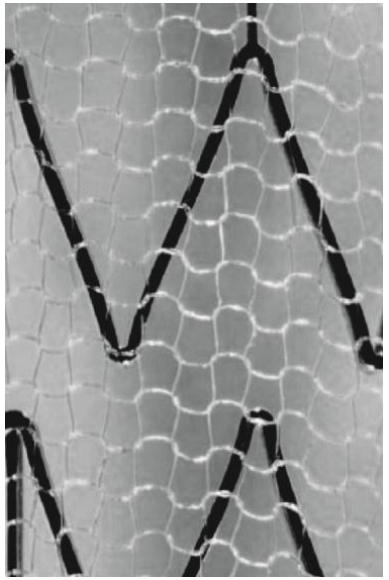




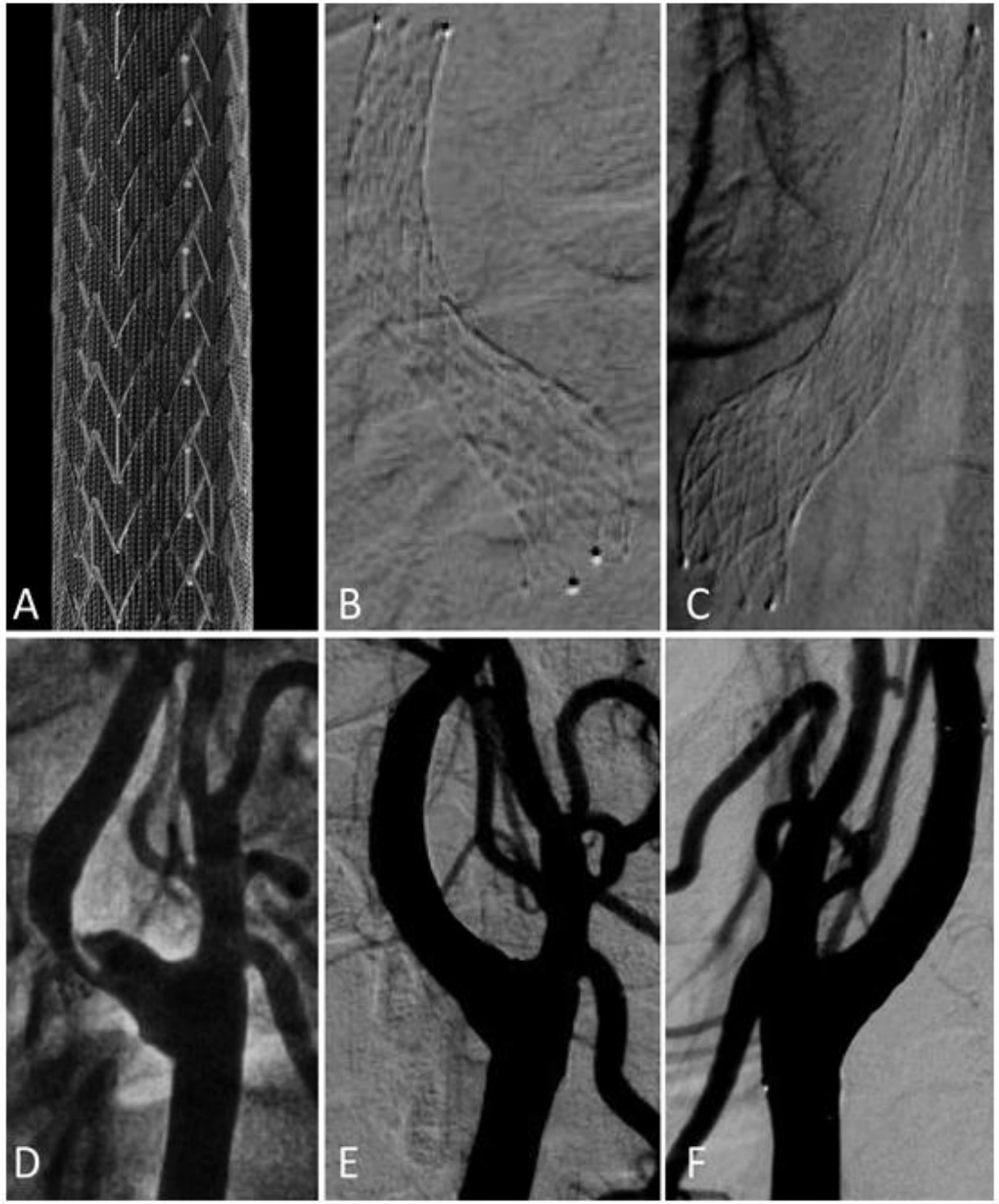
Endovascular Reconstruction of the Carotid Bifurcation

Prevention of embolism, High radial force, Conformability

Human 3D OCT, symptomatic lesion



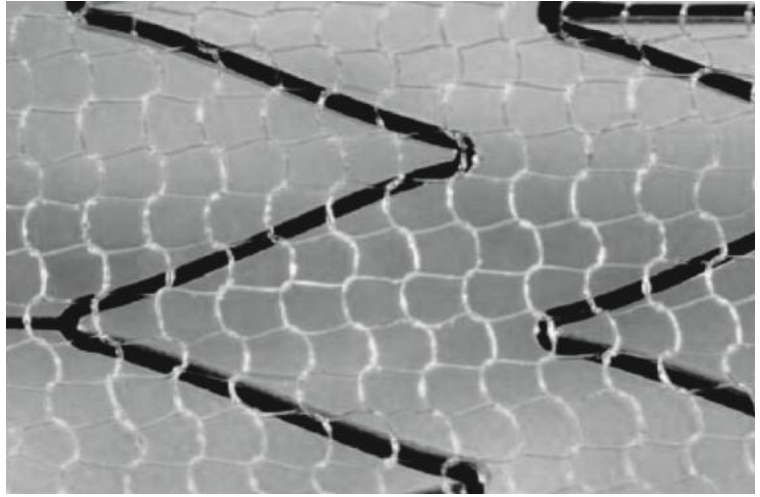
PARADIGM

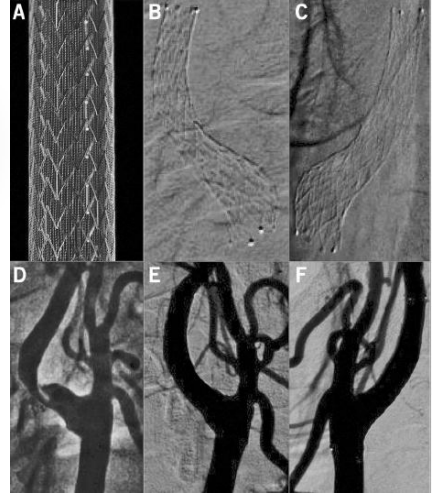


CAROTID PARADIGM REVASCULARIZATION

systematic

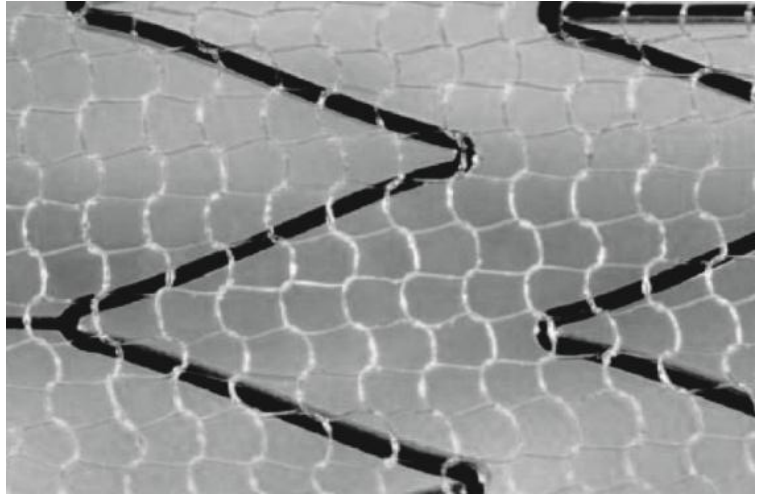
CEA-like effect of CAS

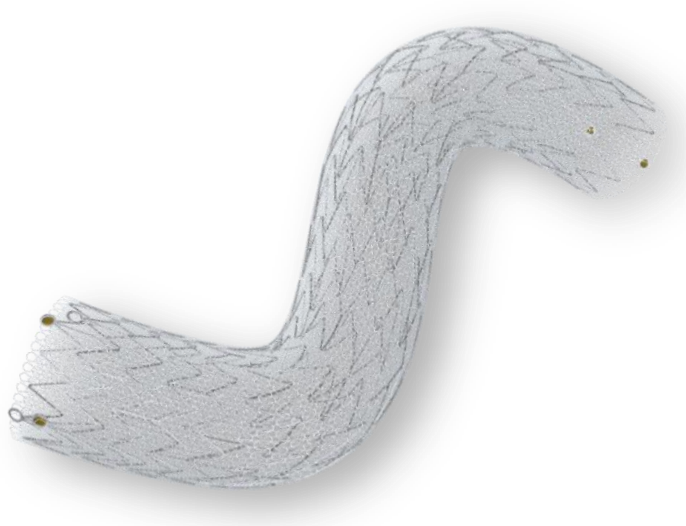


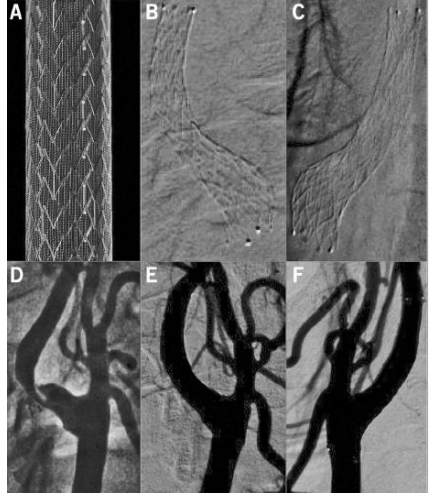


This concept has been desired.

And it works.







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This is the future of Carotid Artery Stenting

Double-Layer Carotid Stents: From the Clinical Need, through a Stent-in-Stent Strategy, to Effective Plaque Isolation… the Journey Toward Safe Carotid Revascularization Using the Endovascular Route

Journal of Endovascular Therapy
2019, Vol. 26(4) 572–577

DOI: 10.1177/1526602819861546
www.jevt.org
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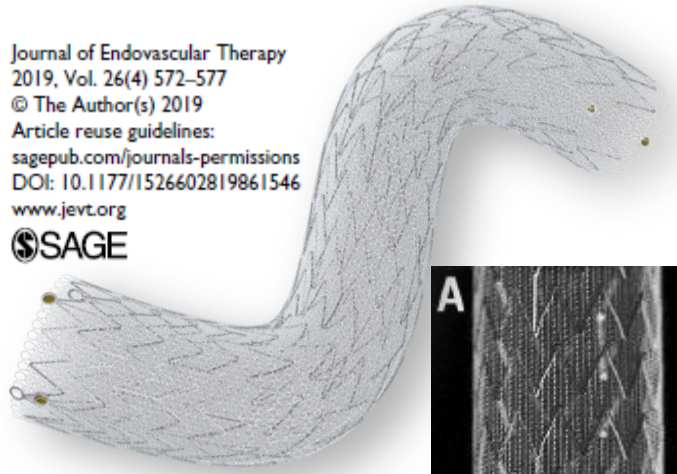

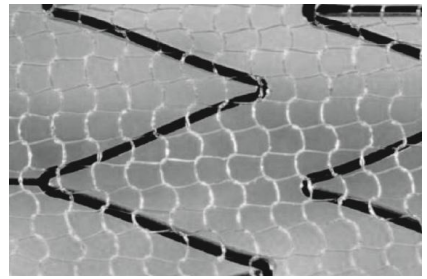

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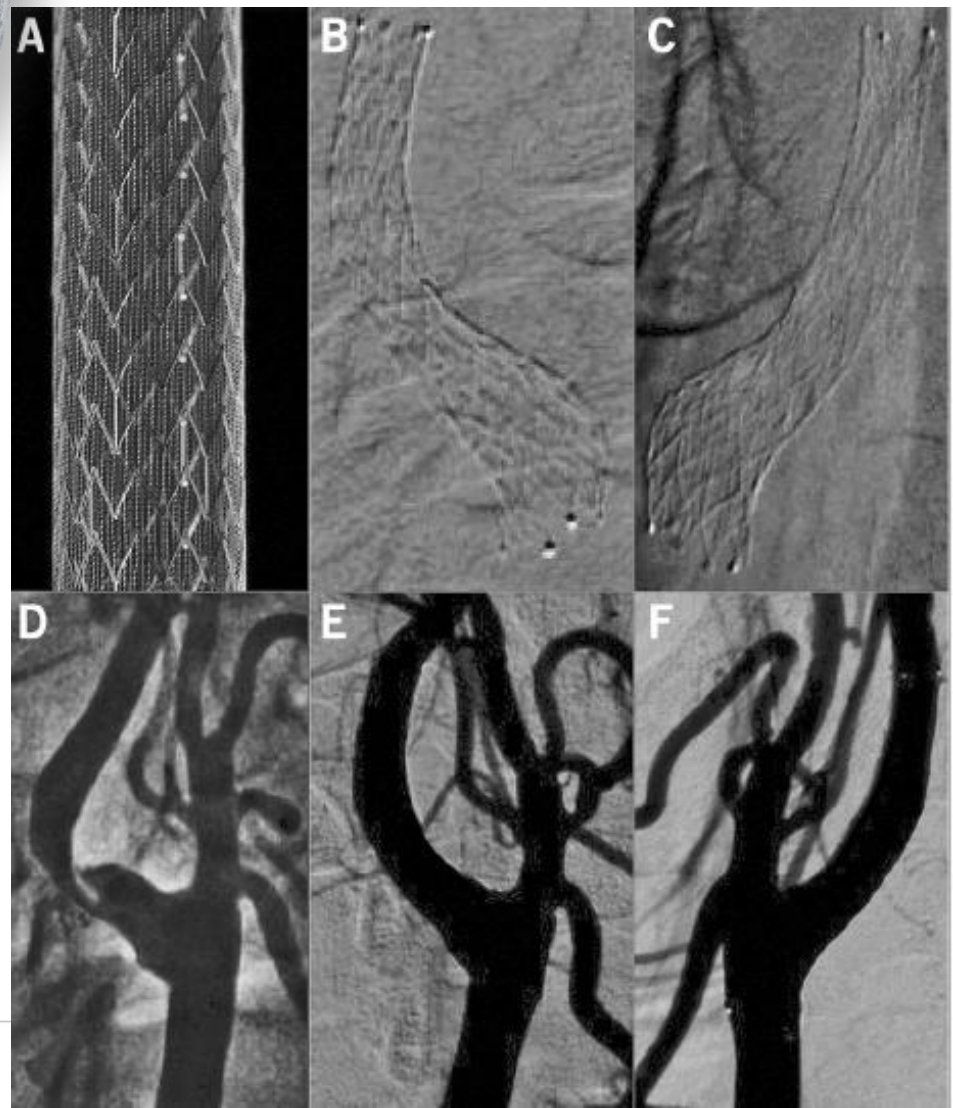
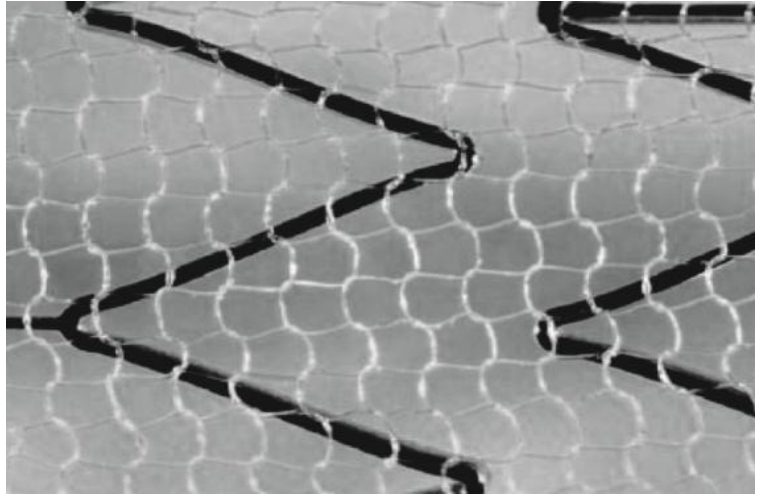
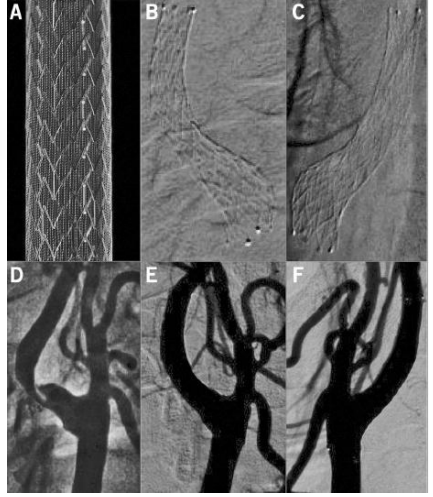
Keywords
carotid artery stenosis, carotid artery stenting, carotid endarterectomy, closed-cell stent, MicroNET, open-cell stent, plaque protrusion, stent-graft, restenosis, double-layer stent, unstable plaque

Both surgical and endovascular routes of carotid revascularization are associated with the risk of symptomatic and asymptomatic cerebral embolism.[1-3] Optimized pharmacotherapy, the mainstay of atherosclerosis management, can reduce or delay but not abolish the risk of stroke from atherosclerotic carotid artery stenosis.[4-7] Interventional elimination or sequestration of the thromboembolic carotid plaque[8-10] remains an important consideration in a significant proportion of patients if carotid stenosis–related strokes are to be prevented rather than experienced. This is the focus and the stent free-cell area also affect the risk of embolism after stent placement. Thus, while optimized neuroprotection during CAS may minimize intraprocedural cerebral embolism,[18-20,23,24] the problem of early or delayed postprocedural embolism remains.[3,25-27] With optimal patient selection technique and antiplatelet therapy, post-stent embolic phenomena are largely related to intrastent plaque prolapse, balloon trauma, and subsequent embolization. This may occur after the period of intraprocedural cerebral protection using flow reversal techniques and/or filters.







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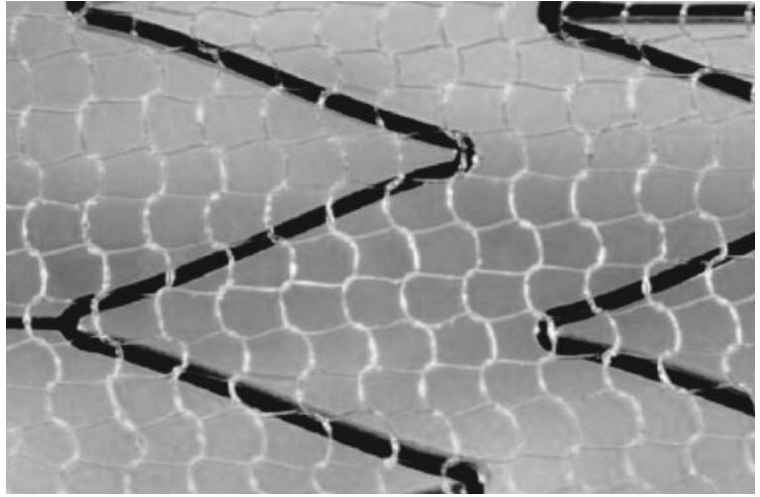
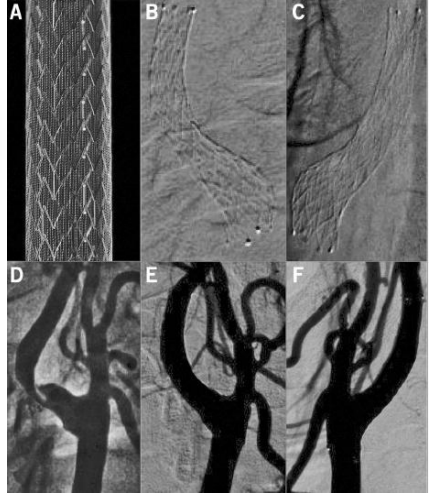
This is the future

of Carotid Artery ~~Stenting~~





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This is the future

of Carotid Artery S[illegible]g

revascularization !