2019
LINC

PARADIGM-EXTEND: Prospective Academic Trial of CGuard™ MicroNET-Covered Self-Expandable Stent System:

Cumulative 3-Year Clinical and Duplex Ultrasound Evidence for Safety, Efficacy and Durability of Stroke Prevention

Piotr Musialek, MD DPhil

on behalf of the PARADIGM-EXTEND Study Team

Jagiellonian University Dept. of Cardiac & Vascular Diseases
John Paul II Hospital, Krakow, Poland

Prospective 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 extension

Disclosure

Speaker name: Piotr Musialek

I have the following potential conflicts of interest to report:

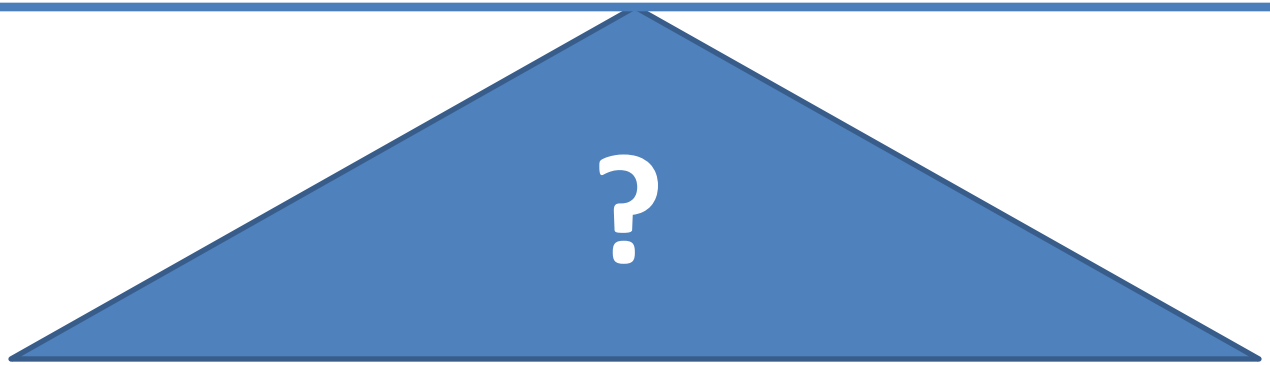
- ☑ Consulting
- ☐ Employment in industry
- ☐ Stockholder of a healthcare company
- ☐ Owner of a healthcare company
- ☐ Other(s)

☐ I do not have any potential conflict of interest

Carotid Stenosis
Decision-making

PHARMACOTHERAPY
+ INTERVENTION

ISOLATED
PHARMACOTHERAPY



Carotid Stenosis
Decision-making

PHARMACOTHERAPY
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ISOLATED
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Conventional Carotid Stents

Do Have A Problem

Conventional Carotid Stents

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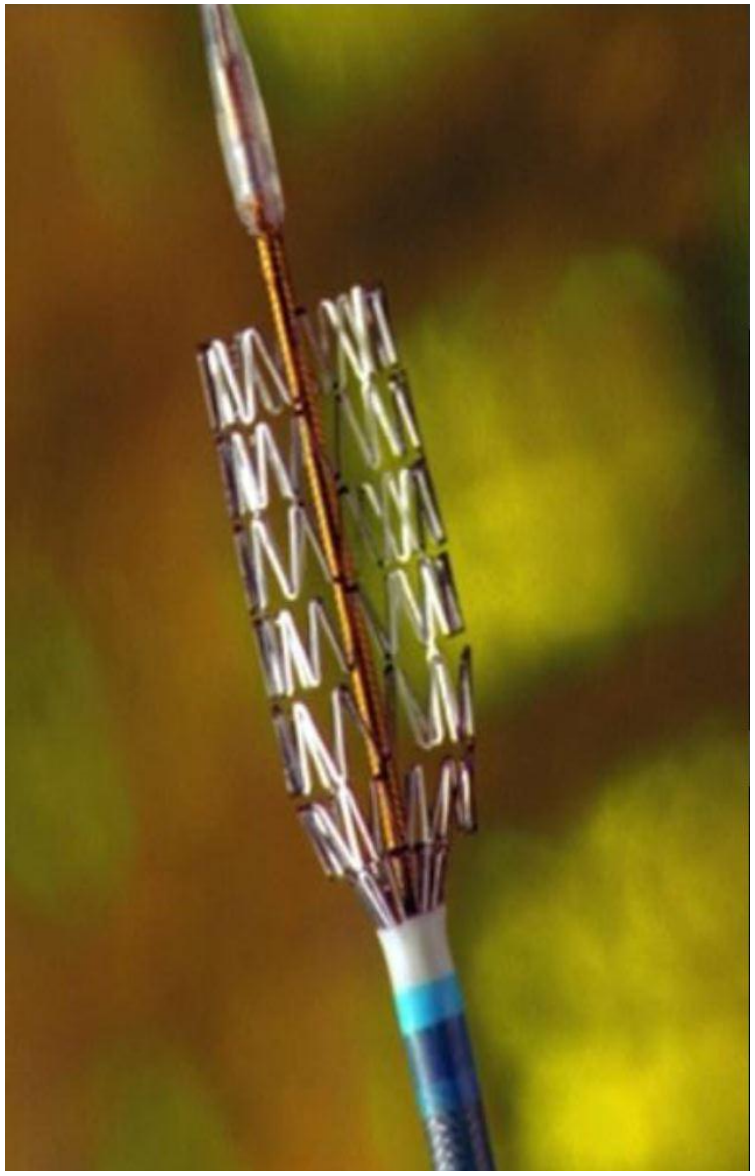

Human carotid artery treated using a conventional stent; OCT

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

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

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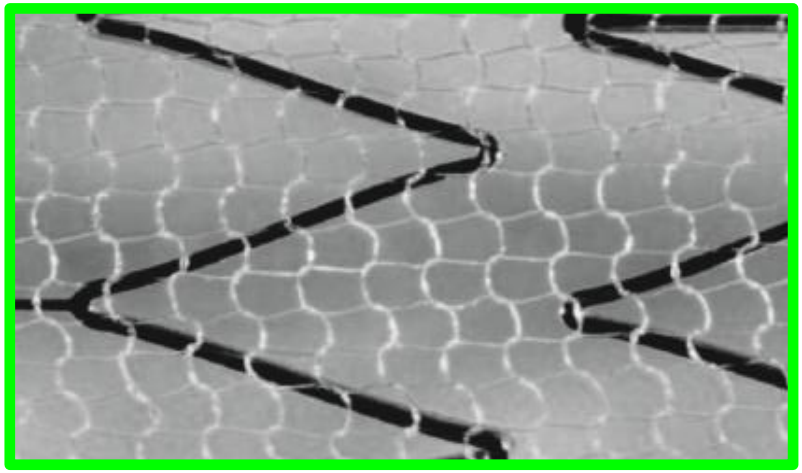
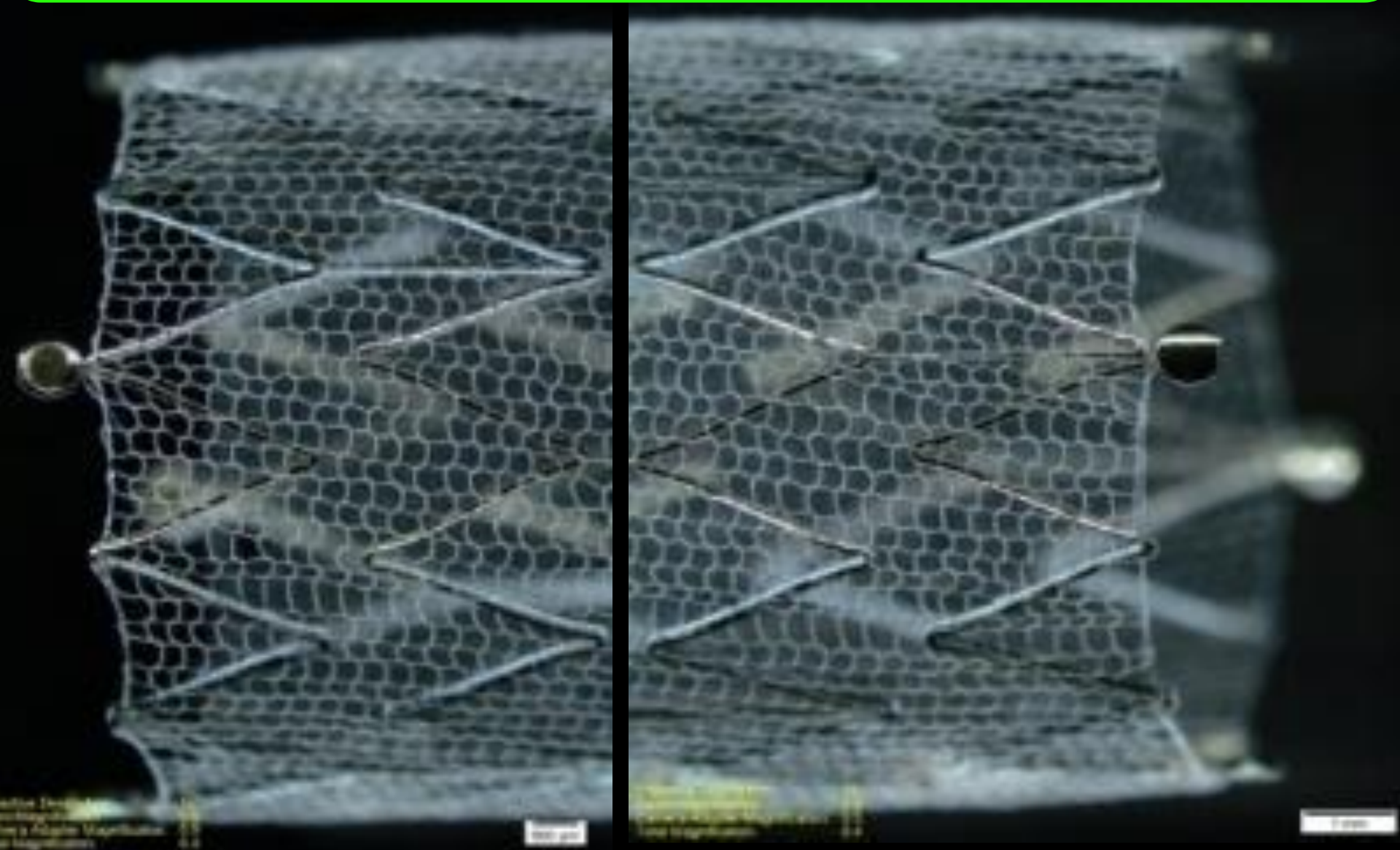
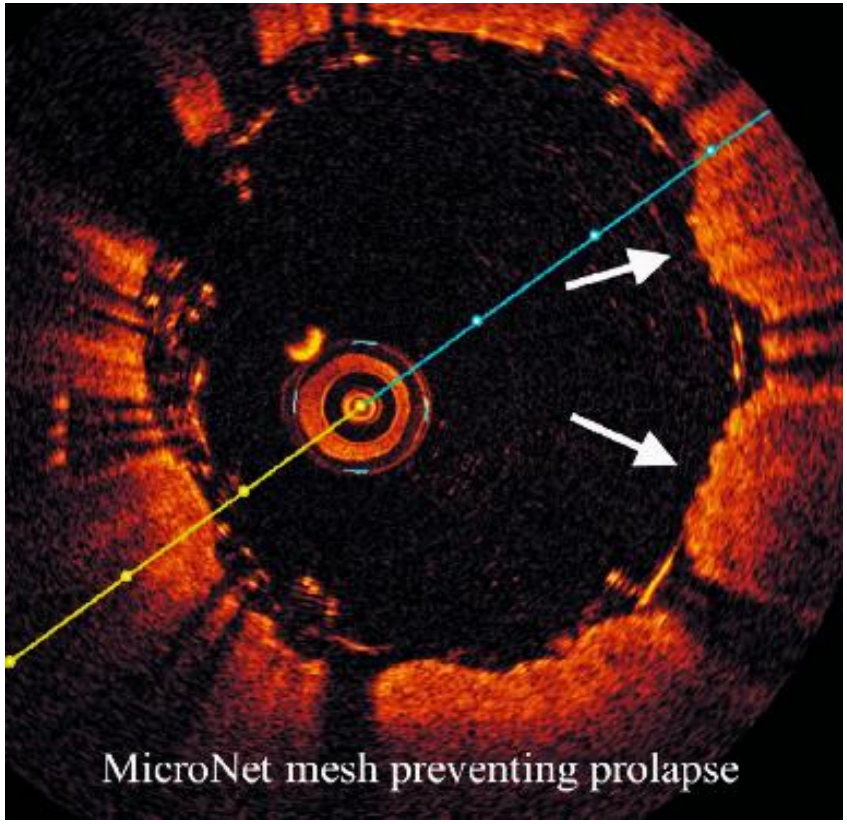
- In CAS, the stent should exclude the plaque too

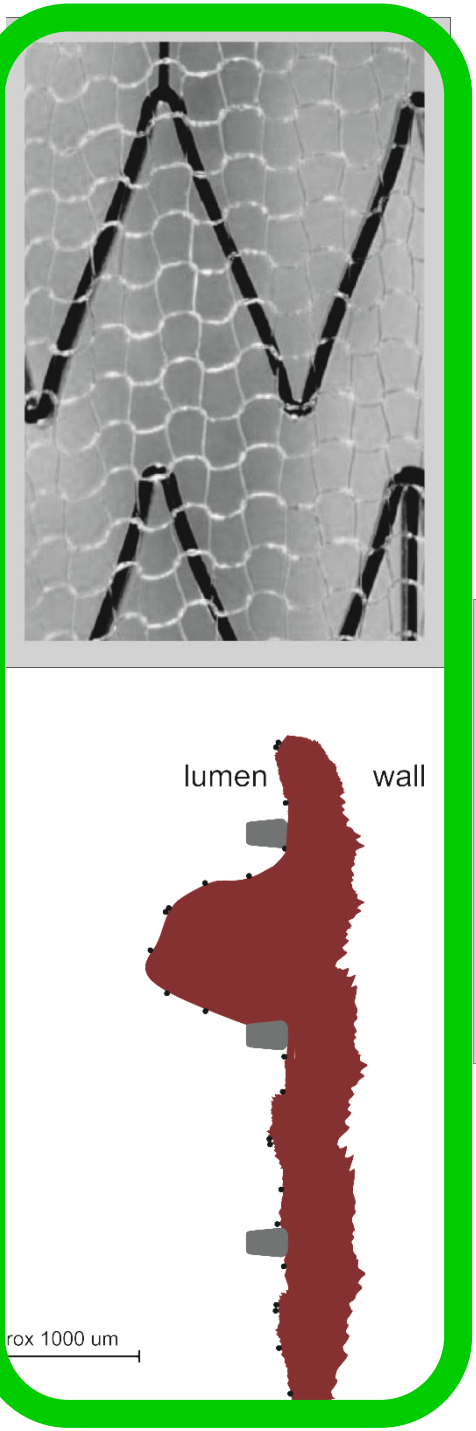


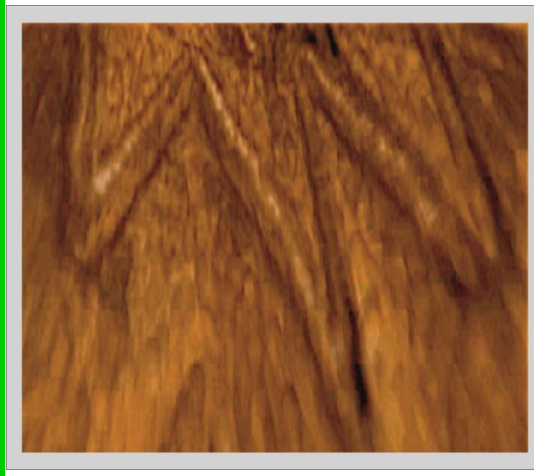
CGuard™ embolic prevention system



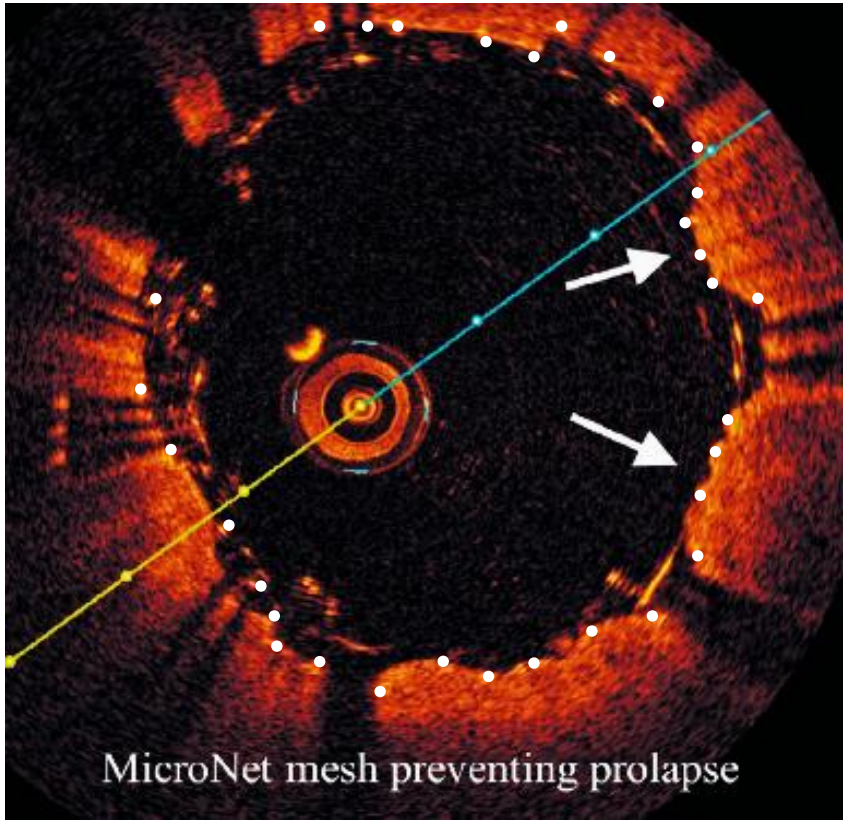


Tomyuki Umemoto et al.
EuroIntervention 2017





Musialek & Stabile
EuroIntervention 2017



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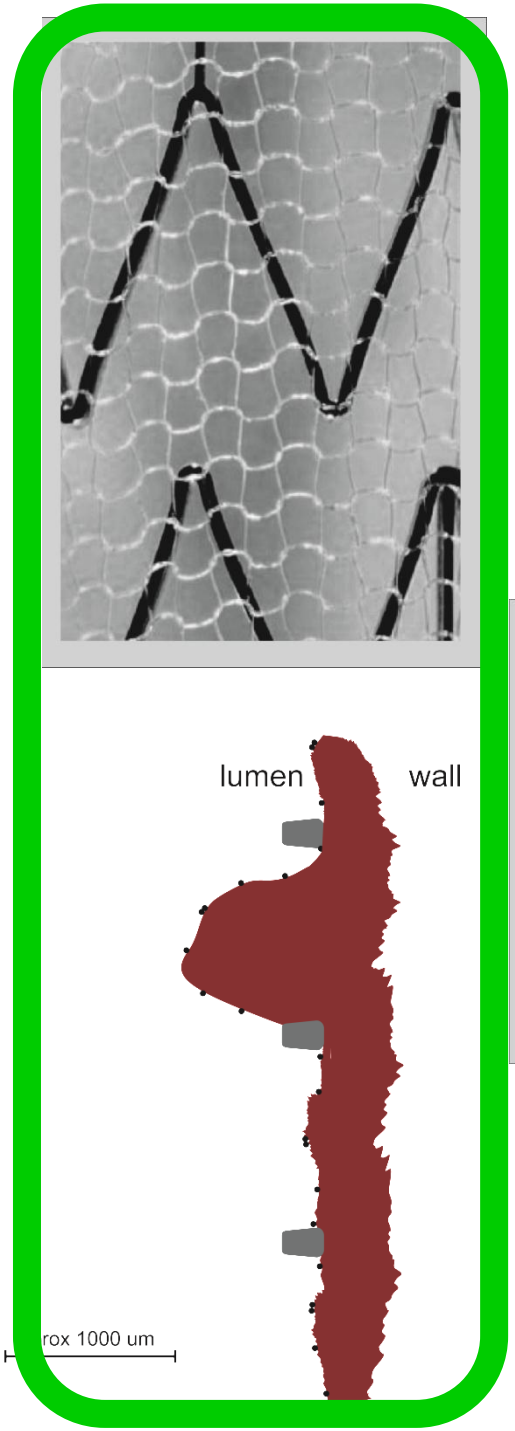

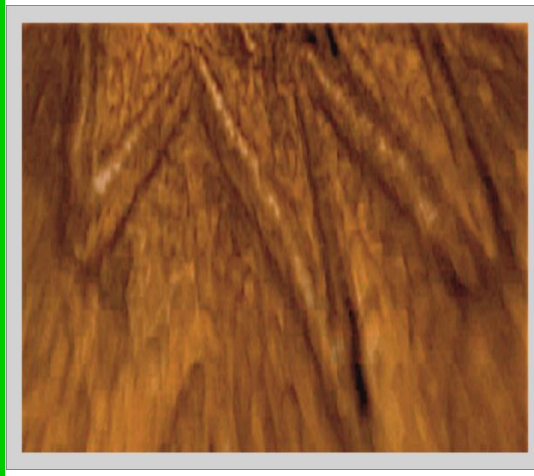

Musialek & Stabile
EuroIntervention 2017

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A Prospective, Multicenter Study of a Novel Mesh-Covered Carotid Stent

The CGuard CARENET Trial (Carotid Embolic Protection Using MicroNet)

CGuard™

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

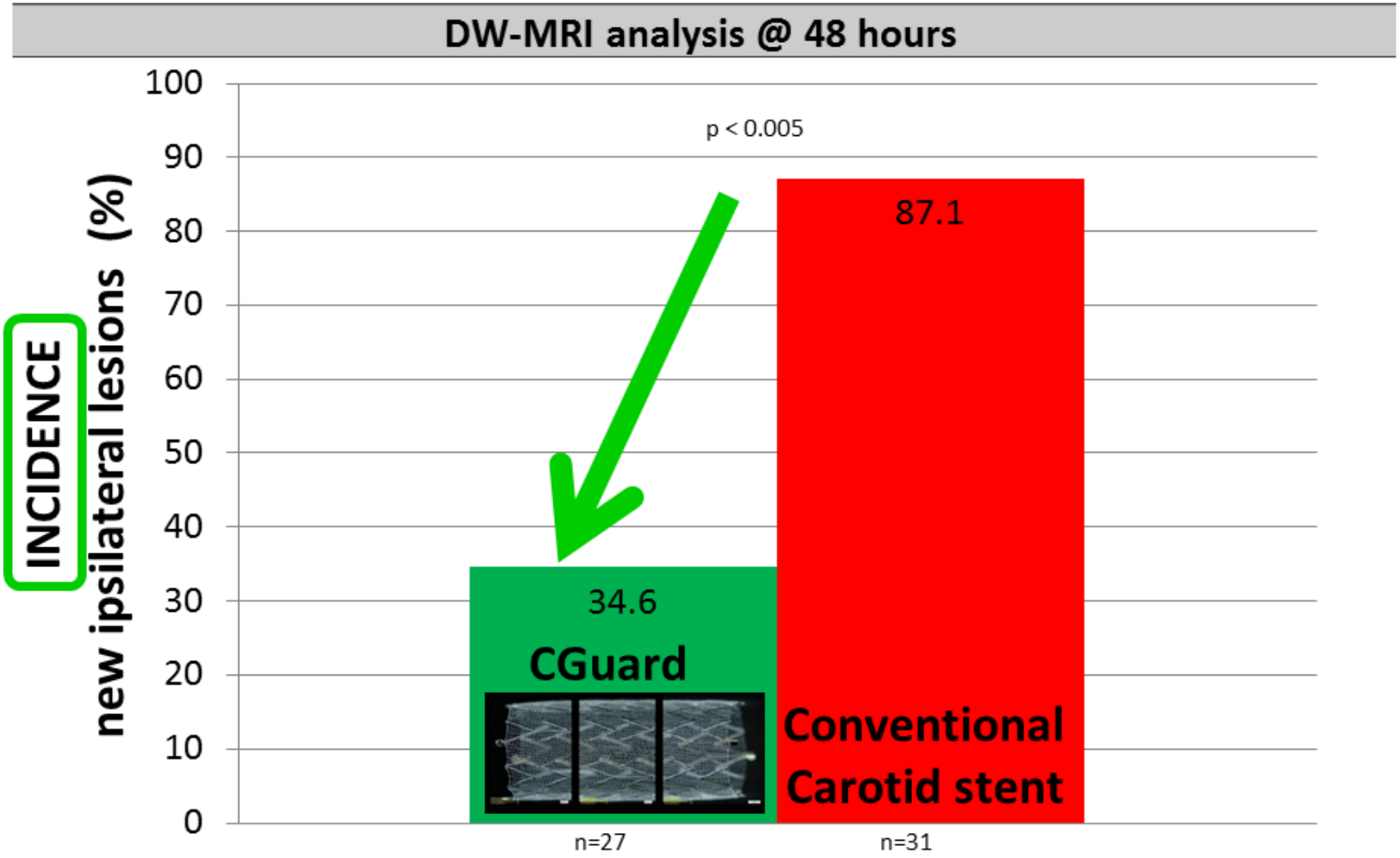
OBJECTIVES This study sought to evaluate the feasibility of the CGuard Carotid Embolic Protective Stent system—a novel thin strut nitinol stent combined with a polyethylene terephthalate mesh covering designed to prevent embolic events from the target lesion in the treatment of carotid artery lesions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

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)

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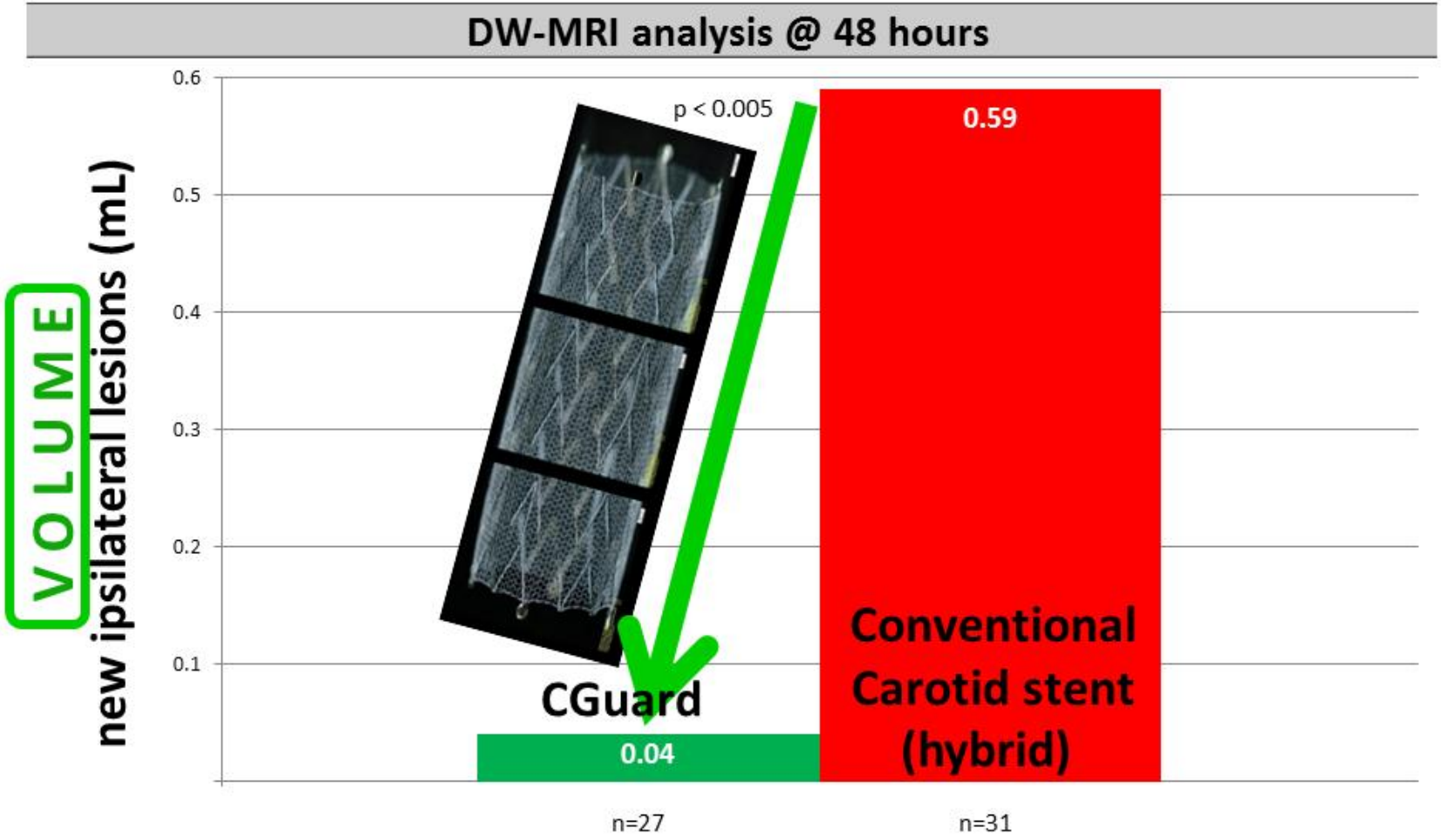

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Bijuklic et al. (manuscript in preparation)

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

=> near-elimination of post-procedural embolism!

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

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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)

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

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

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.)

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

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

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**

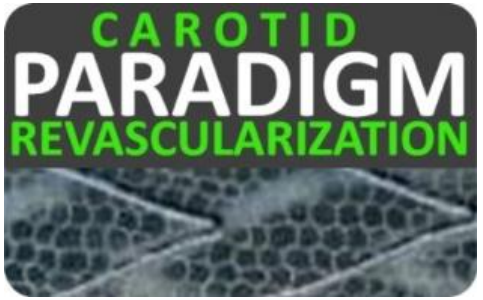
euro PCR 2016 LATE BREAKING TRIALS

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 – Extend

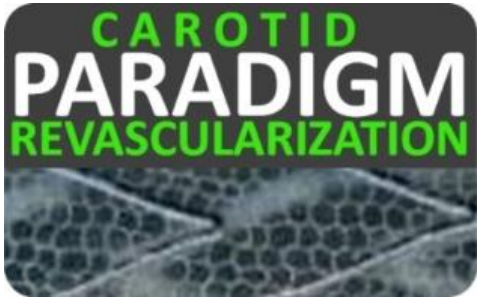
continues as an ALL-Comer Study



- 251 patients / 263 arteries
  NeuroVascular Team decision-making on revascularization
- Age 51-87 years, 57.1% symptomatic
- Crossed the trial first follow-up window (30d)
- 100% CGuardEPS use, Proximal/distal EPD ≈ 50% : 50%
- Angiographic diameter stenosis was reduced from 83±9% to only 6.7±5% (p<0.001, 'CEA-like' effect of CAS)

PARADIGM – Extend

251 patients / 263 arteries



- *Peri-procedural outcome*

  0 death/major stroke – **0%**
  1 minor stroke – 0.4%
  1 MI (type2) **– 0.4%**

- *By 30 days*

  1 haemorrhagic transformation of prior ischaemic cerebral infarct, leading to **death – 0.4%**

PARADIGM – Extend

1-12 mo	*12-24 mo*	*24-36 mo*
n=251	n=185	n=93

PARADIGM – Extend

	1-12 mo	*12-24 mo*	*24-36 mo*
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ipsilateral stroke	**0**	**0**	**0**

PARADIGM – Extend

	1-12 mo	*12-24 mo*	*24-36 mo*
	n=251	n=185	n=93
ipsilateral stroke	**0**	**0**	**0**
any stroke	**0**	**1** (cerebellal)	**1** (brain stem)

PARADIGM – Extend

	1-12 mo	*12-24 mo*	*24-36 mo*
	n=251	n=185	n=93
ipsilateral stroke	**0**	**0**	**0**
any stroke	**0**	**1** (cerebellal)	**1** (brain stem)
stroke-related death	**0**	**0**	**0**

PARADIGM – Extend

	1-12 mo	*12-24 mo*	*24-36 mo*
	n=251	n=185	n=93
ipsilateral stroke	**0**	**0**	**0**
any stroke	**0**	**1** (cerebellal)	**1** (brain stem)
stroke-related death	**0**	**0**	**0**
MI or other non-cerebral VA	**0**	**3**	**2**

PARADIGM – Extend

	1-12 mo	*12-24 mo*	*24-36 mo*
	n=251	n=185	n=93
ipsilateral stroke	**0**	**0**	**0**
any stroke	**0**	**1** (cerebellal)	**1** (brain stem)
stroke-related death	**0**	**0**	**0**
MI or other non-cerebral VA	**0**	**3**	**2**
any death	**6** (CHF-2, Ca-2, PE-1, urosepsis -1)	**5** (CHF-2, Ca-2, MI-1)	**2** (Ca-1, MI-1)

PARADIGM – Extend

	1-12 mo	*12-24 mo*	*24-36 mo*
	n=251	n=185	n=93
ipsilateral stroke	**0**	**0**	**0**
any stroke	**0**	**1** (cerebellal)	**1** (brain stem)
stroke-related death	**0**	**0**	**0**
MI or other non-cerebral VA	**0**	**3**	**2**
any death	**6** (CHF-2, Ca-2, PE-1, urosepsis -1)	**5** (CHF-2, Ca-2, MI-1)	**2** (Ca-1, MI-1)
in-stent velocities	PSV **0.82**±0.48 m/s EDV **0.22**±0.13 m/s	PSV **0.73**±0.31 m/s EDV **0.19**±0.09 m/s	PSV **0.75**±0.27 m/s EDV **0.18**±0.06 m/s

PARADIGM – Extend

By 36 months

- **Normal healing**
- **No ISR signal**

	1-12 mo	12-24 mo	24-36 mo
	n=251	n=185	n=93
ipsilateral stroke	0	0	0
any stroke	0	1 (cerebellal)	1 (brain stem)
stroke-related death	0	0	0
MI or other non-cerebral VA	0	3	2
any death	6 (CHF-2, Ca-2, PE-1, urosepsis -1)	5 (CHF-2, Ca-2, MI-1)	2 (Ca-1, MI-1)
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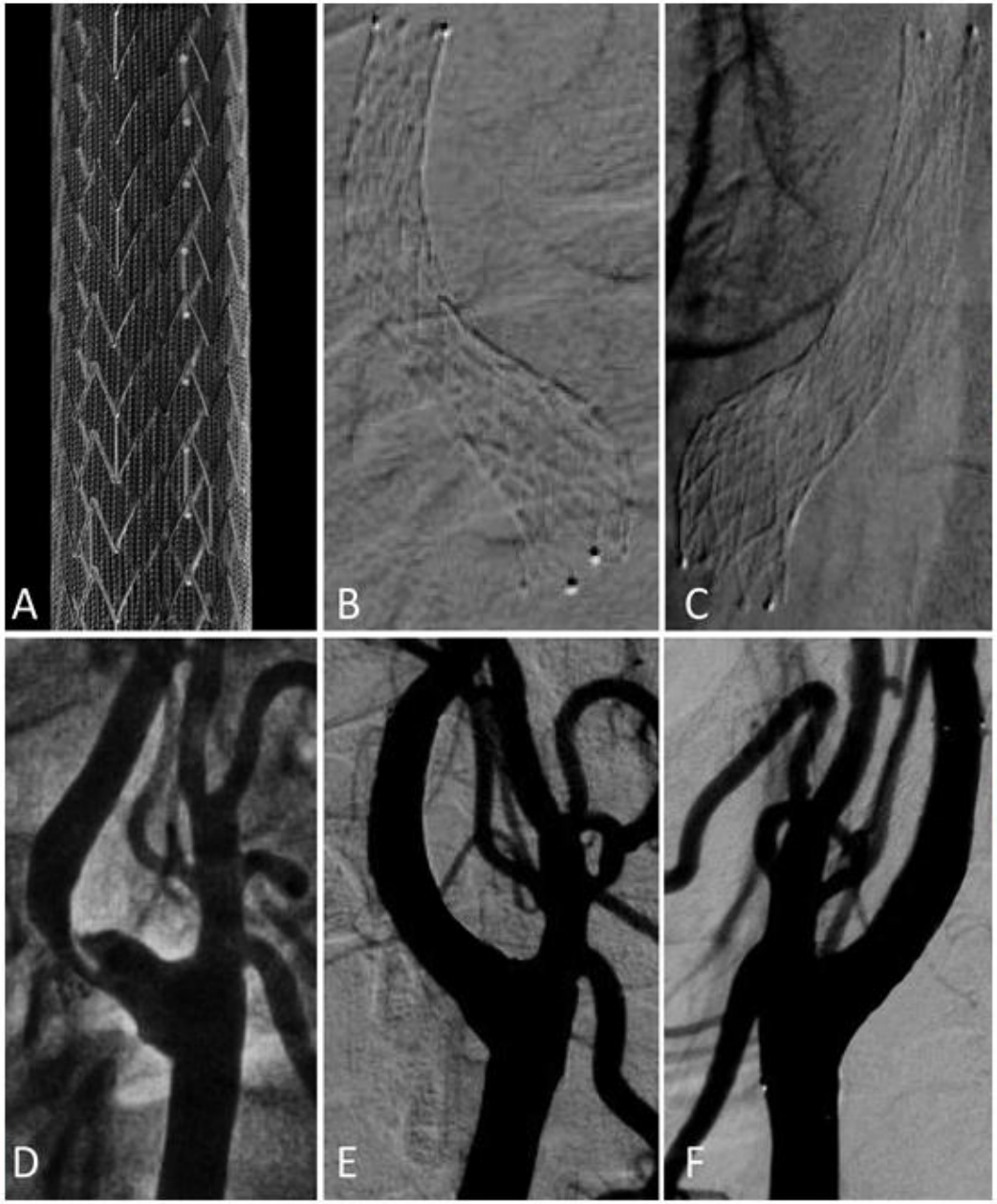
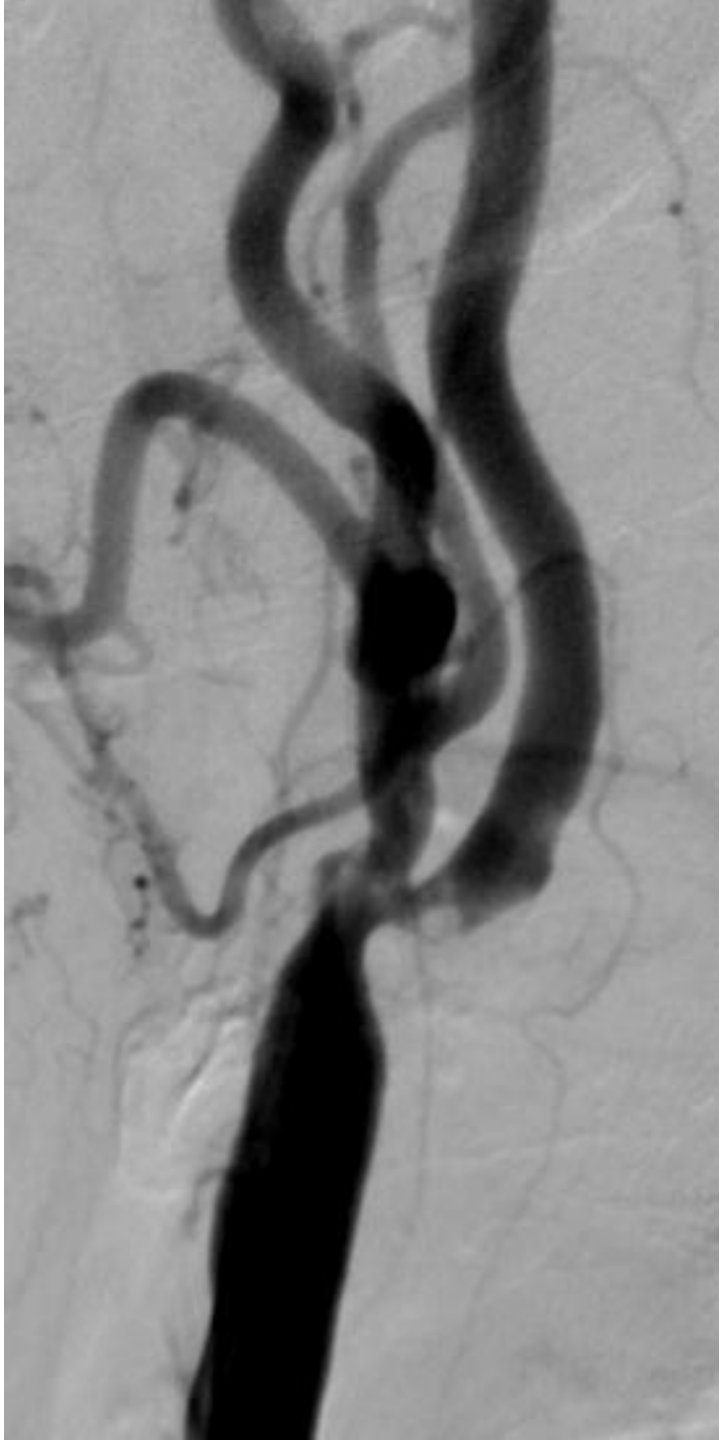


CAROTID PARADIGM REVASCULARIZATION

systematic

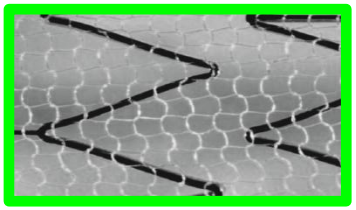
CEA-like effect of CAS

EuroIntervention 2016;12:e658-70




The Outcome Difference

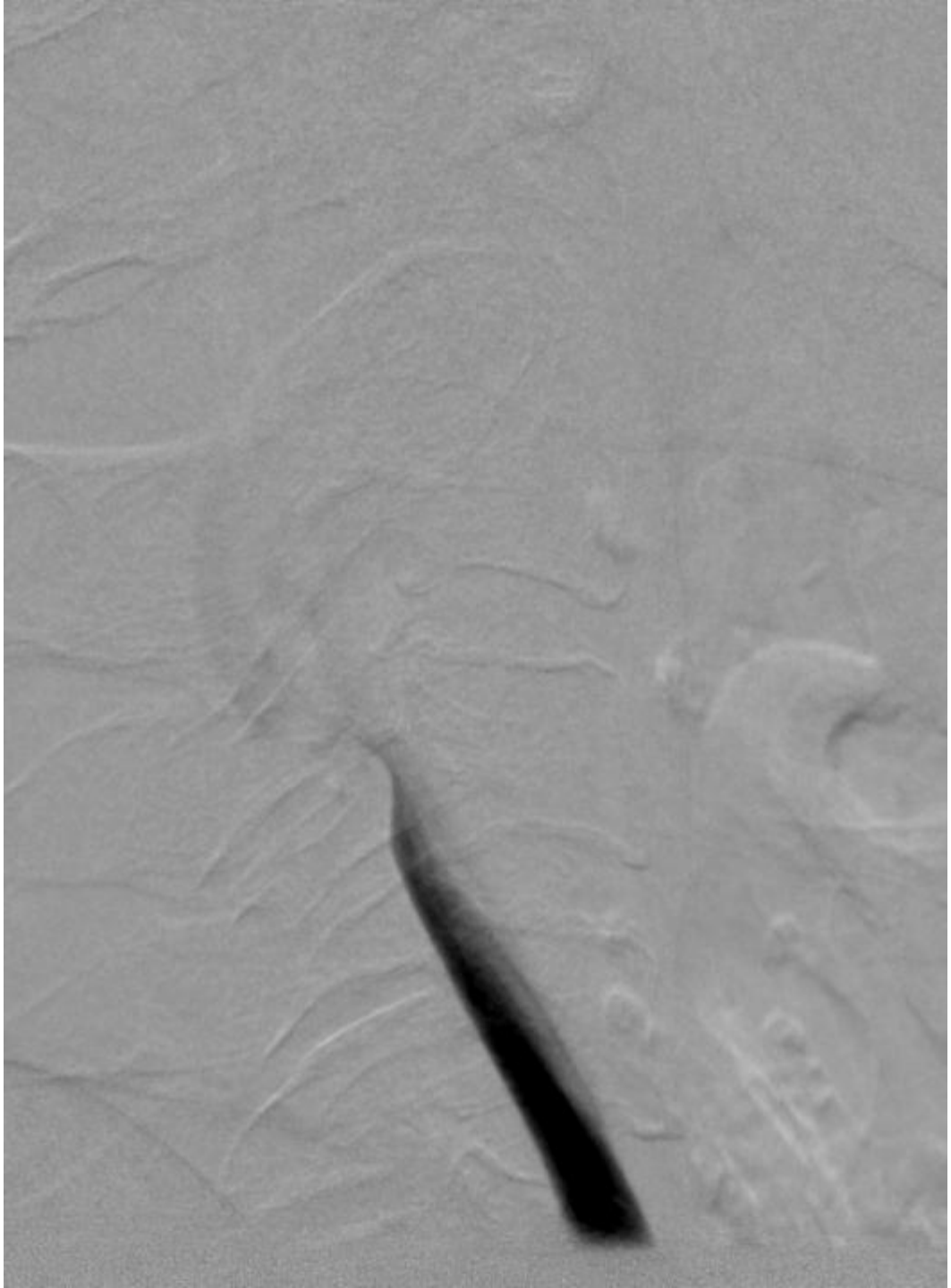
Between the MicroNet-Covered Stent



vs.

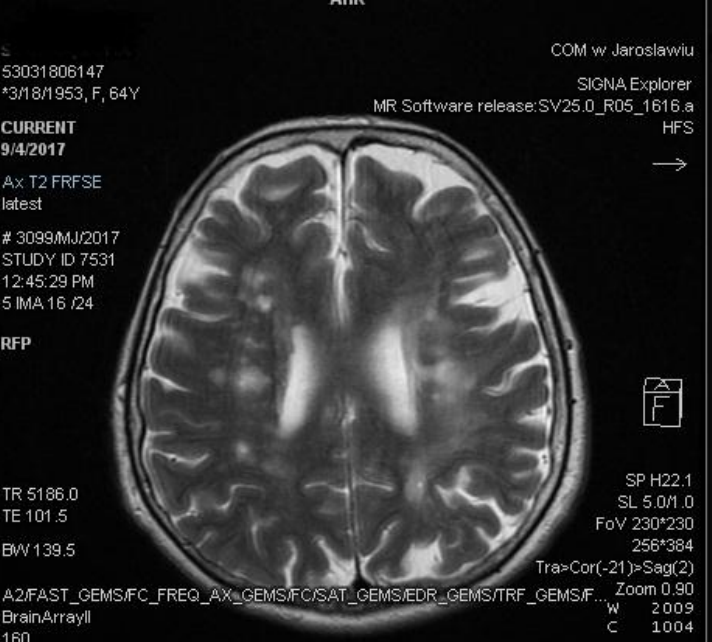
Conventional Carotid Stent(s)

driven by HIGH-RISK Plaques and Patients

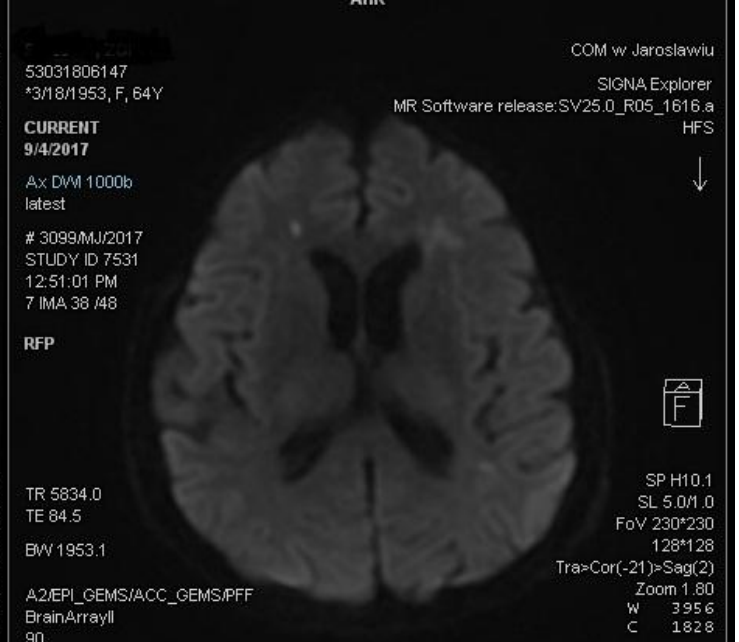


(LICA chronic occlusion)

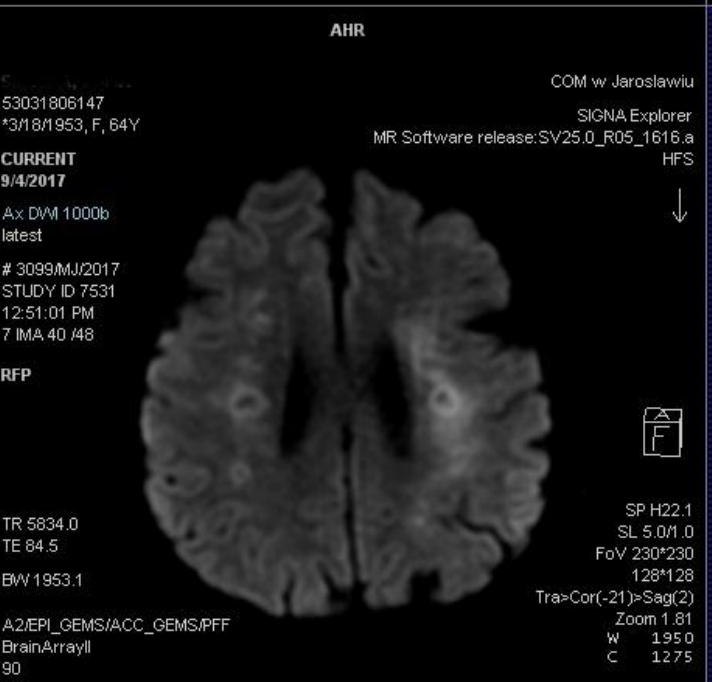
B/L MRI scan



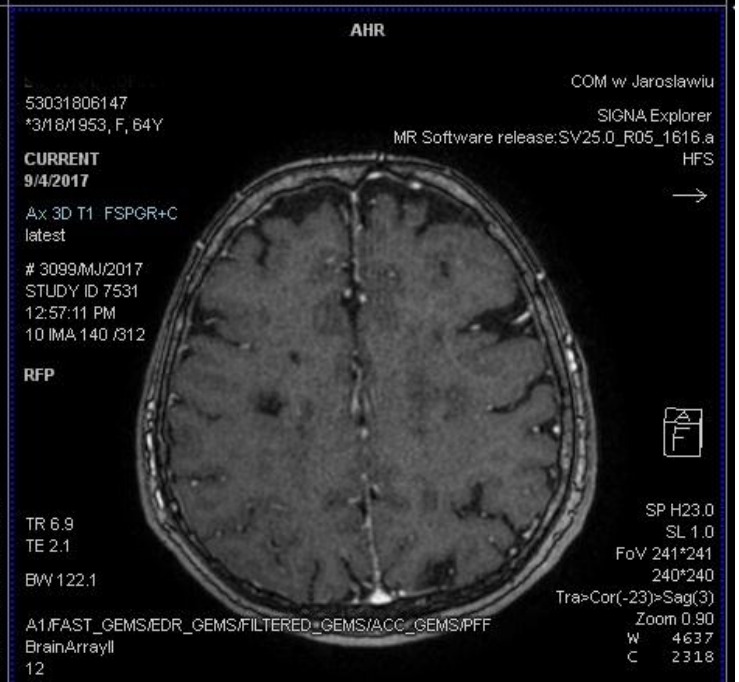
chronic ischemic lesions in both hemispheres



new DWI lesion in **R** hemisphere



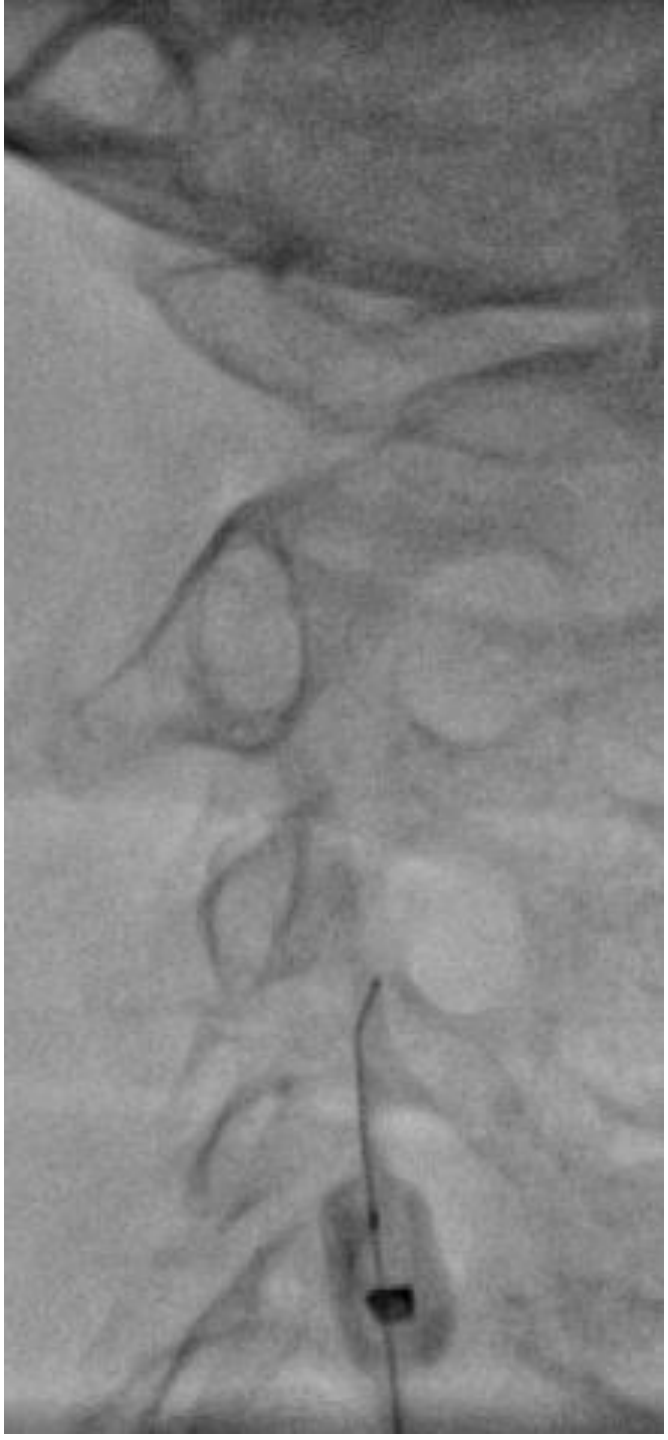
” fresh” ischemia surrounding old lesions

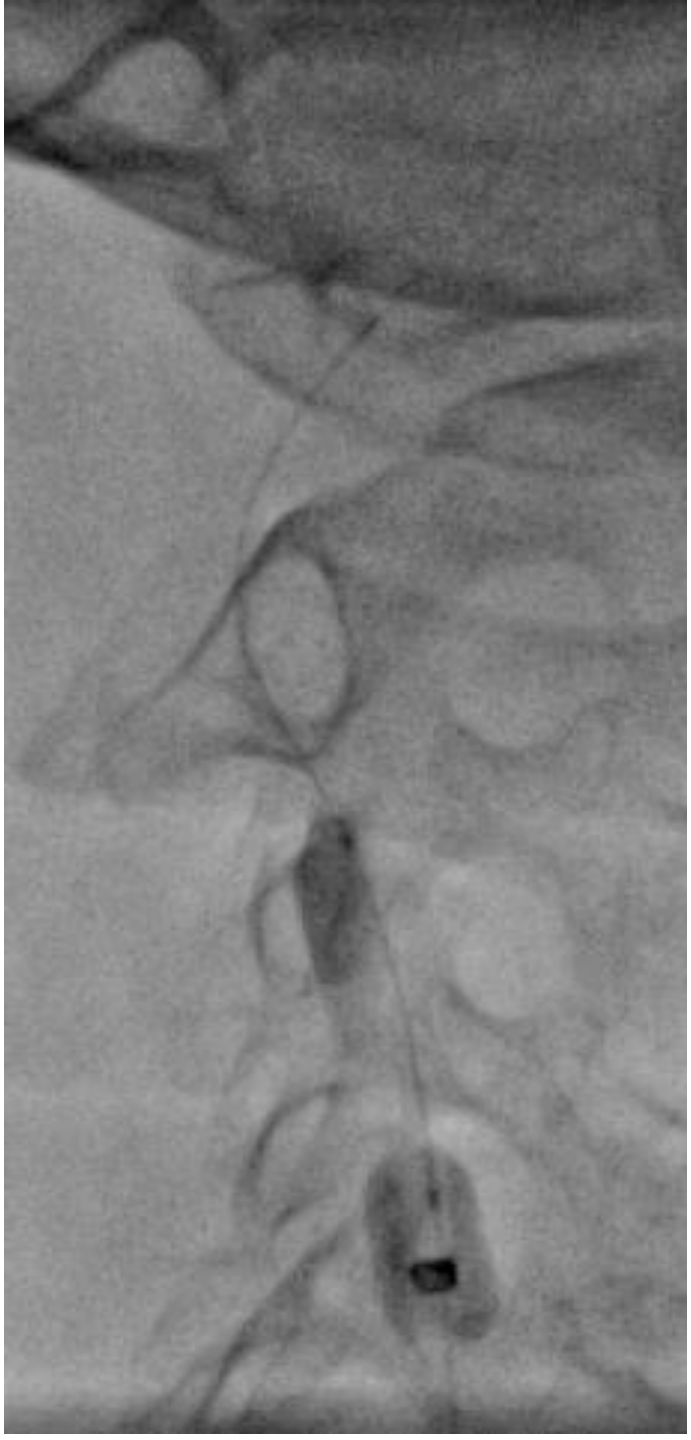


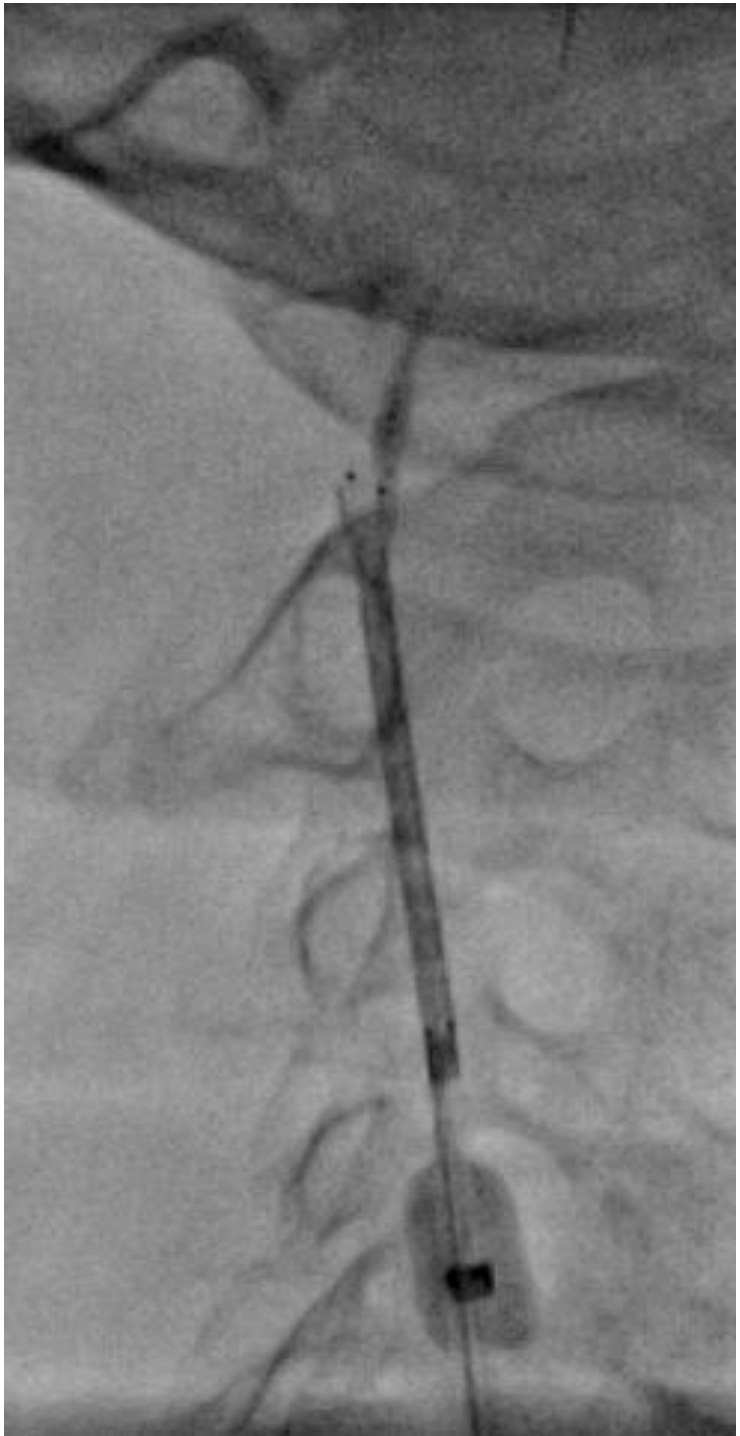
chronic ischemic lesion in R hemisphere

RICA high-grade highly-thromboltic stenosis

LICA chronic occlusion

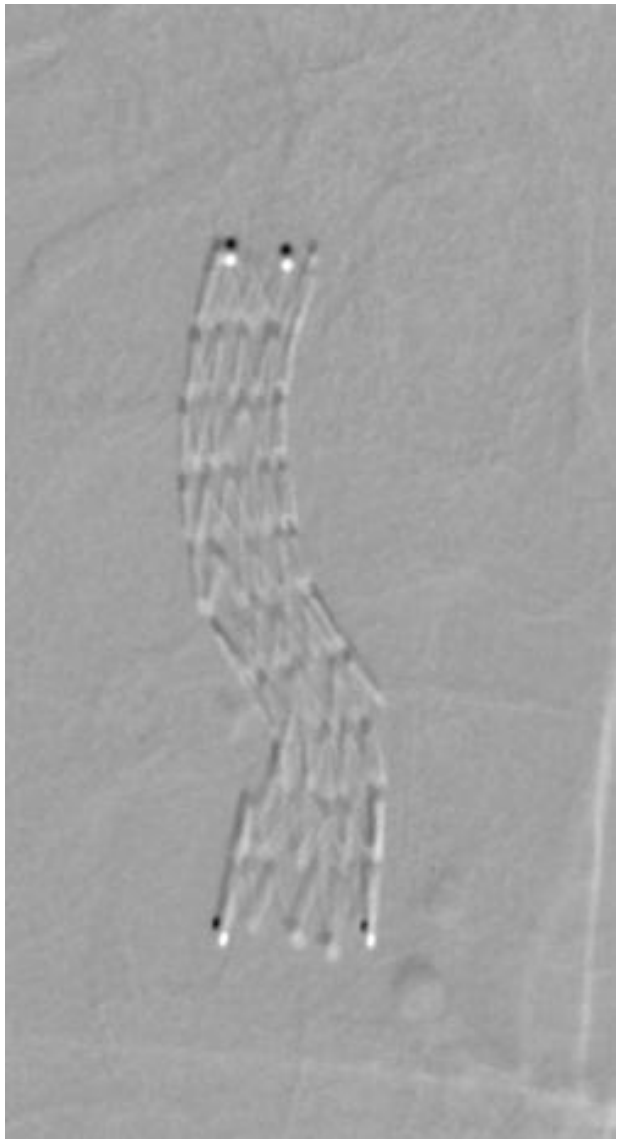


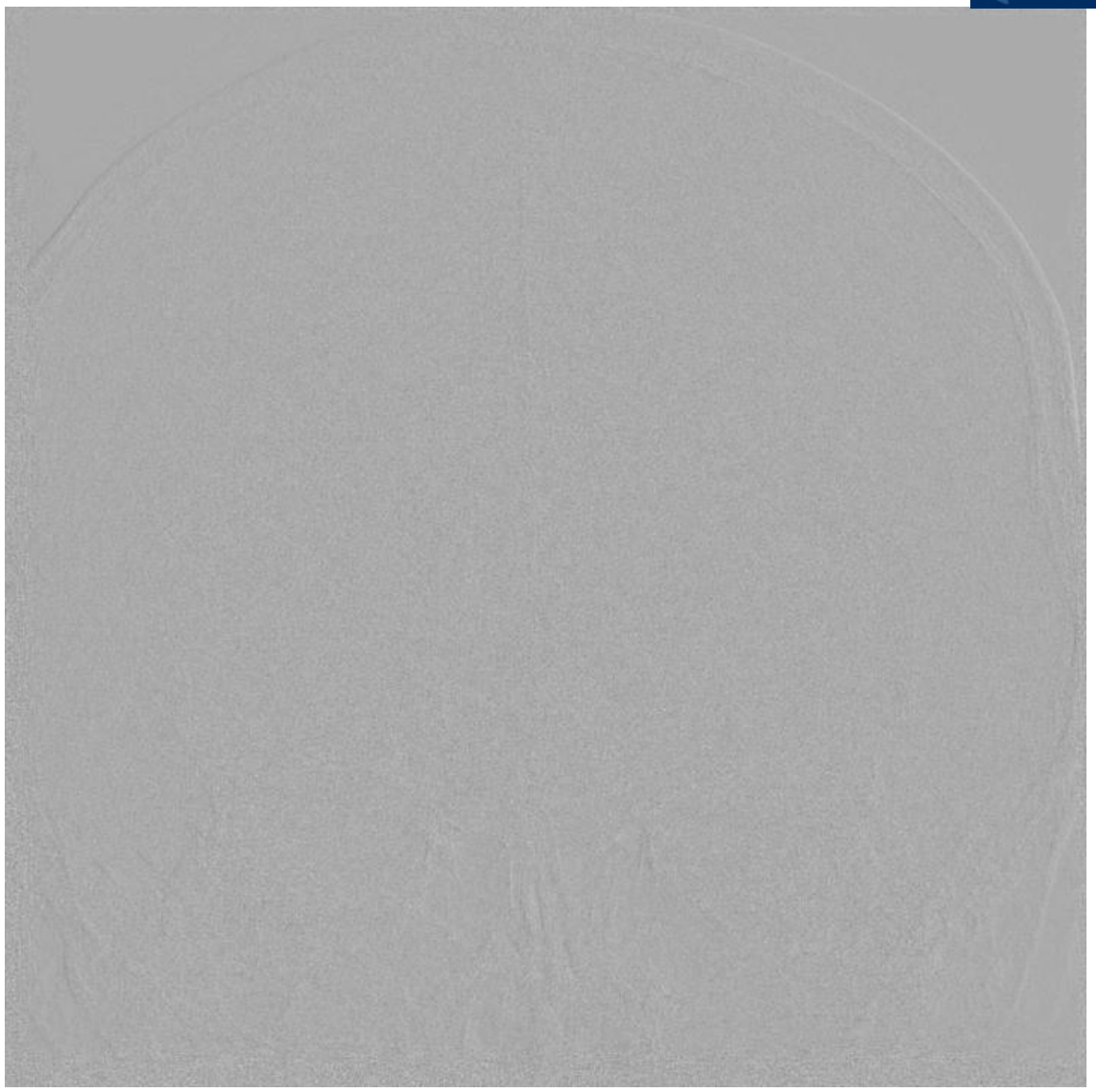




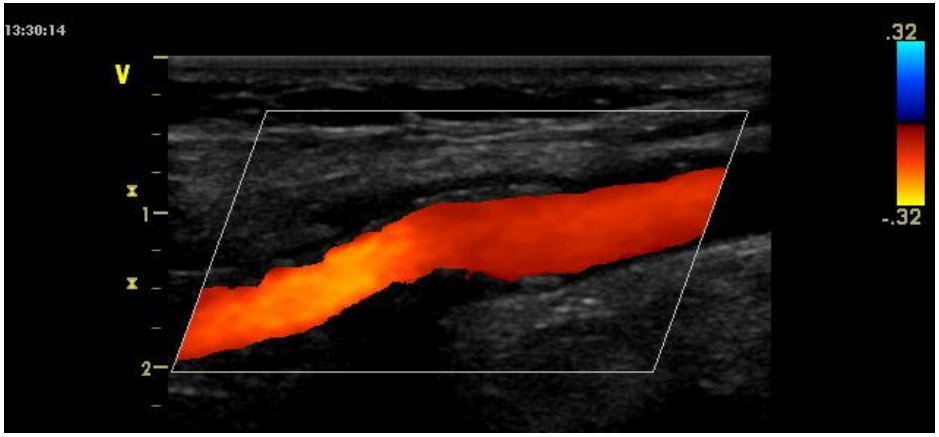
Flow reversal time 7min 10sec
Intolerance in the last 80sec
(active aspiration still !! performed)

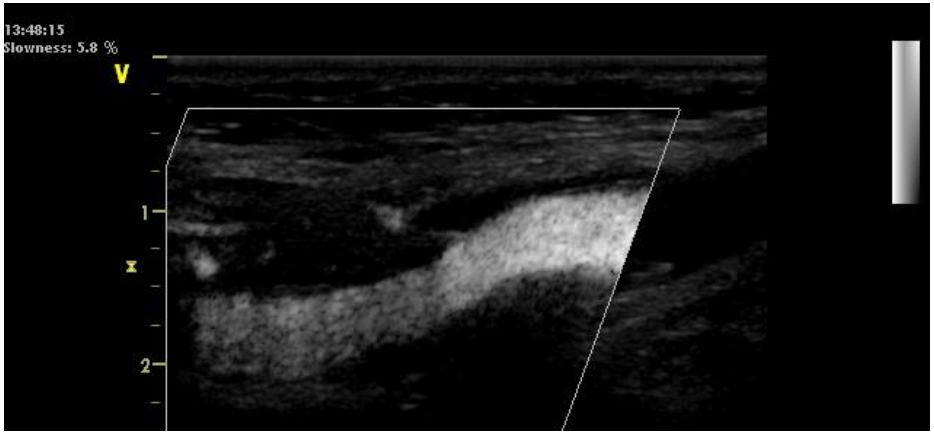
Final Result



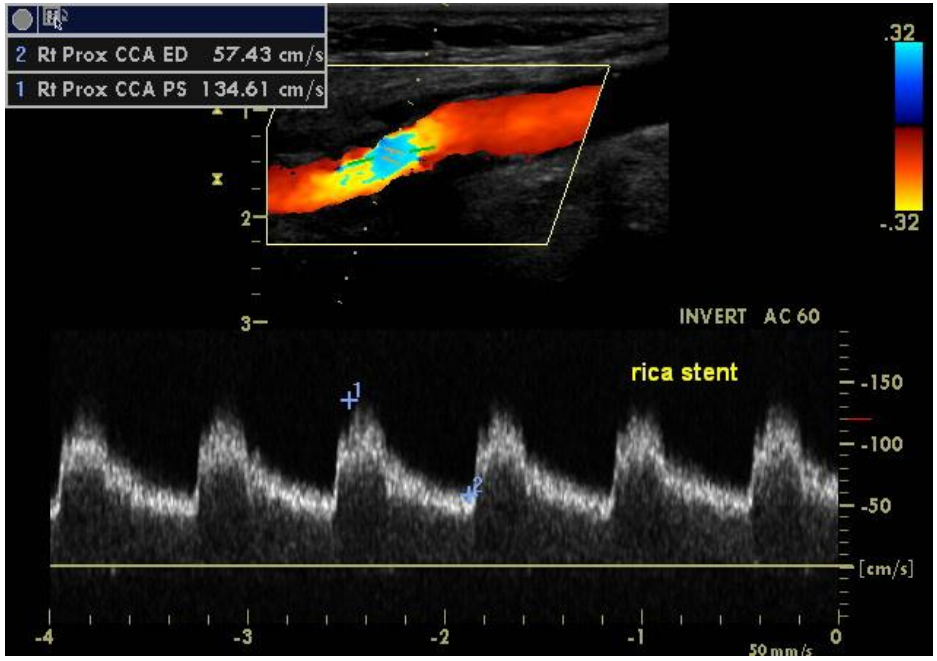


Patient A/S, discharged home, unremarkable follow-up

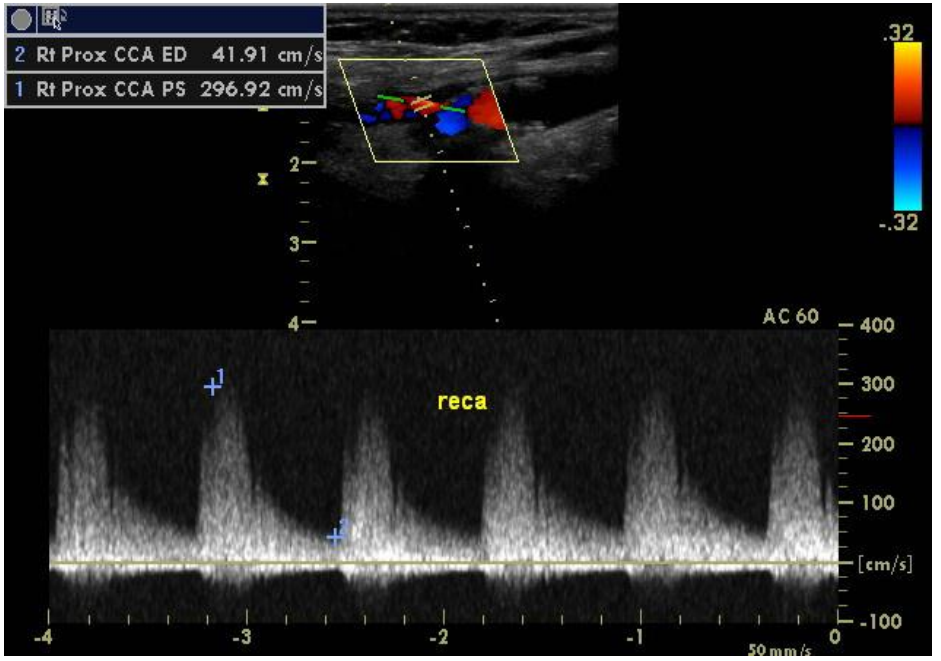




Normal stent image



Normal velocities



ECA patent

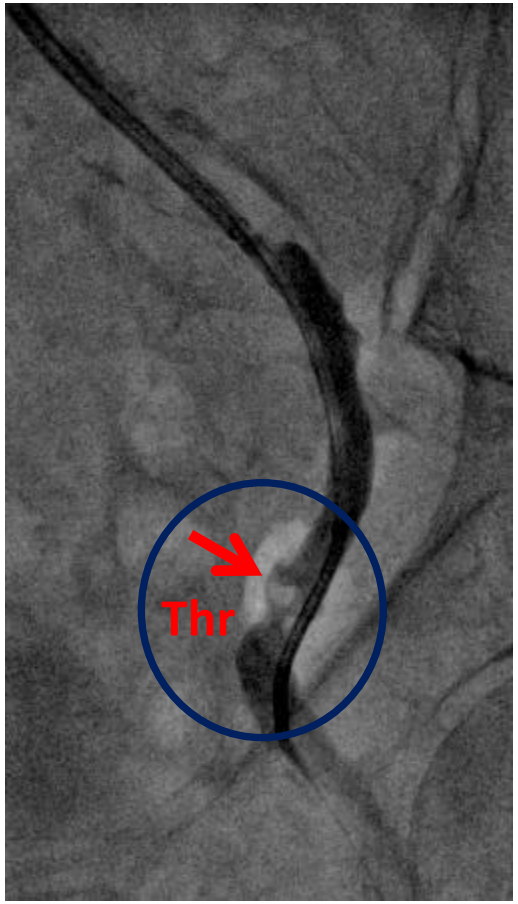
P Musialek @ VEITH 2018

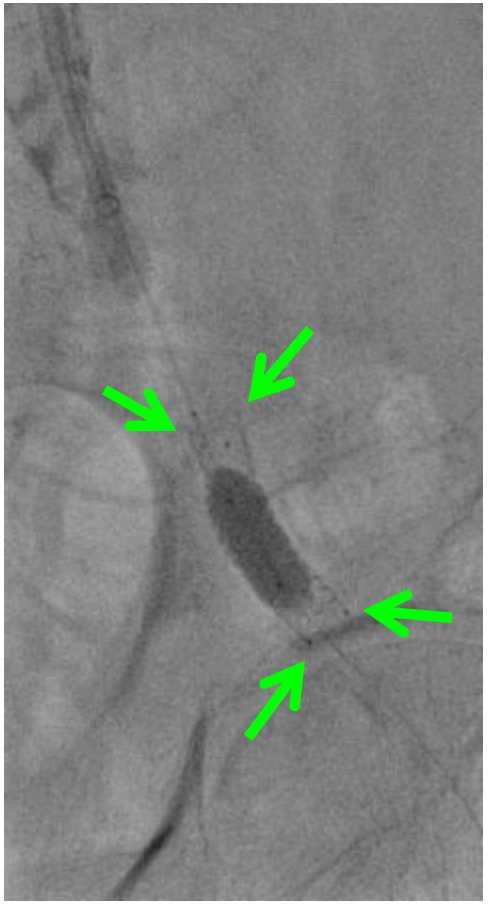
Moving beyond routine CAS…

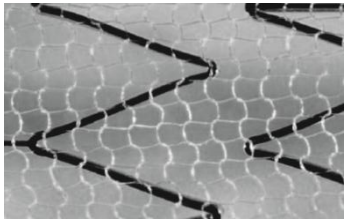
CGuard™ MicroNet Covered Stent:

ADDRESSING UNMET NEEDS IN OTHER VASCULAR BEDS

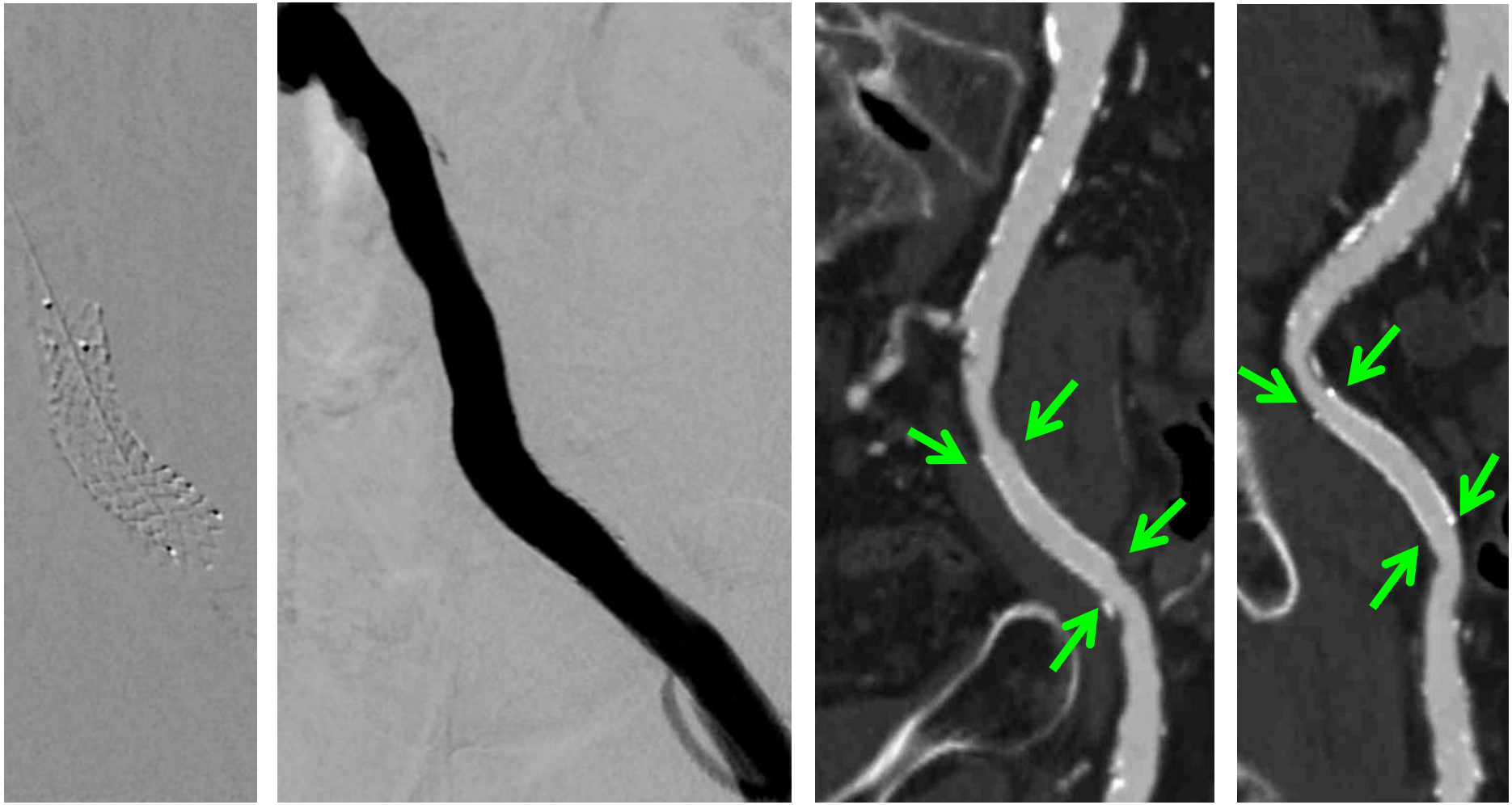
Thrombus-containing/high-embolic risk lesions in iliacs or subclavians







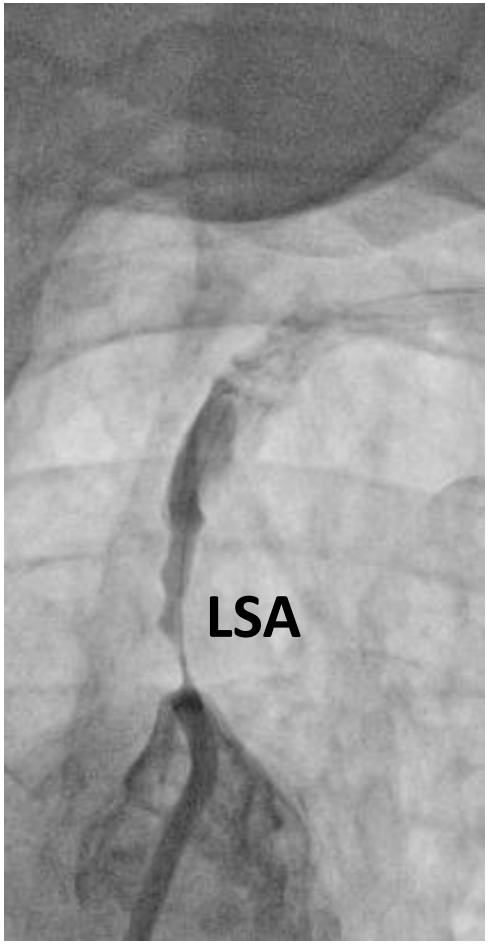
Thrombus-containing/high-embolic risk lesions in iliacs or subclavians

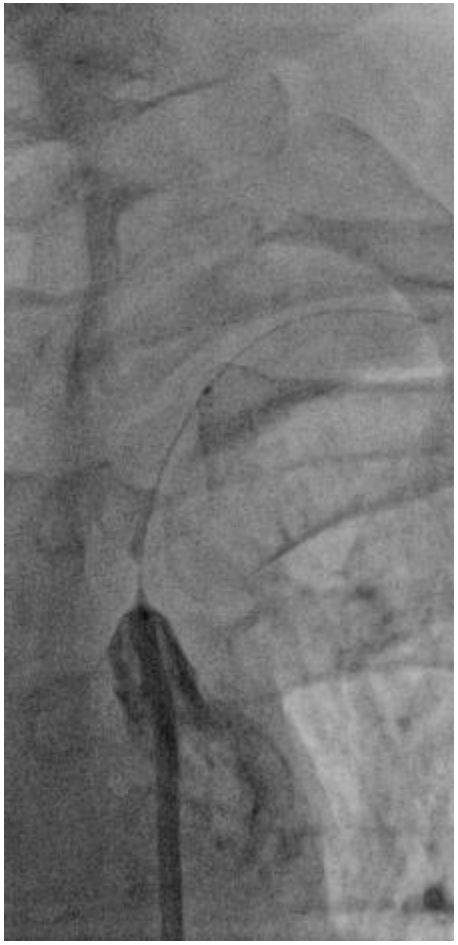


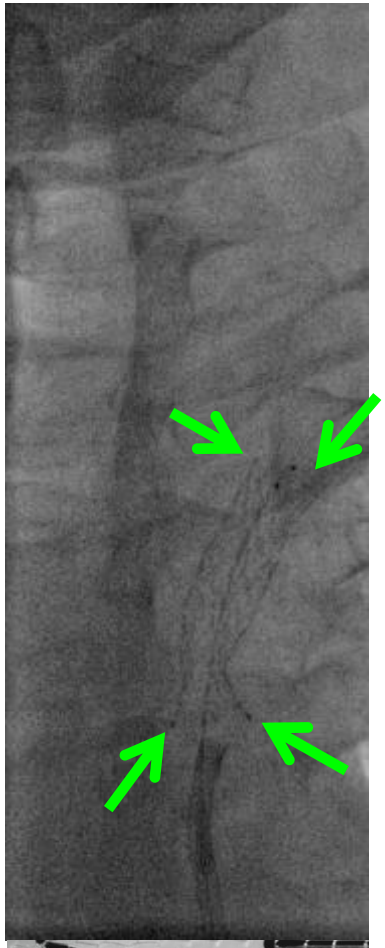
OPTIMAL procedural result

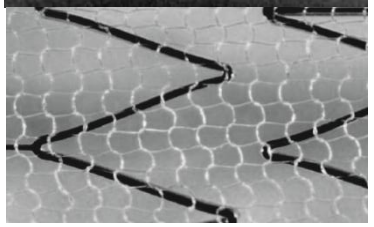
Normal 6mo follow-up

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



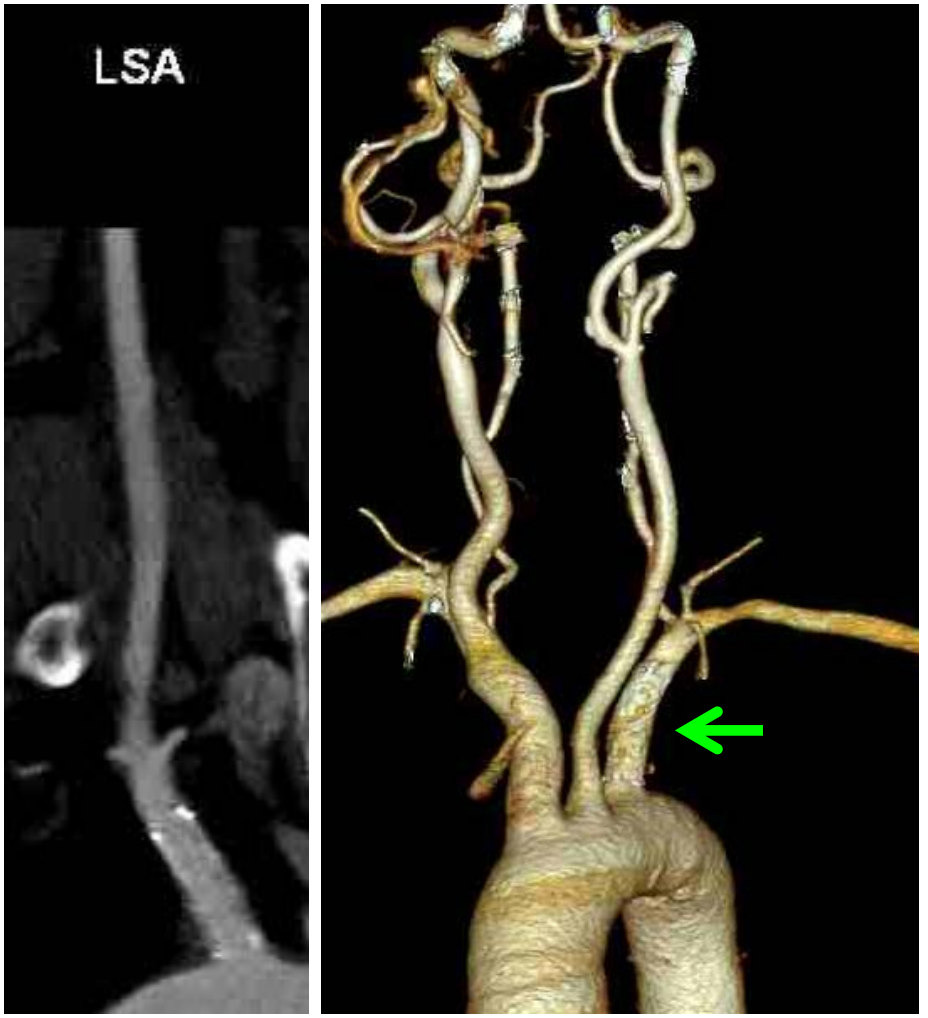






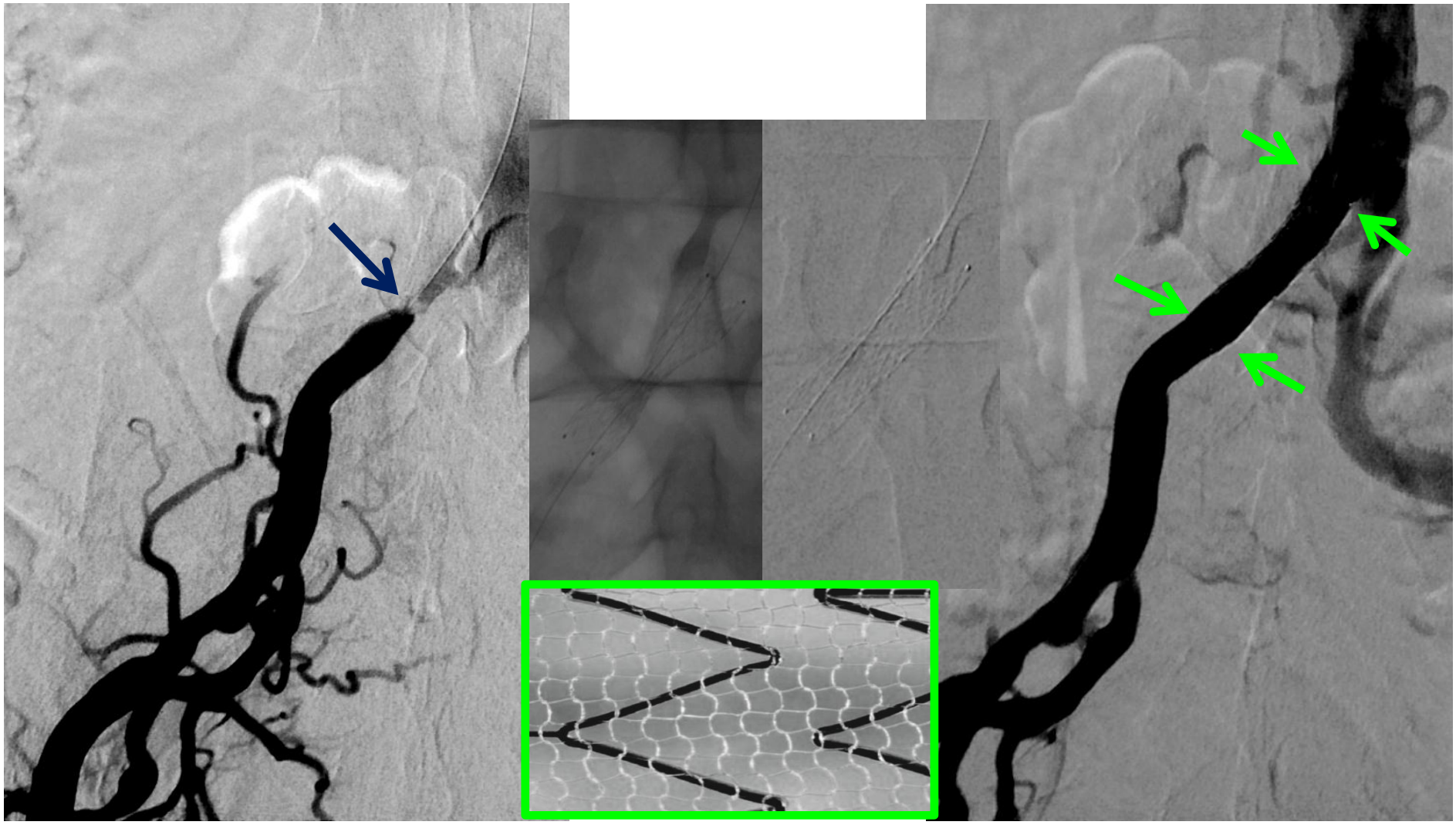
Thrombus-containing/high-embolic risk lesions in iliacs or subclavians

Procedural result



Normal 6mo follow-up

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



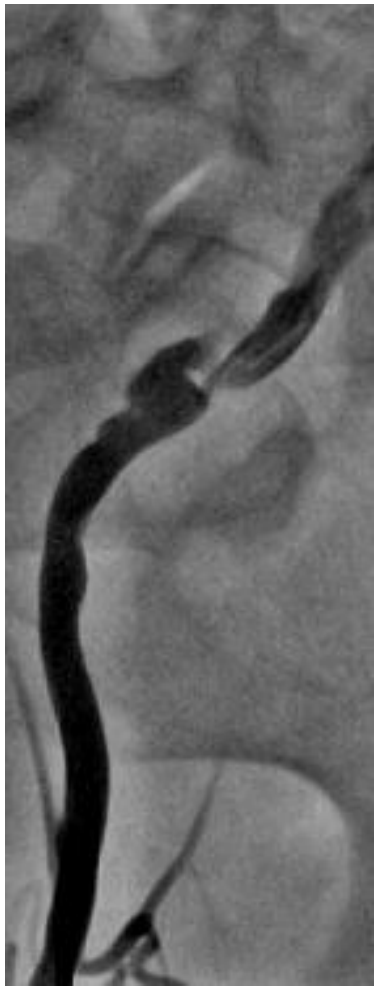
Procedural result

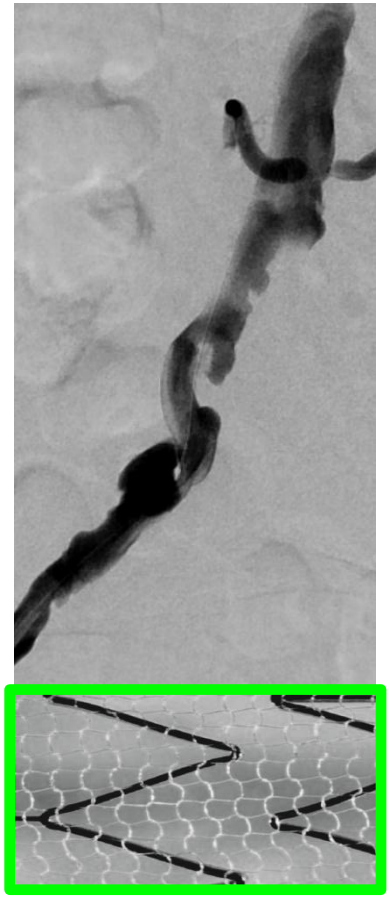
Thrombus-containing/high-embolic risk lesions in iliacs or subclavians

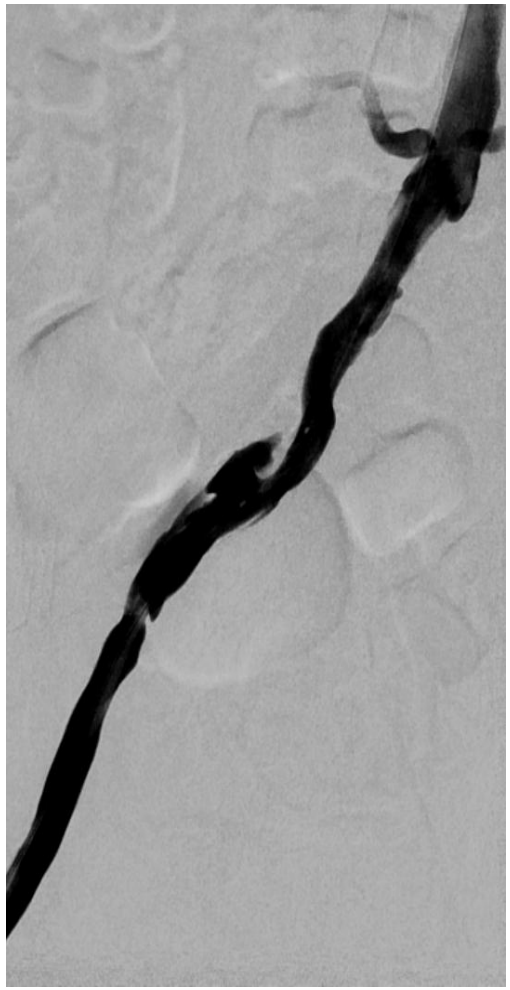
CGuard™

Normal Result @follow-up

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



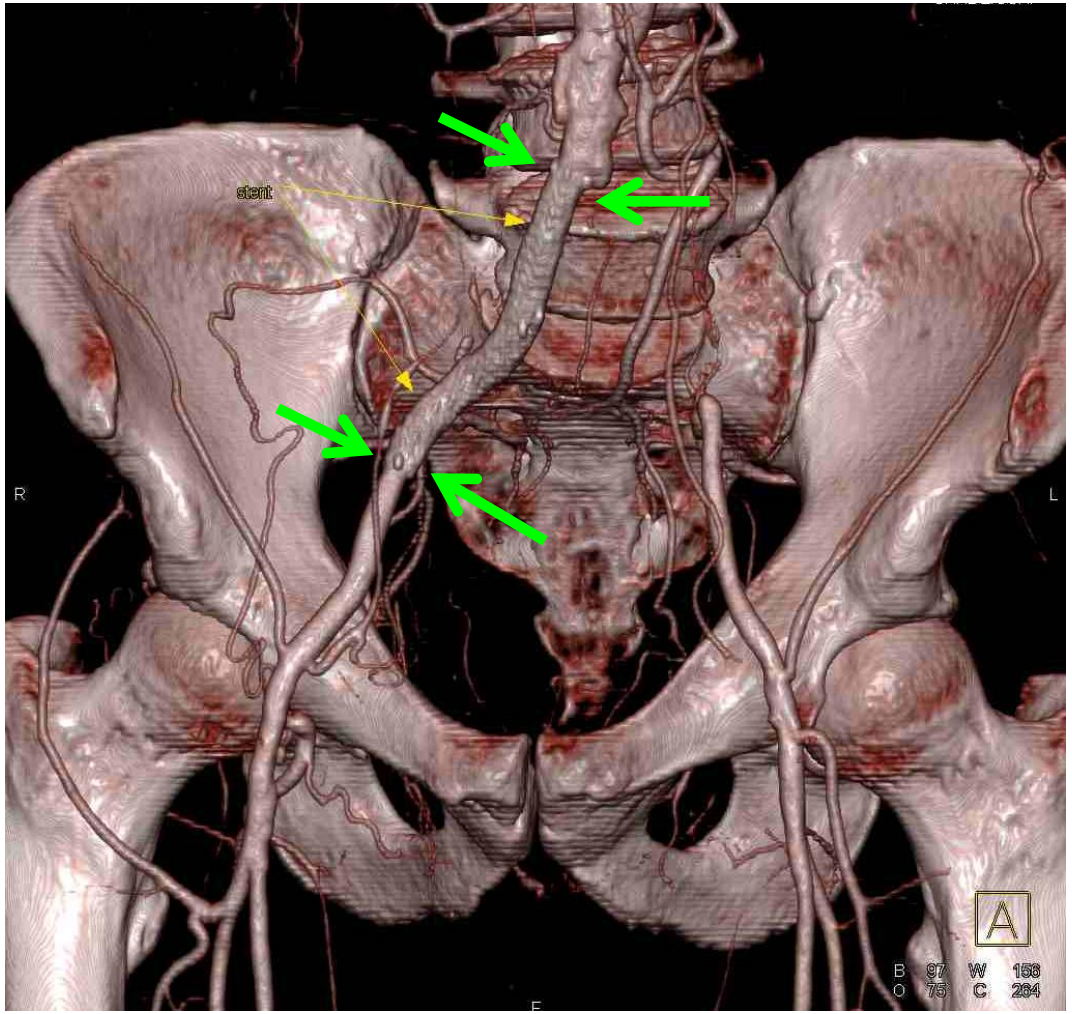




Procedural acute outcome

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

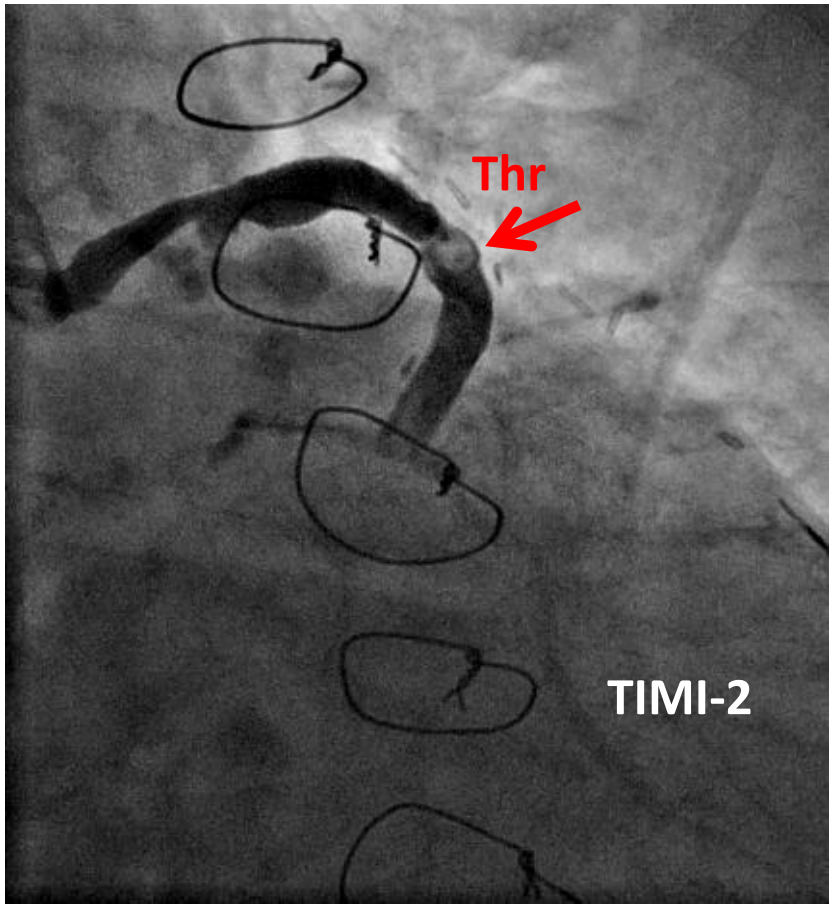
OPTIMAL 6mo result

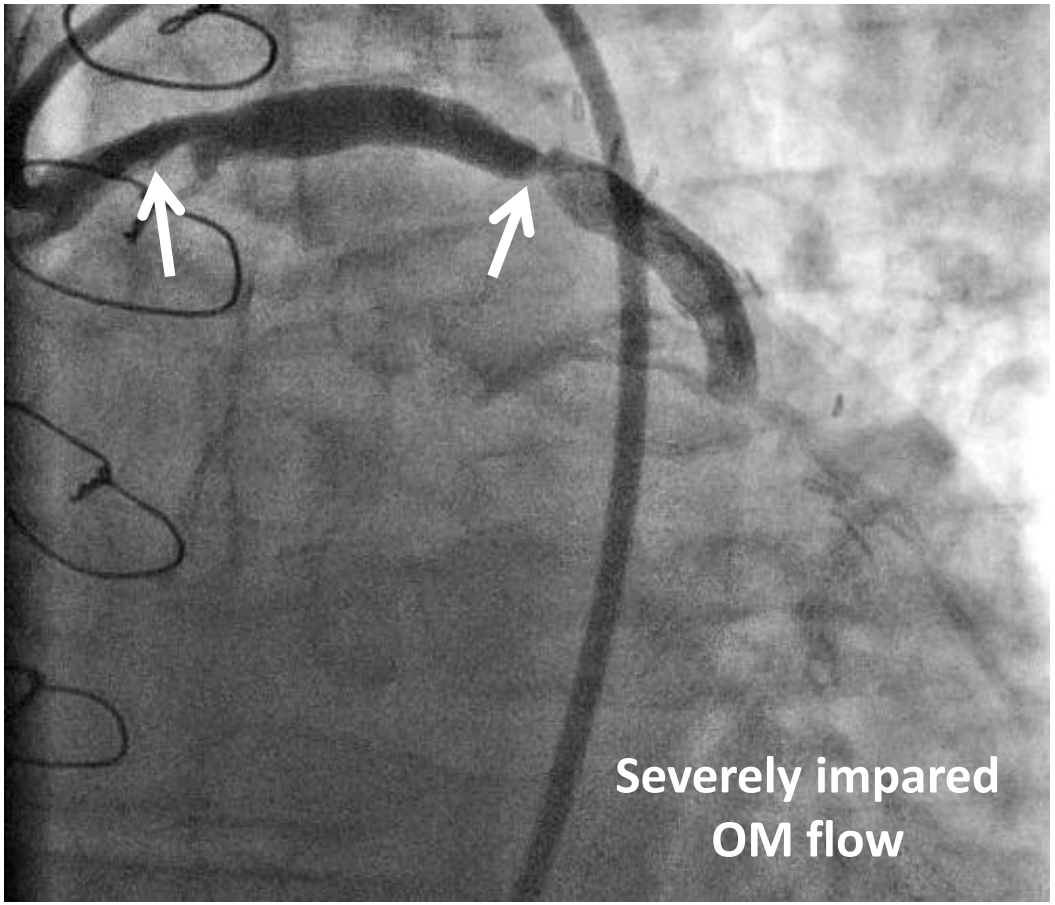


Pt ready for fem-fem (NB. several prior attempts to recanalize LCIA had failed)

Large-diameter SVG disease problem

AK, 58y, NSTE Acute Myocardial Infarction

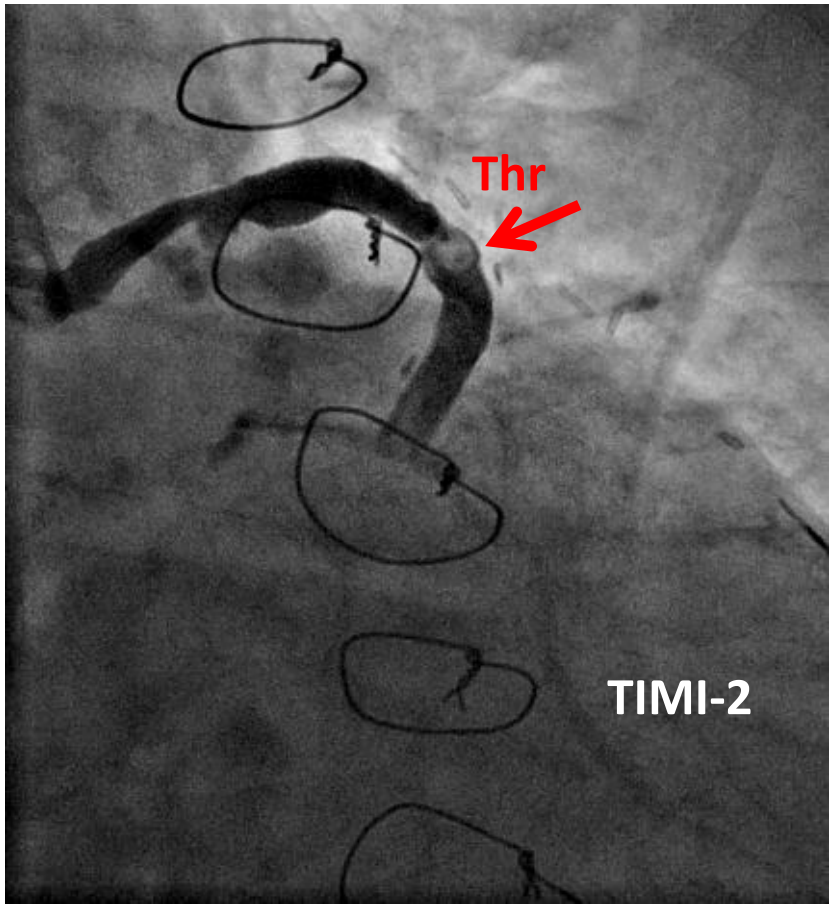


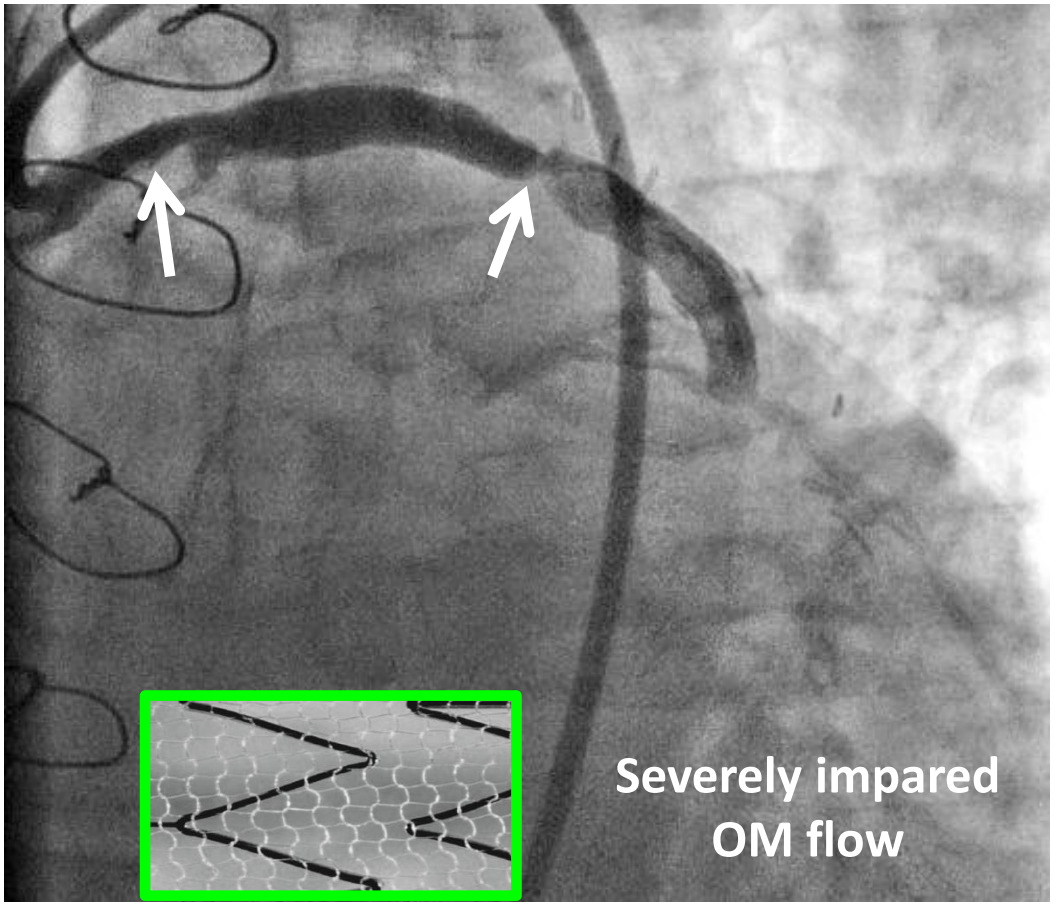


SVG RD 7.5 mm (!)

Large-diameter SVG disease problem

AK, 58y, NSTE Acute Myocardial Infarction

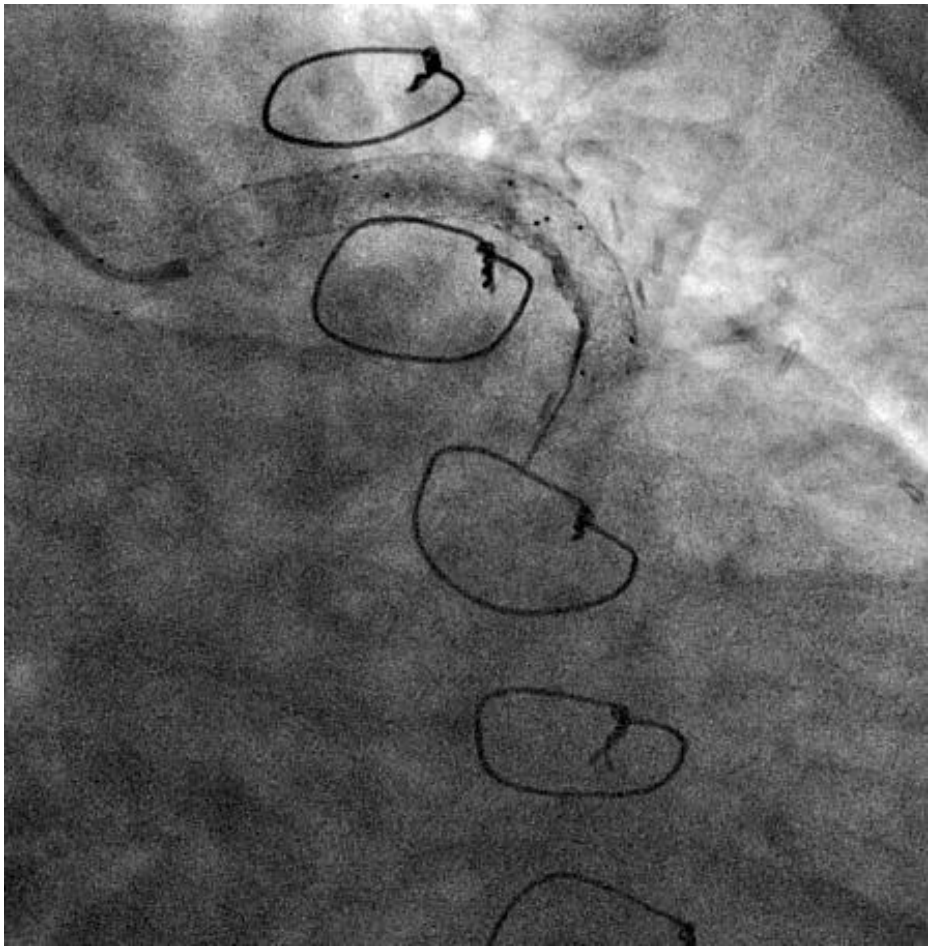


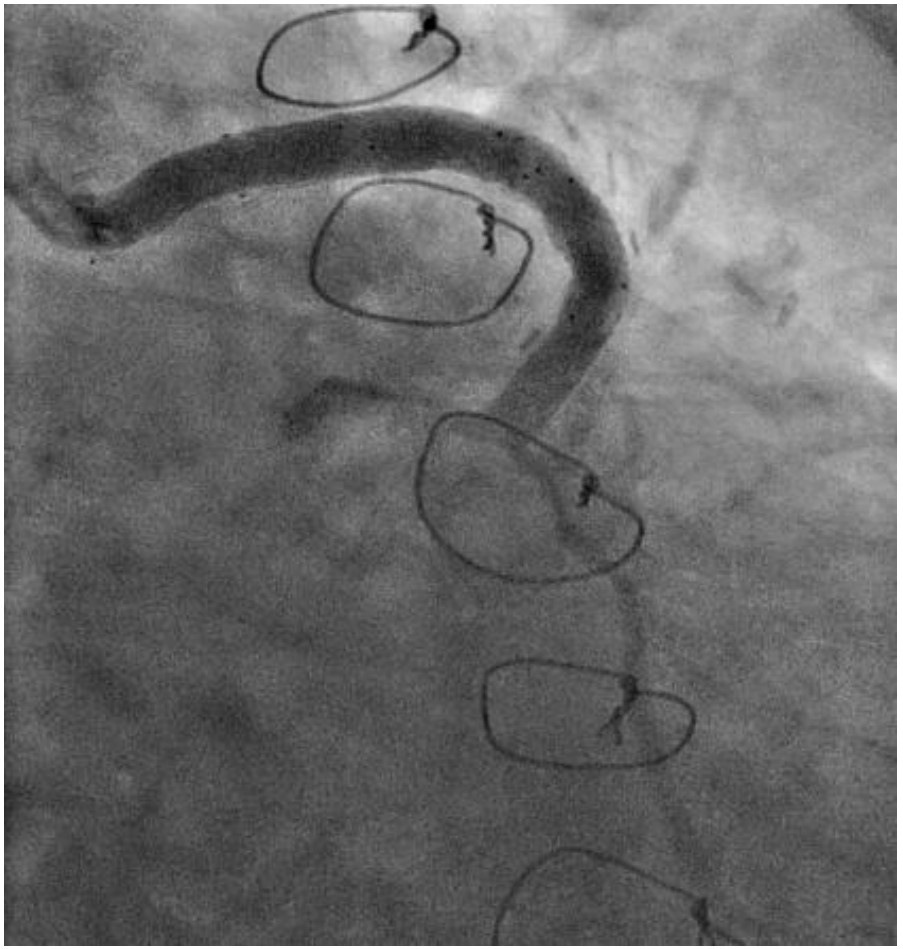


SVG ref diameter 7.5 mm (!)

Large-diameter SVG disease / NSTE-acute MI

post PCI/direct stenting with overlapping MicroNet–covered CGuard™ stents

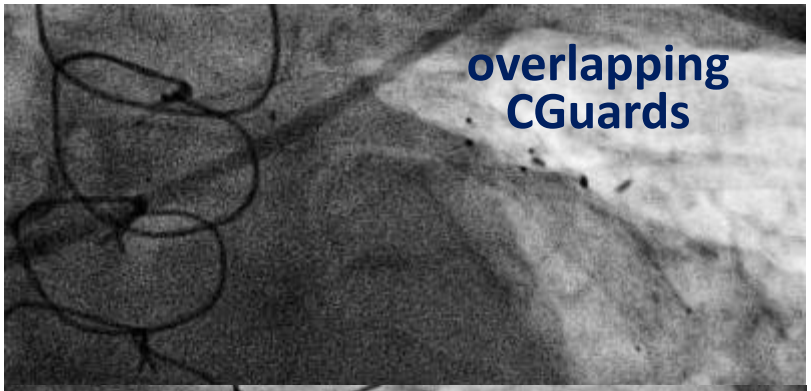


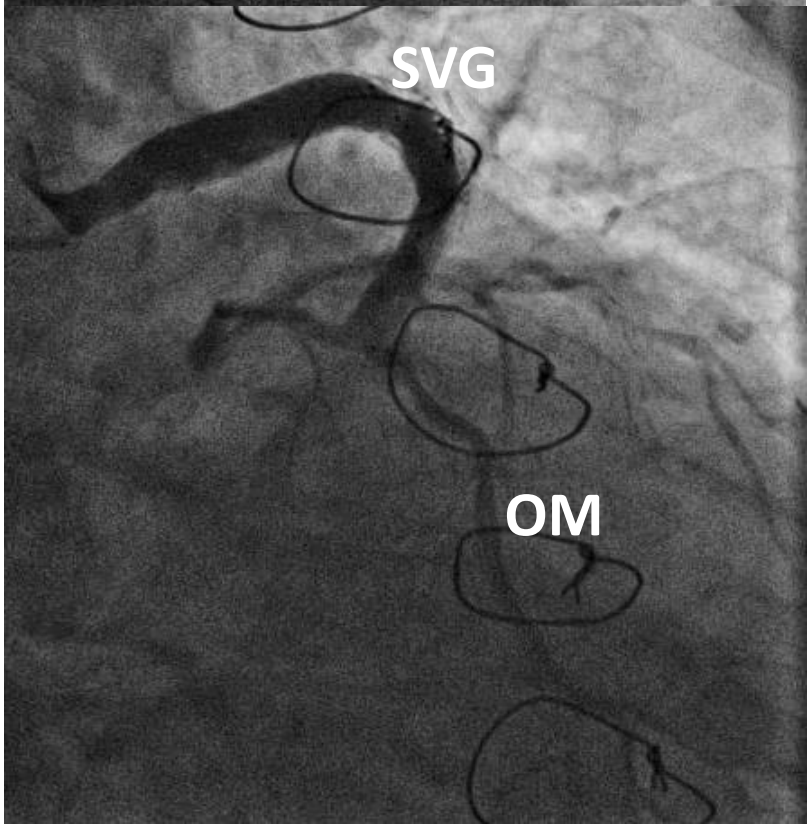


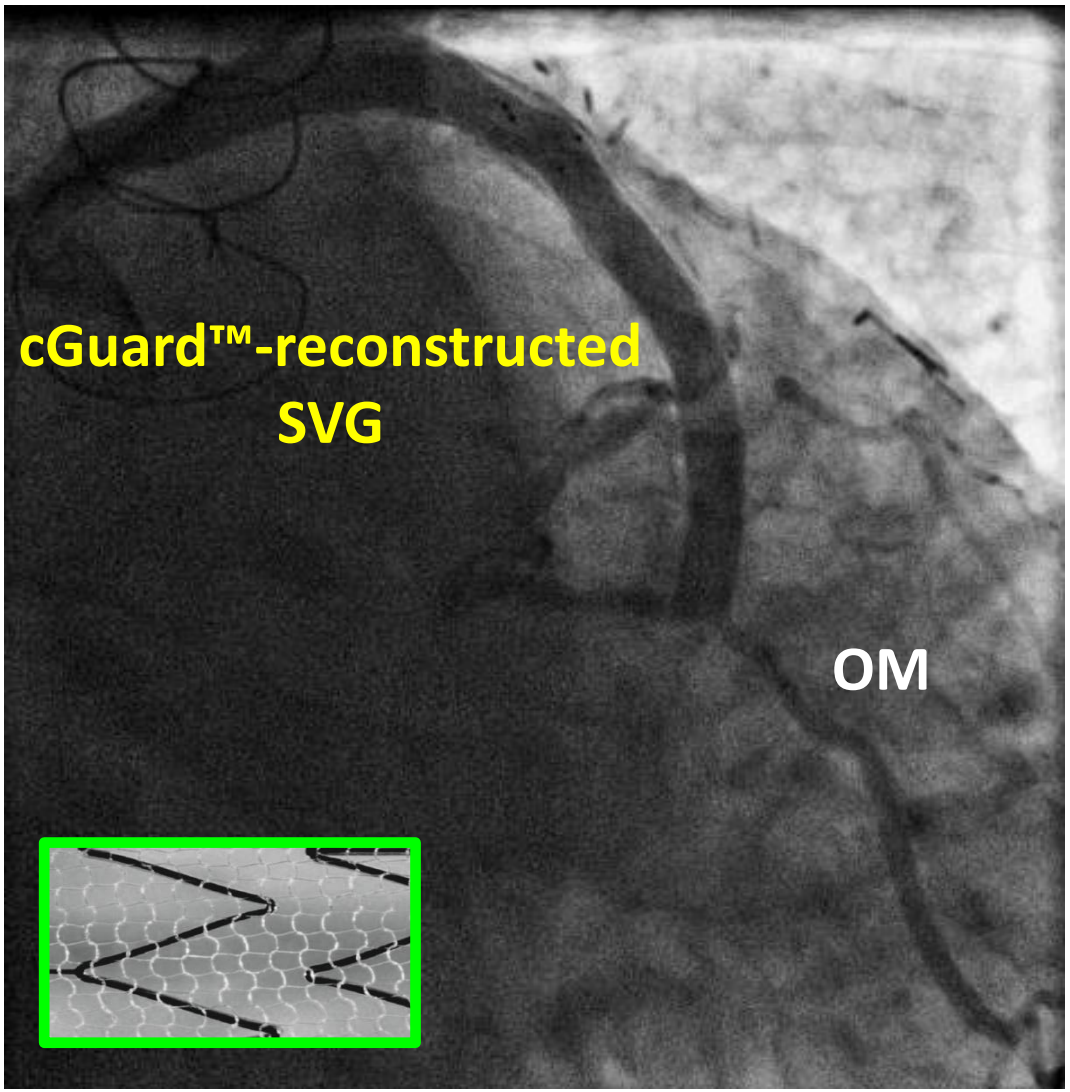
NB. absence of distal embolizm, normal OM flow, no further troponin rise

OPTIMAL acute result

Large-diameter SVG disease treated with CGuards (angio @3mo)

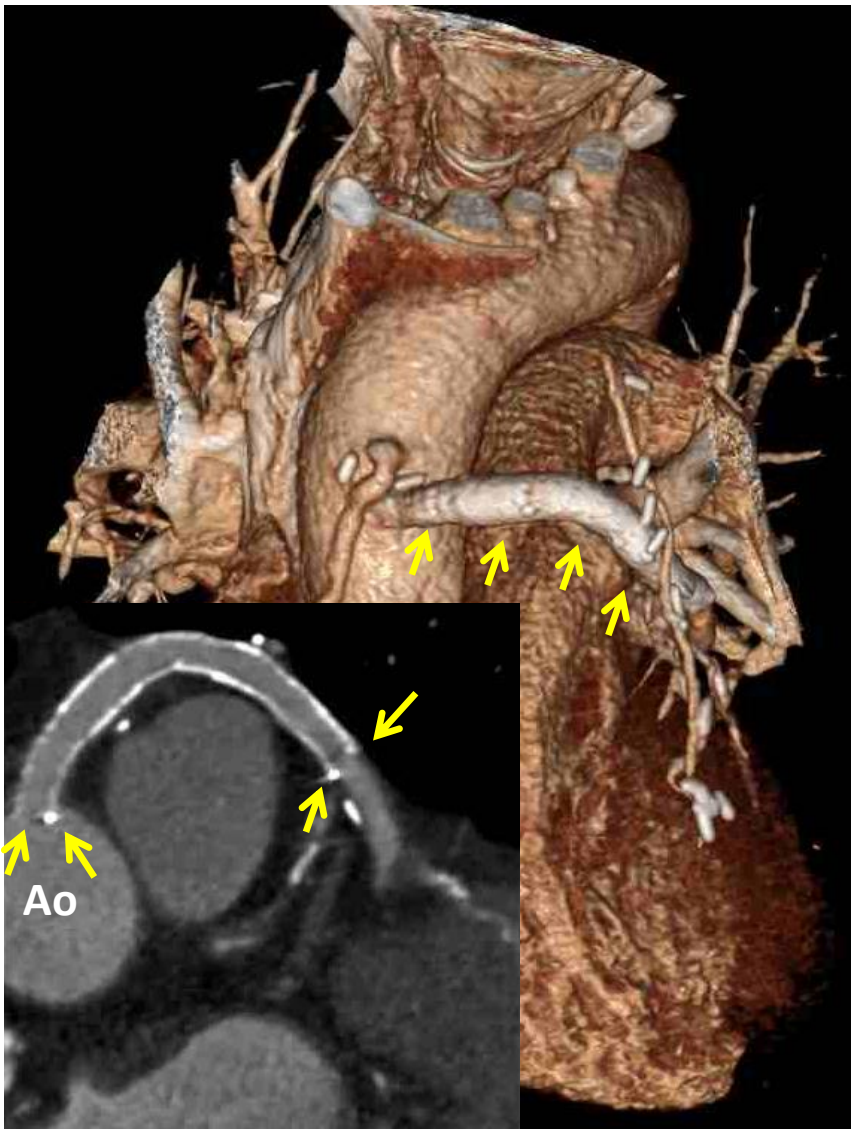


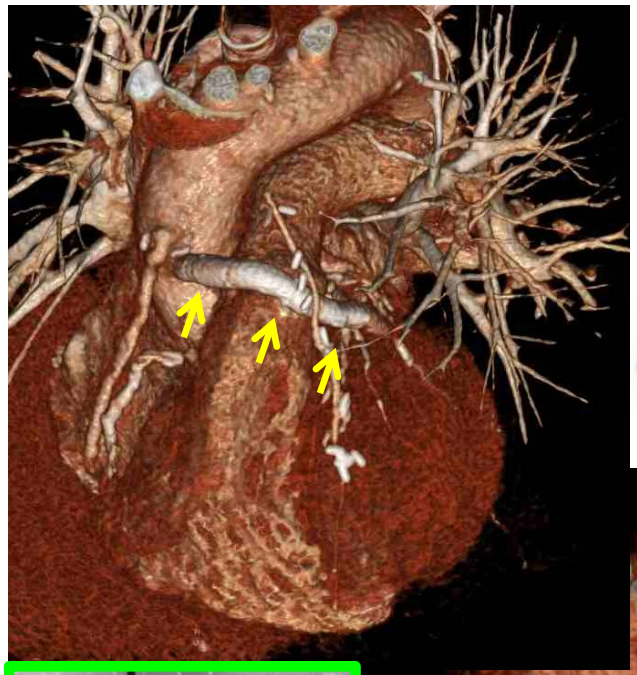


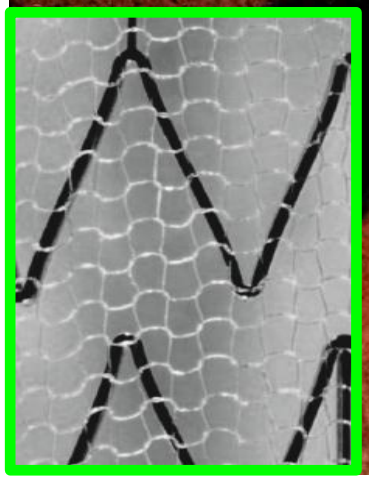


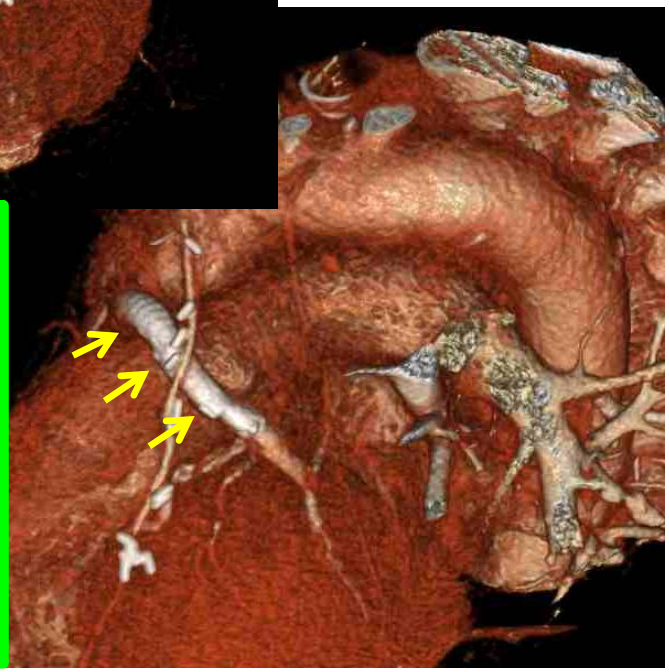
OPTIMAL result @ 3mo

Large-diameter SVG disease treated with CGuards (CT-angio @6mo)







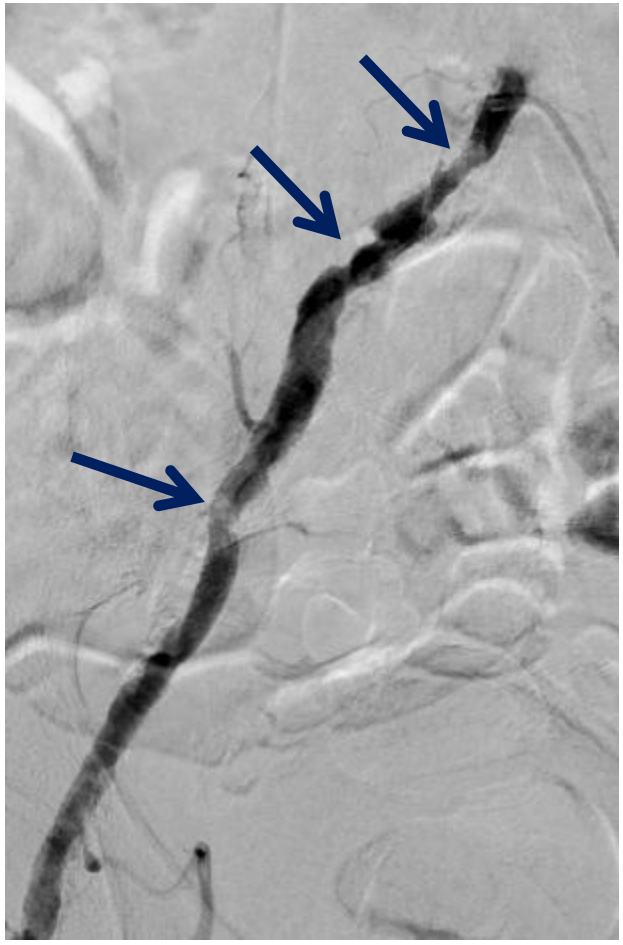


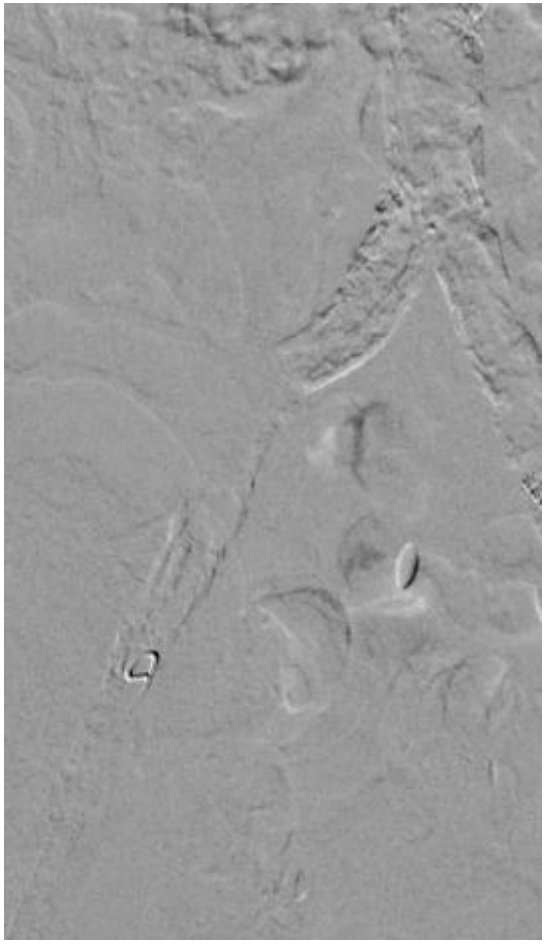
NOTE ostial placement precision feasibility

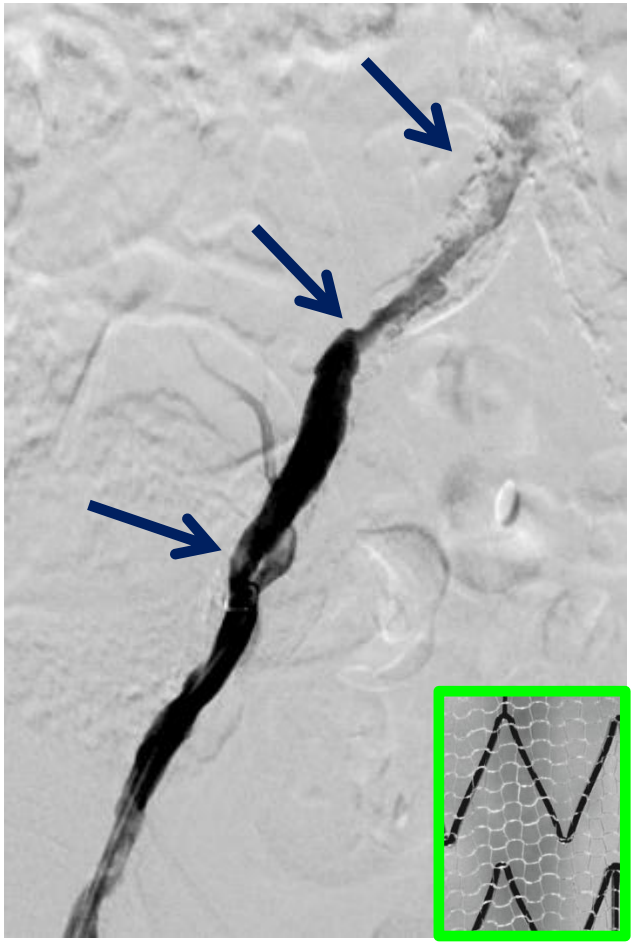
OPTIMAL result @ 6mo

(V) Higly calcific disease

(note: adequate radial force need)

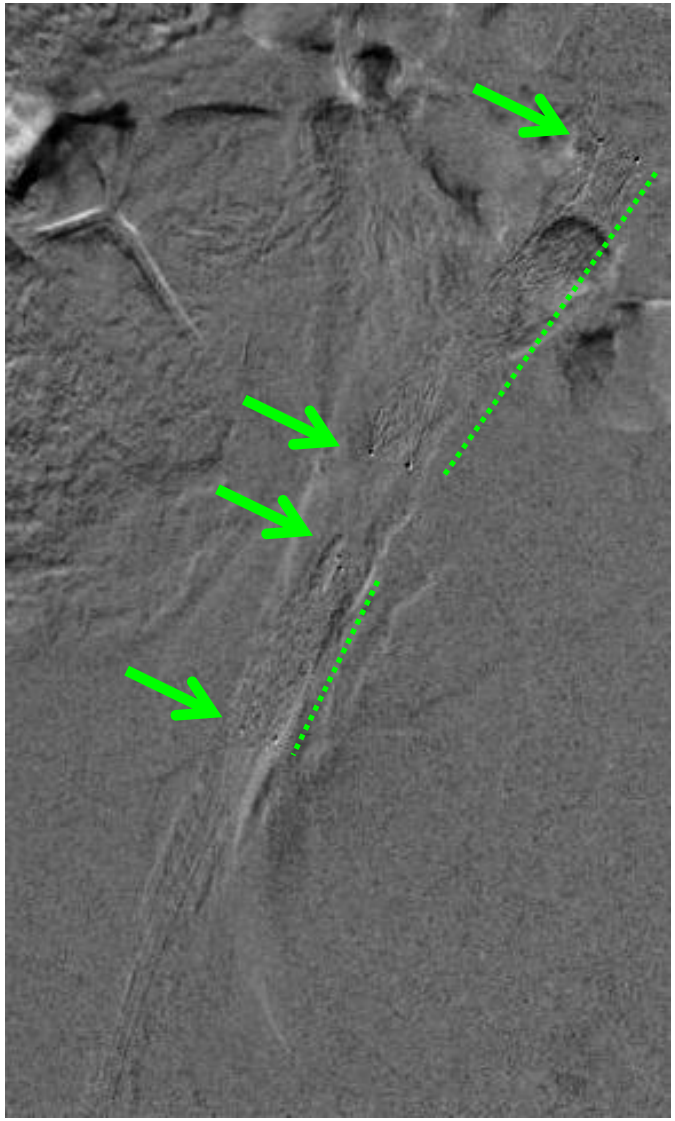






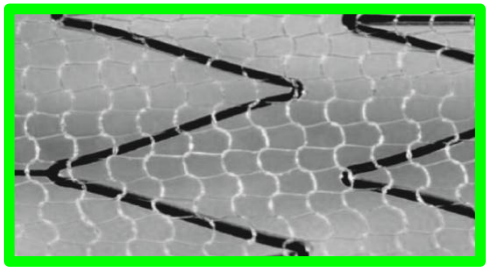
(V) Higly calcific disease

(note adequate radial force need)



CGuard™

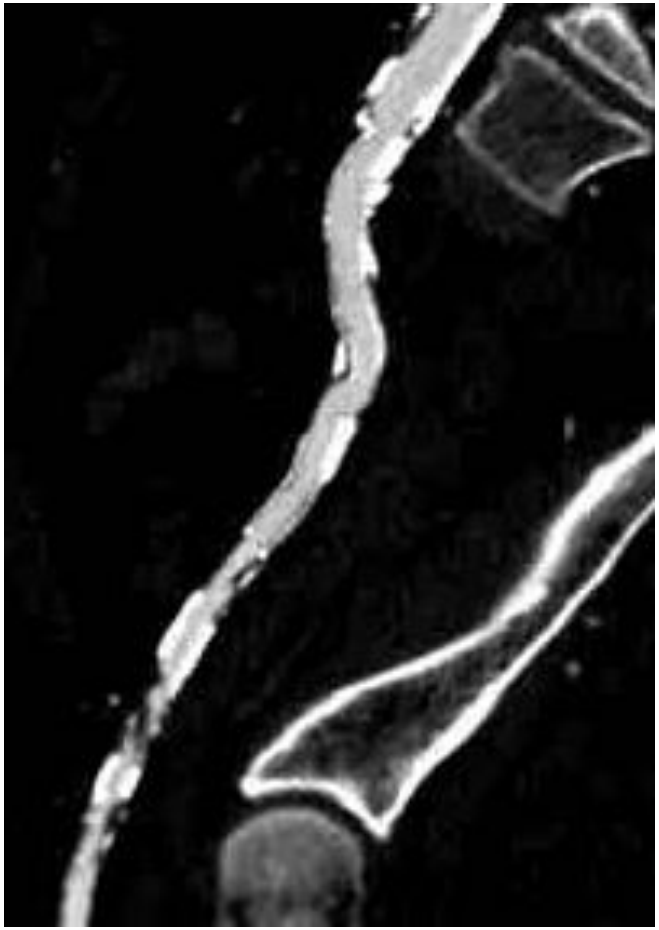
Acute Procedural Result

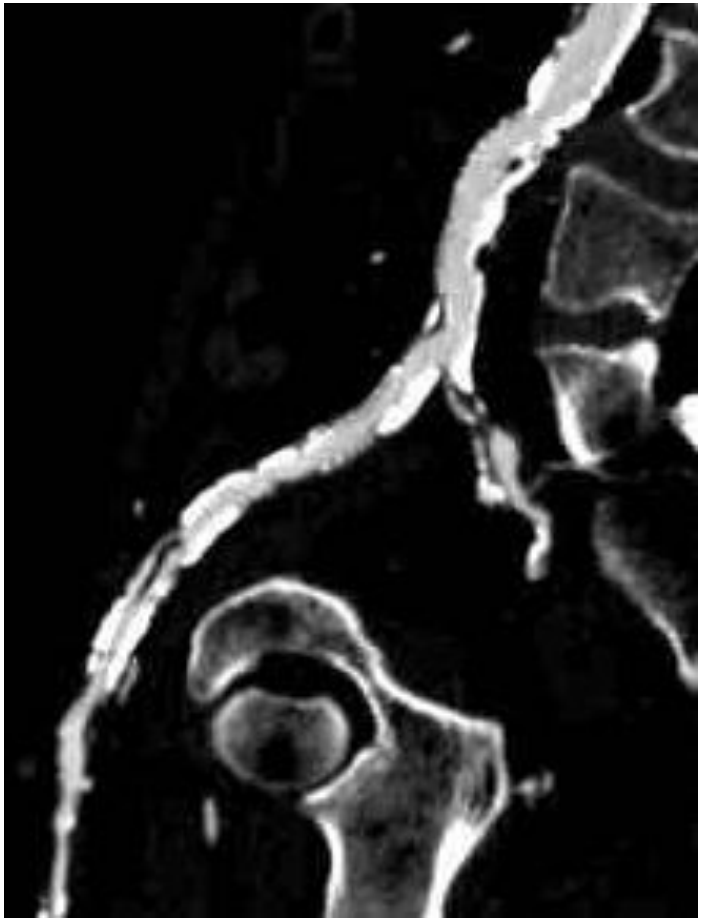


(V) Higly calcific disease

(note: adequate radial force provided)

CGuard™



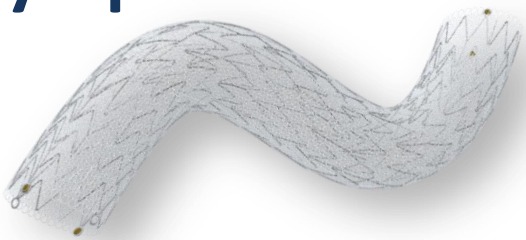


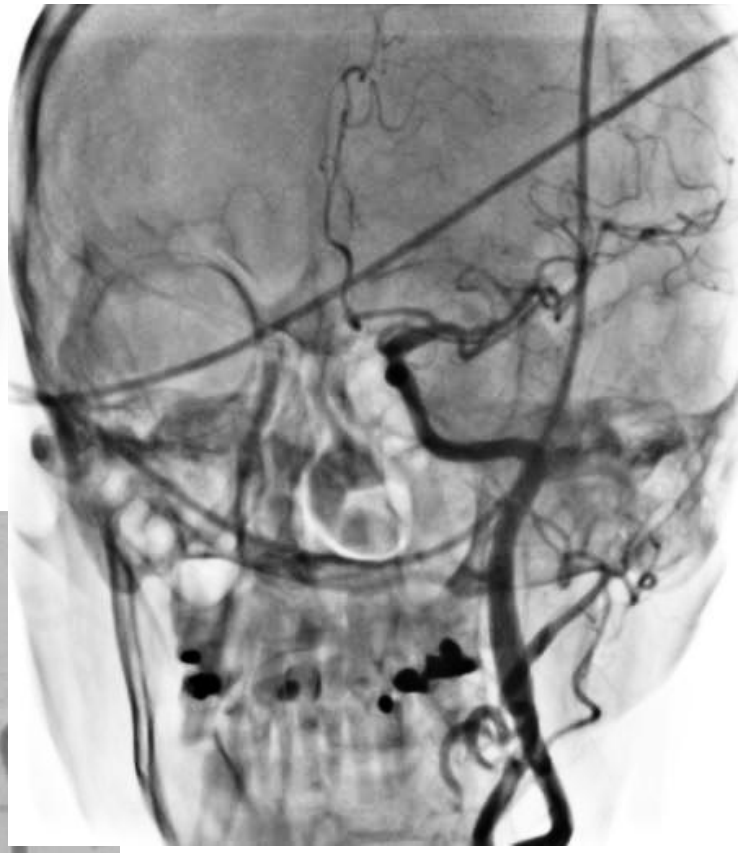
OPTIMAL result @ 6mo

Non-Healing Dissection

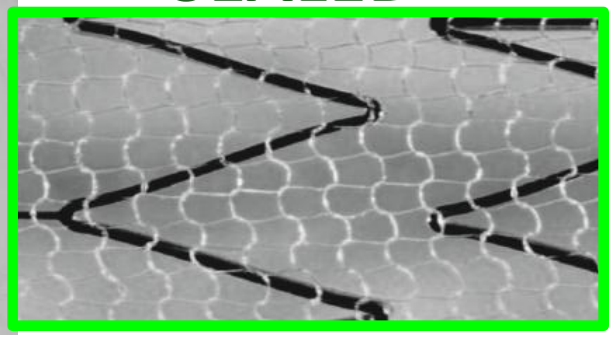
with recurrent symptoms

CGuard™





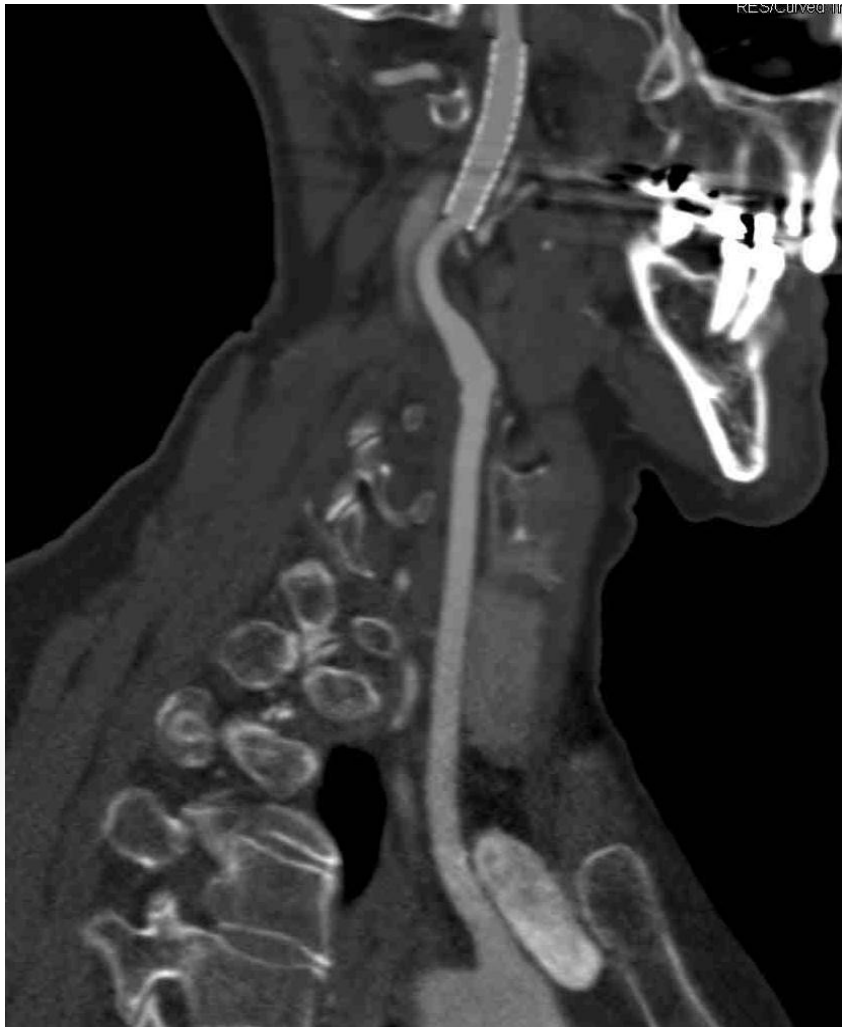
Immediately SEALED



MoMa, IVUS

Non-Healing Dissection

with recurrent symptoms

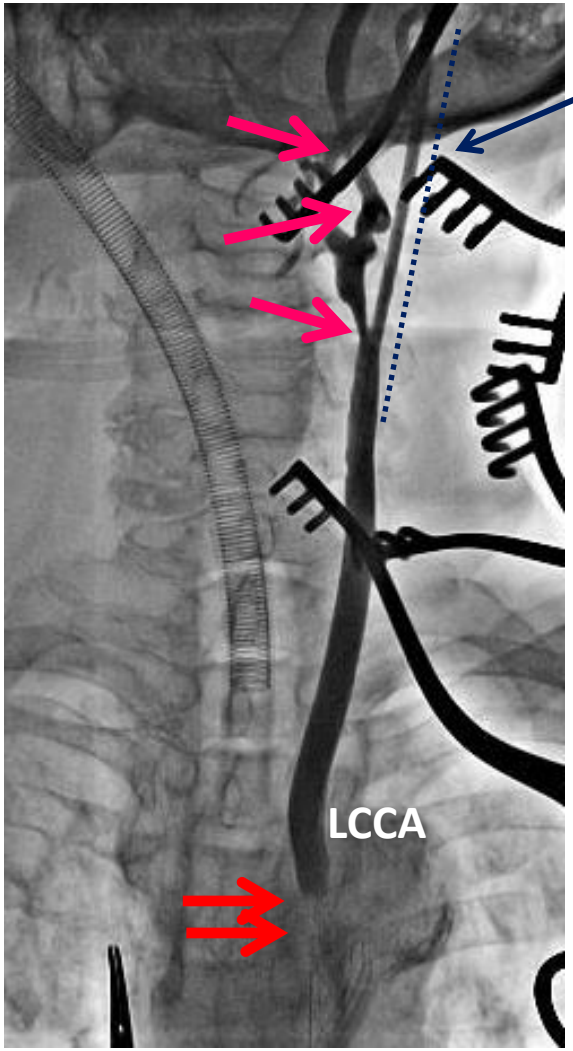


CGuard™

Normal 12 mo Follow-up Result

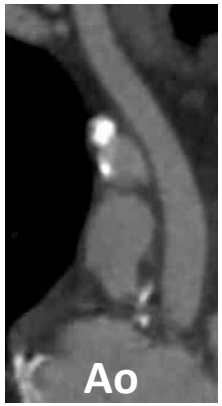
Ostial CCA lesions

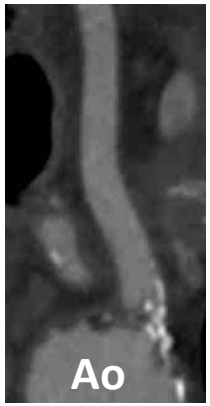
(note adequate radial force and placement percision need)

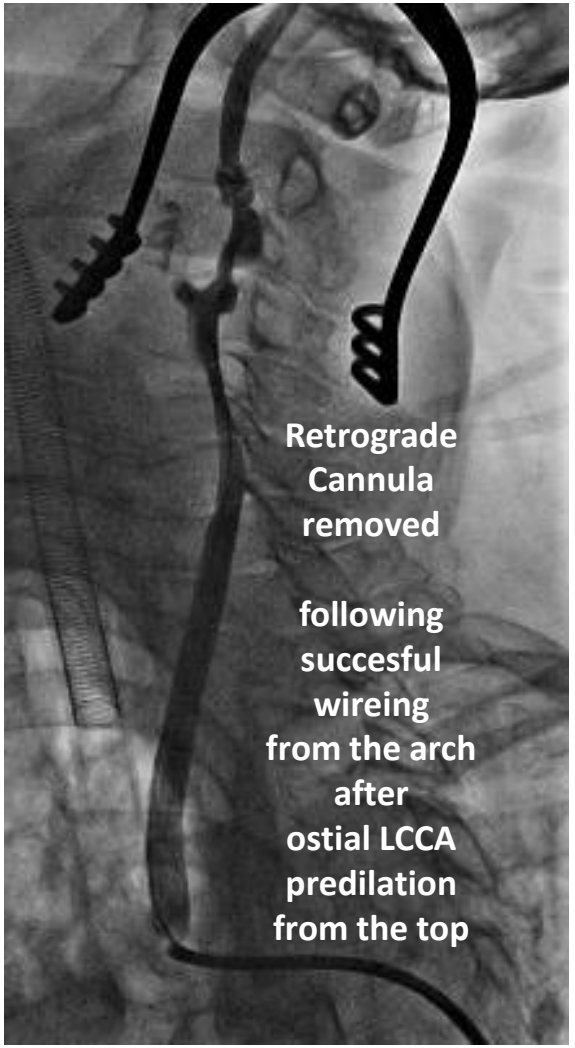


LCCA Retrograde Cannulation from the neck

(to wire and predilate the subtotal ostial LCCA; NB. failed access from the arch)



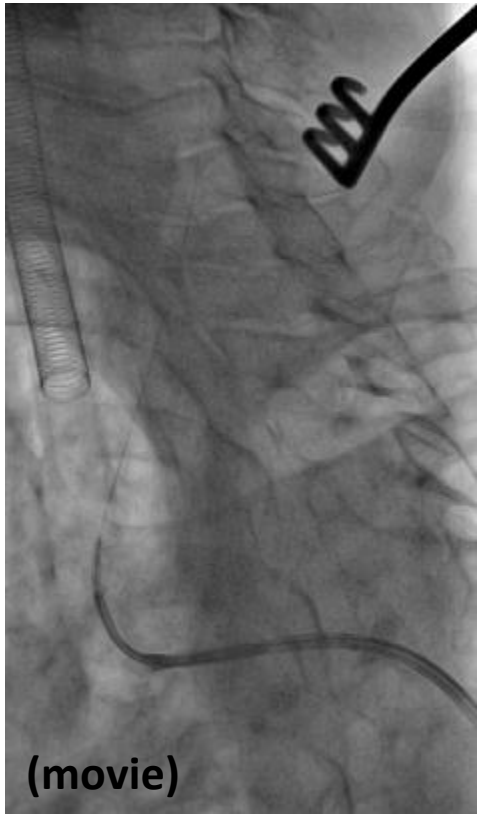


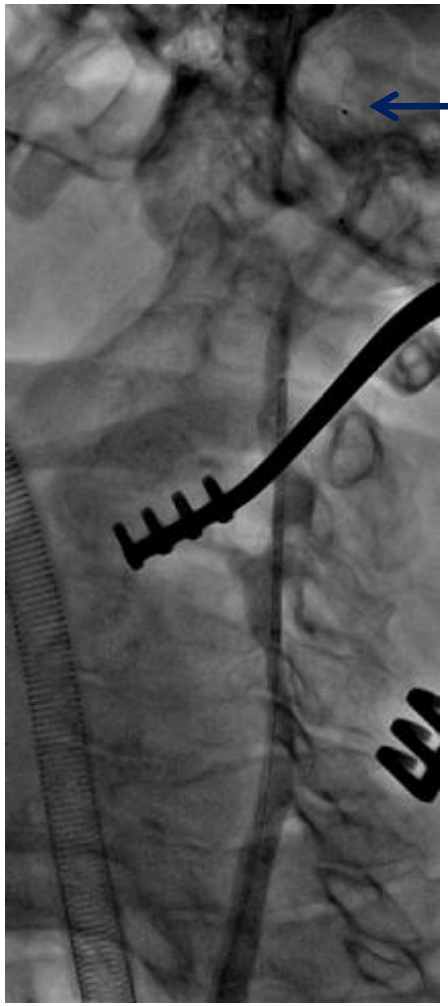


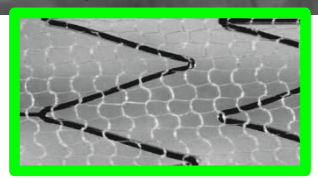
Lady 68 yo, retinal TIAs followed by <u>retinal stroke</u> while on OMT (mother to cathlab nurse)

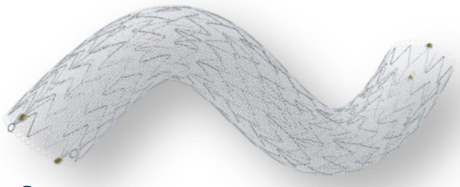
Ostial CCA lesions

(note adequate radial force and placement percision)



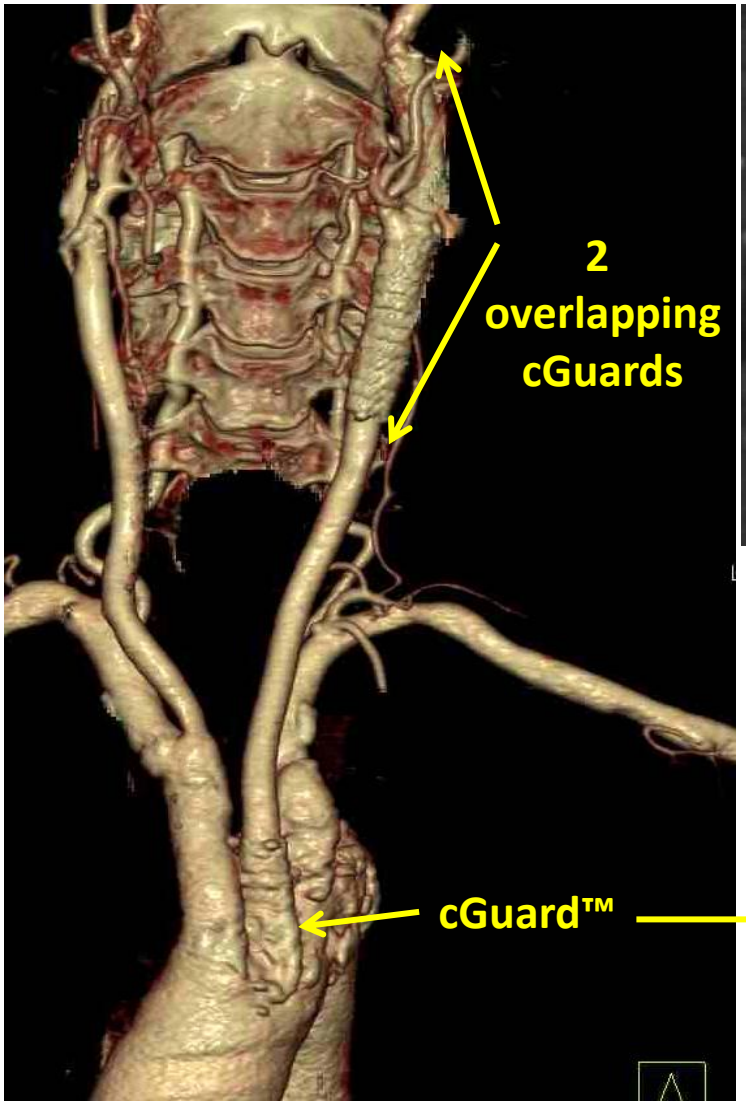


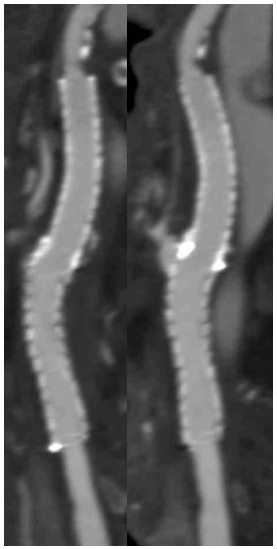




Ostial CCA lesions

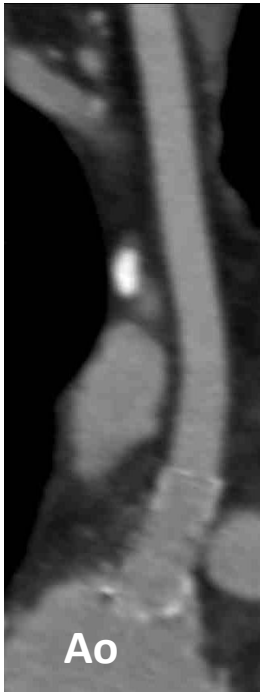
(note adequate radial force and placement percision)





OPTIMAL angiographic + clinical + duplex result @ 12mo

(and LECA patent)



Acknowledgements

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Mariusz Trystuła
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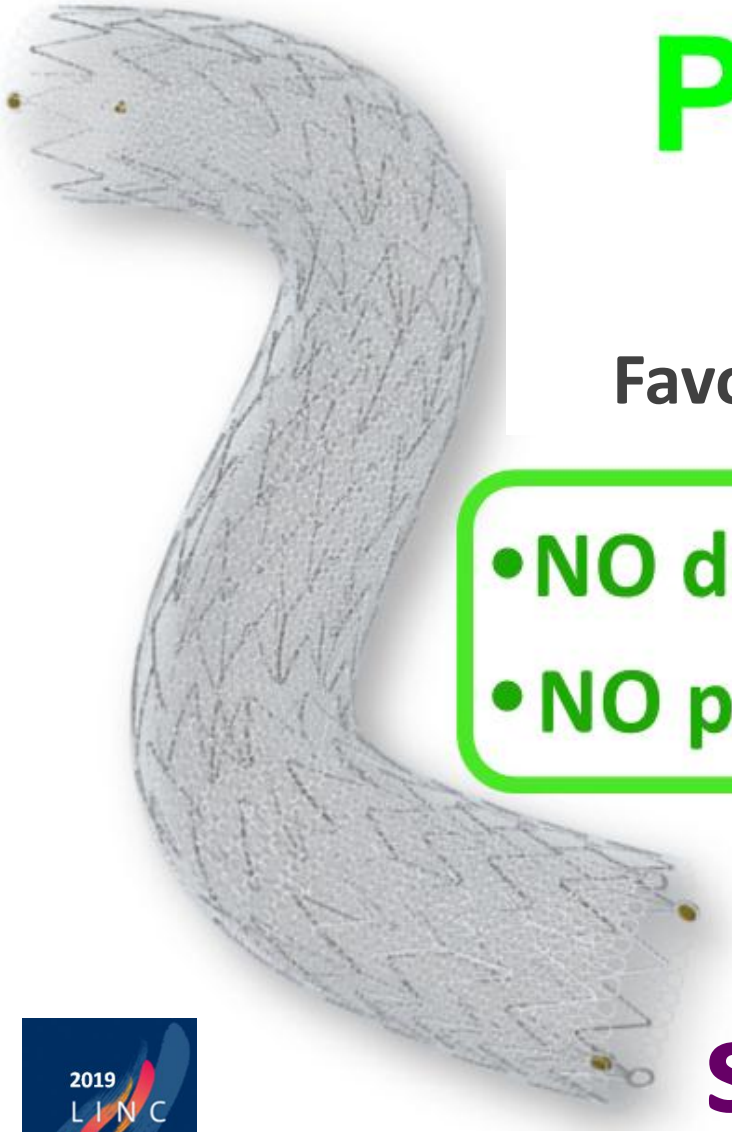
Piotr Wilkołek
Agnieszka Zwolińska

CGUARD™
Carotid Embolic Prevention System

CAROTID PARADIGM REVASCULARIZATION

36-month data



PARADIGM

@ 36 months

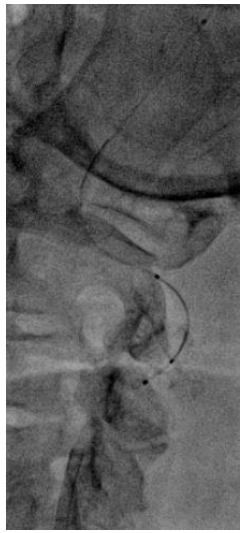
Favourable Clinical Outcome

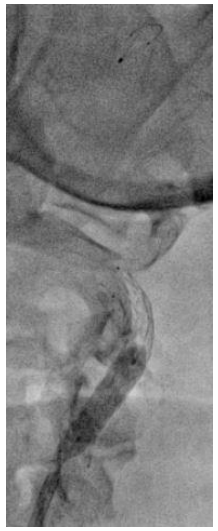
- NO device-related adverse events
- NO procedure-related events

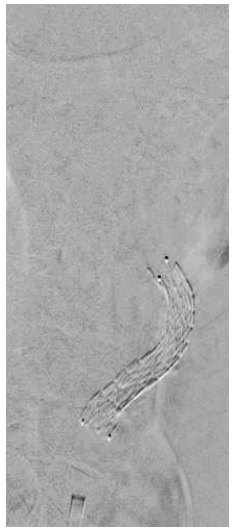
sustained stroke prevention

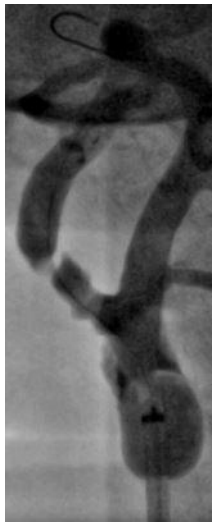
2019 LINC

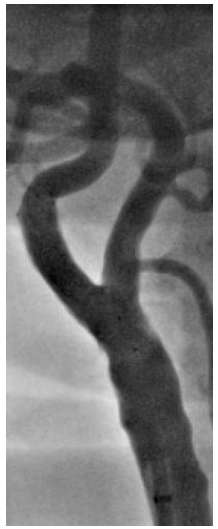
Endovascular Solution for All-Comers





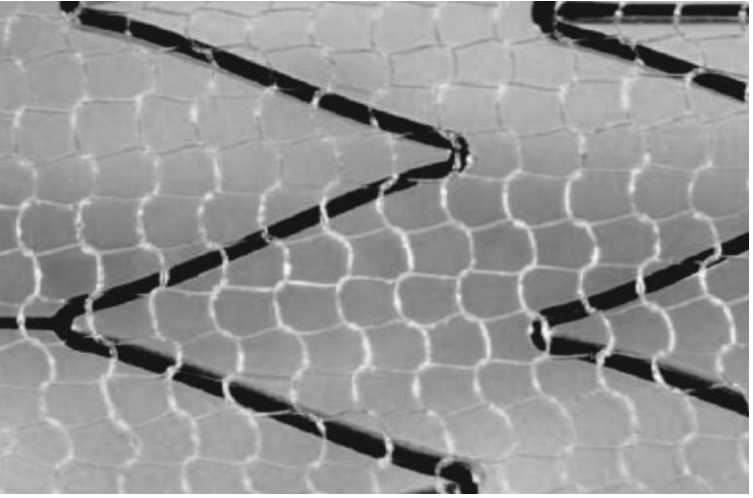


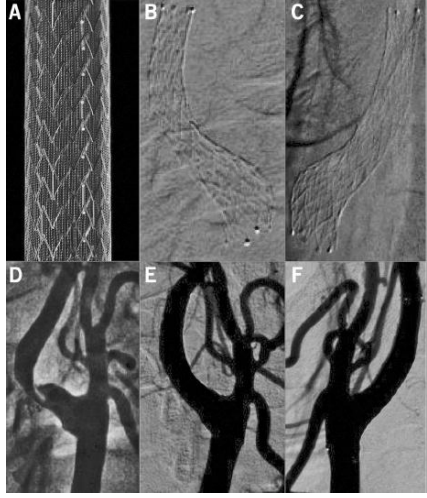




Endovascular Reconstruction of the Carotid Bifurcation

Prevention of embolism, High radial force, Conformability



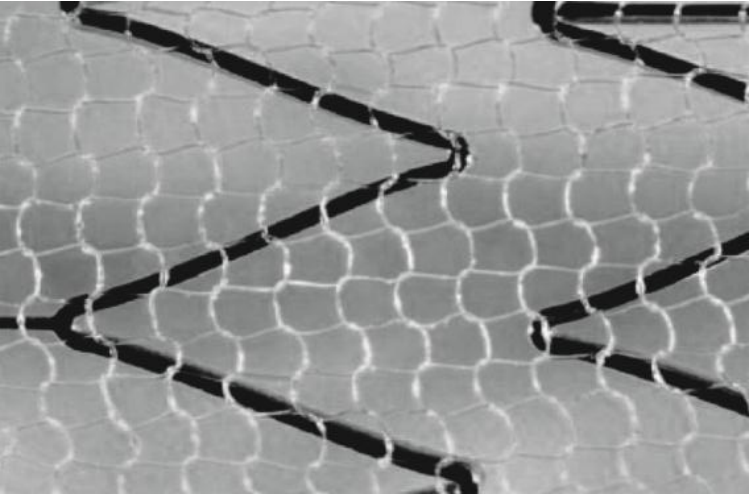


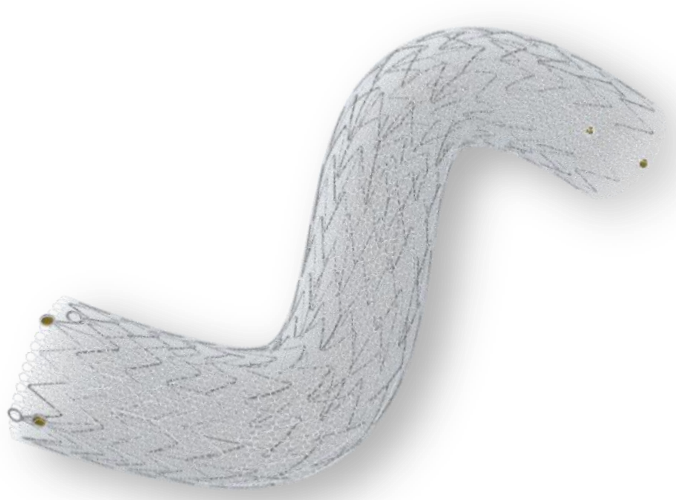
This concept has been desired.

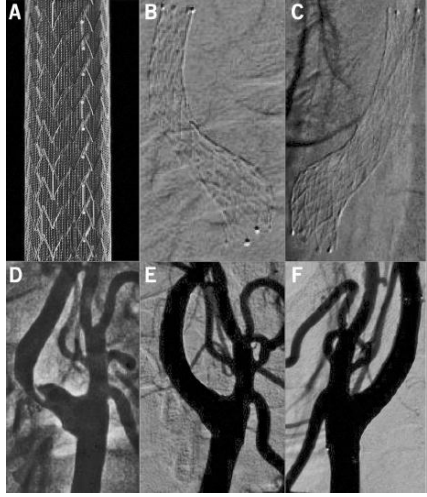
And it works.

This is the future

of Carotid Artery ~~Stenting~~







This concept has been desired.

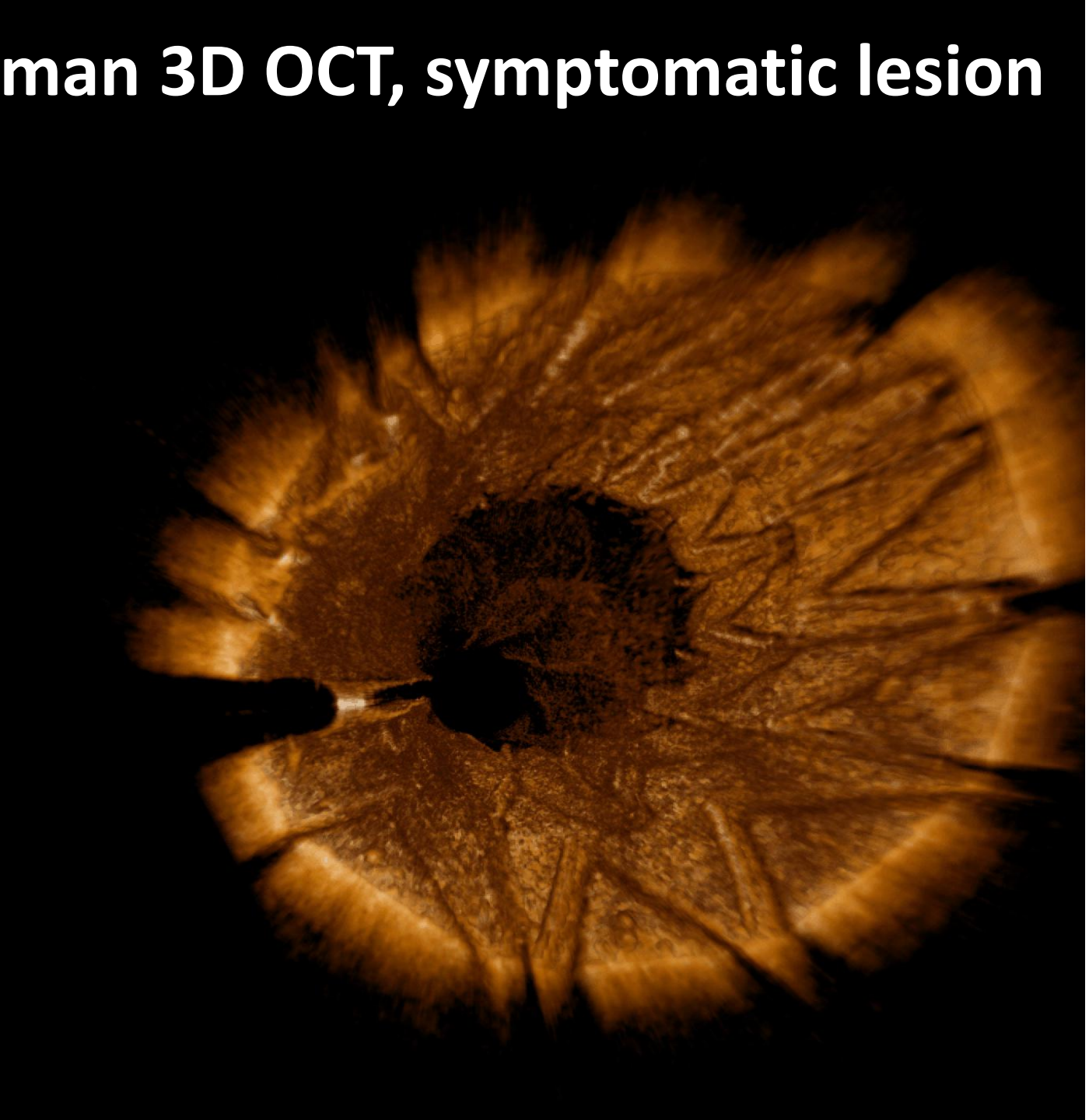
And it works.

This is the future

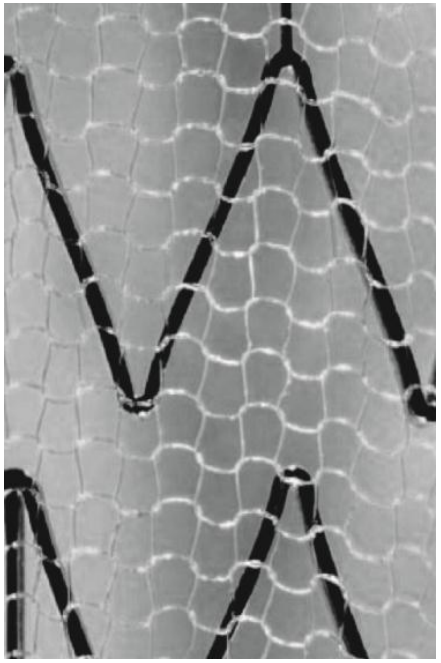
of Carotid Artery S[illegible]g

revascularization !

man 3D OCT, symptomatic lesion



CGuard™ EPS



One swallow does not a summer make but many swallows do: accumulating clinical evidence for nearly-eliminated peri-procedural and 30-day complications with mesh-covered stents transforms the carotid revascularisation field

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Abstract

Atherosclerotic carotid artery stenosis (CS) continues to be a common cause of acute ischaemic stroke. Optimised medical therapy (OMT), the first-line treatment modality in CS, may reduce or delay – but it does not abolish – CS-related strokes. As per current AHA/ASA and ESC/ESVS/ESO guidelines, carotid artery stenting (CAS) is a less-invasive alternative to carotid endarterectomy (CEA) for CS revascularisation in primary and secondary stroke prevention.

Ten-year follow-up from the CREST trial in patients with symptomatic and asymptomatic CS confirmed equipoise of CAS and CEA in the primary endpoint. Nevertheless CAS – using a widely open-cell, first-generation stent and first-generation (distal/filter) neuroprotection – has been criticised for its relative excess of (mostly minor) strokes by 30 days, a significant proportion of which were post-procedural.

Atherosclerotic plaque protrusion through conventional carotid stent struts, confirmed on intravascular imaging, has been implicated as a leading mechanism of the relative excess of strokes with CAS vs. CEA, including delayed strokes with CAS. Different designs of mesh-covered carotid stents have been developed to prevent plaque prolapse. Several multi-centre/multi-specialty clinical studies with CGurad MicroNet-Covered Embolic Prevention Stent System (EPS) and RoadSaver/Casper were recently published and included routine DW-MRI cerebral imaging peri-procedurally and at 30 days (CGuard EPS).

Data from more than 550 patients in mesh-covered carotid stent clinical studies to-date show an overall 30-day complication rate of ~1% with near-elimination of post-procedural events. While more (and long-term) evidence is still anticipated, these results – taken together with optimised intra-procedural neuroprotection in CAS (increased use of proximal systems including trans-carotid dynamic flow reversal) and the positive 12-month mesh-covered stent data reports in 2017 – are transforming the carotid revascularisation field today.

Establishing effective algorithms to identify the asymptomatic subjects at stroke risk despite OMT, and large-scale studies with mesh-covered stents including long-term clinical and duplex ultrasound outcomes, are the next major goals.

Key words: carotid artery stenting, mesh, stroke, endarterectomy, neuroprotection.

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PARADIGM-EXTEND: Prospective Academic Trial of CGuard™ MicroNET-Covered Self-Expandable Stent System:

Cumulative 3-Year Clinical and Duplex Ultrasound Evidence for Safety, Efficacy and Durability of Stroke Prevention

Piotr Musialek, MD DPhil

on behalf of the PARADIGM-EXTEND Study Team

Jagiellonian University Dept. of Cardiac & Vascular Diseases
John Paul II Hospital, Krakow, Poland

Prospective 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 extension