ESC Essential Update 2020

Carotid Disease

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Disclosures

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

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Atherosclerotic Carotid Disease

- Relatively common condition (prevalence similar to AFib)
- Mechanistic –and modifiable– risk factor for ischaemic stroke (thrombo-embolic more often than haemodynamic)

Table 14-2. Modifiable Stroke Risk Factors

Factor	Prevalence, %	PAR, %*	RR
Cigarette smoking			
Overall	19.8	12–14†	1.9
Men	22.3		
Women	17.4		
Hypertension		‡	8
Diabetes mellitus	7.3	5–27	1.8–6.0
High total cholesterol	Data calculated for highest quintile (20%) vs lowest quintile	9.1 (5.7–13.8)	1.5 (95% CI, 1.3–1.8)
	Continuous risk for ischemic stroke	…	1.25 per 1-mmol/L (38.7 mg/dL) increase
AF (nonvalvular)			
Overall age, y			
50–59	0.5	1.5	4.0
60–69	1.8	2.8	2.6
70–79	4.8	9.9	3.3
80–89	8.8	23.5	4.5
Asymptomatic carotid stenosis	2–8	2–7§	2.0

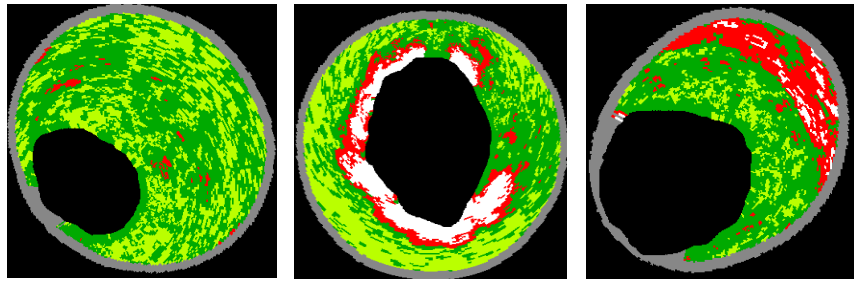
AHA Heart Disease and Stroke Statistics

ESC Congress 2020
The Digital Experience

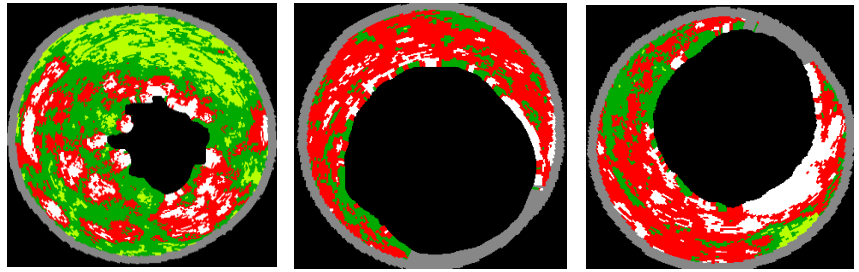
Atherosclerotic Carotid Disease

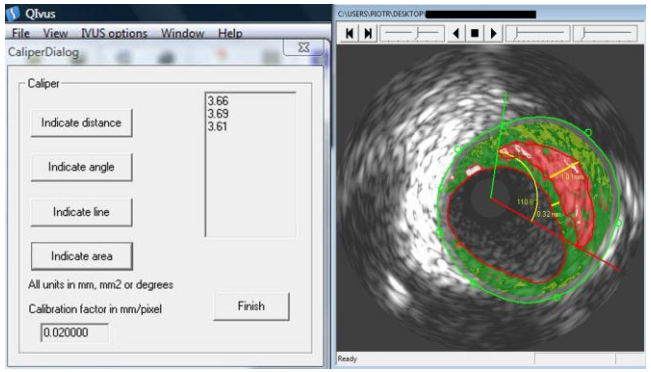
- **The disease is in the <u>wall</u>**, luminal are its manifestations…

(relatively)
safe
carotid plaques



↑ risk
carotid plaques



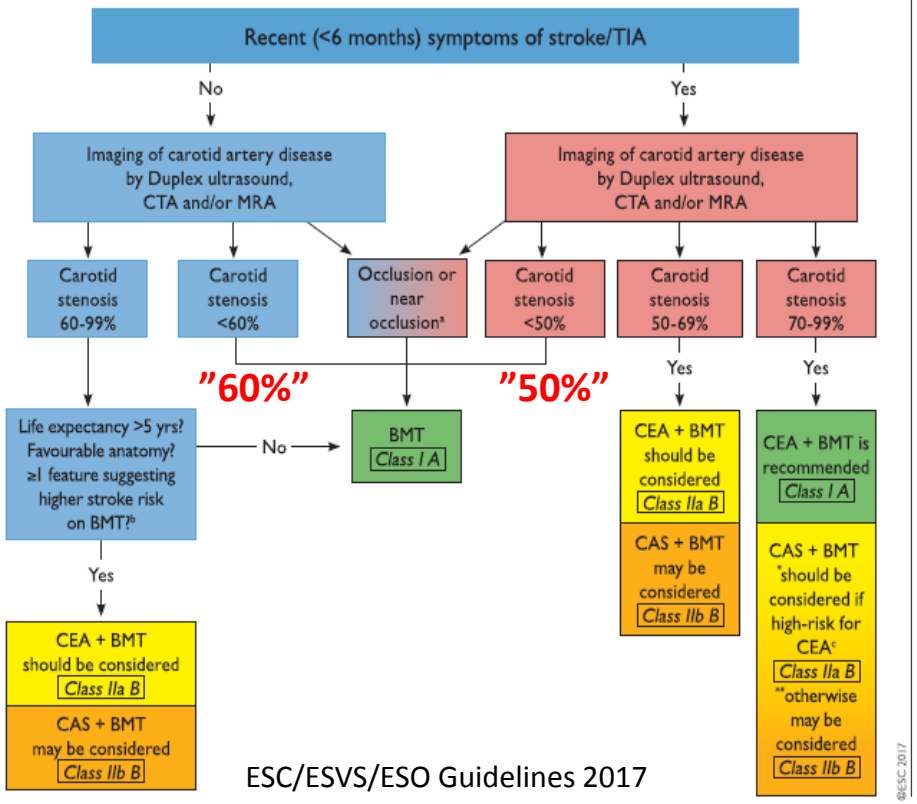


- Lumen stenosis severity, once it exceeds "≈50%", is a poor inde of the disease severity and stroke risk (see eg. Derdeyn CP. *Stroke* 2007 Pooled ACAS and ACST Trials data)
- Most strokes, including major, occur *without* any warning
- **'*Waiting for clinical symptoms*' harms stroke-affected patients**

cf. **Intravascular Ultrasound: From Acquisition to Advanced Quantitative Analysis** (ed. S. Balocco), Elsevier 2000, ISBN: 978-0-12-818833-0
Note several other imaging techniques including eg. NIRS for lipid-rich content and non-invasive modalities as MRI or CT that have the advantage of ability to screen larger populations on an out-patient basis and without vessel interrogation – but have a significantly lower resolution that is critical in determining the thin fibrous cap

WHAT is a ”50%”… ”60%”… ”69%”… ”70%”… (or ”90/95%”) carotid stenosis?

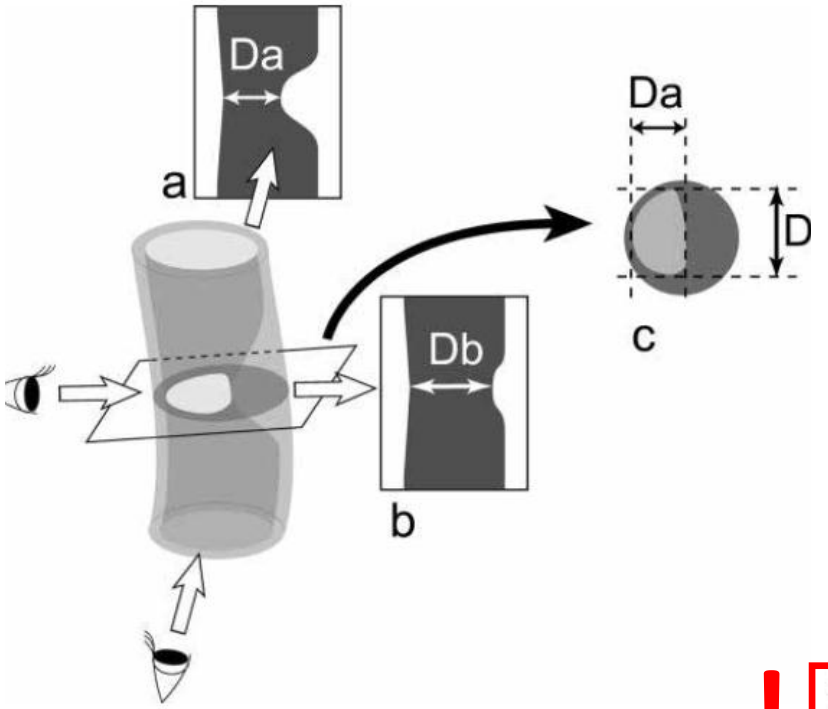
Guidelines continue
to put a lot weight to ”stenosis severity”
-that remains v. poorly defined-
(assessment modality? measurement method?)



ESC/ESVS/ESO Guidelines 2017

”50%” is also (and at the same time) ”75%” – and ”75%” is ”95%”!

Plaque excentricity and projection angle(s)

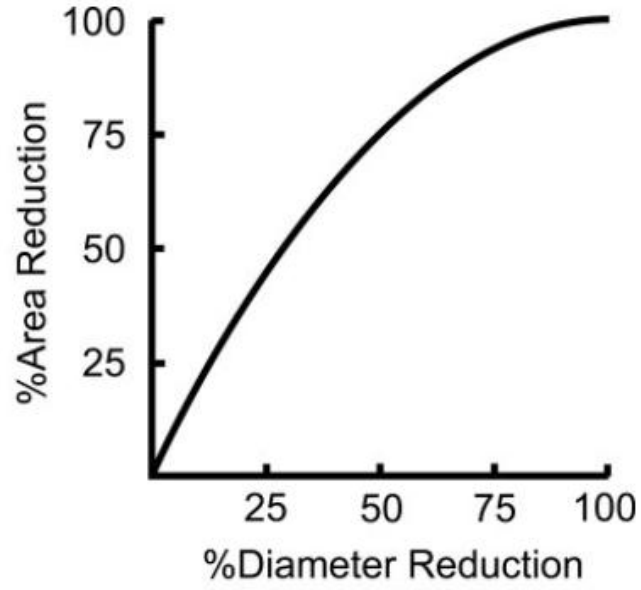


Ota H et al. *RadioGraphics* 2005

AREA vs. DIAMETER reduction

different ***routine*** modalities in studies

CT_{angio} MRI_{angio} classic QA



%Area	44%	75%	94%	99%
%Diameter	25%	50%	75%	90%

+ other confounders (DUS velocity in contralateral occlusion & lesion length, velocity vs. anatomy/angio)

Annual stroke rate with paroxysmal AFib on ASA

- **2.1% per year** (Vanassche T et al. *Eur Heart J* 2015)

A **HUGE** concern, attracting **A LOT** of attention & research efforts

Annual stroke rate with asymptomatic carotid stenosis in contemporary cardiovascular clinic patients on Optimized Medical Therapy

- **2.4% per year** (Conrad MF et al. *J Vasc Surg* 2013)… 5 years… 10 years…
- **2.9% per year** (Kakkos SK et al. *J Vasc Surg* 2014)… 5 years… 10 years…

SPECIAL COMMUNICATION

Best medical treatment alone may not be adequate for all patients with asymptomatic carotid artery stenosis

Kosmas I. Paraskevas, MD, PhD,[a] Frank J. Veith, MD, FACS,[b,c] *and* Jean-Baptiste Ricco, MD, PhD, FEBVS,[d]
London, United Kingdom; New York, NY; Cleveland, Ohio; and Poitiers, France

See also Cambria RP, Conrad MF. *J Vasc Surg* **2020**;71:2-4.

JAMA Neurology | Original Investigation

Prevalence of High-Risk Plaques and Risk of Stroke in Patients With Asymptomatic Carotid Stenosis

A Meta-analysis

JAMA Neurology Published online August 3, 2020

Joseph Kamtchum-Tatuene, MD; Jean Jacques Noubiap, MD; Alan H. Wilman, PhD; Maher Saqqur, MD; Ashfaq Shuaib, MD; Glen C. Jickling, MD

20 751 participants
mean follow-up (only!) 2.8 years

Incidence of ipsilateral ischaemic cerebrovascular events (CVA) in relation to selected plaque-level risk features (echolucency, neovascularization, lipid-rich necrotic core)

Overall incidence of ipsilateral ischaemic CVAs was 3.2 events per 100 person-years and it was **higher in patients with high-risk plaques** (4.3 events per 100 person-years) than in those without high-risk plaques (1.2 events per 100 person-years), with an **odds ratio of 3.0** (95%CI, 2.1-4.3).

!!

In studies focusing on **severe stenosis** the overall incidence of ipsilateral ischaemic CVAs was 3.7 events per 100 person-years and it was **also higher in patients with high-risk plaques** (7.3 events per 100 person-years) than in those without high-risk plaques (1.7 events per 100 person-years), with an **odds ratio of 3.2** (95%CI, 1.7-5.9).

=> Extension of routine assessment of asymptomatic carotid stenosis beyond the grade of stenosis may help improve risk stratification and optimize therapy

ESC European Society of Cardiology

European Heart Journal (2018) **39**, 763–821
doi:10.1093/eurheartj/ehx095

ESC GUIDELINES

2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)

Endorsed by: the European Stroke Organization (ESO)

Features associated with increased risk of stroke in patients with 'asymptomatic' carotid stenosis treated medically

Clinical[a]	• Contralateral TIA/stroke[121]
Cerebral imaging	• Ipsilateral silent infarction[122]
Ultrasound imaging	• Stenosis progression (> 20%)[123] • Spontaneous embolization on transcranial Doppler (HITS)[124] • Impaired cerebral vascular reserve[125] • Large plaques[b][126] • Echolucent plaques[96] • Increased juxta-luminal black (hypoechogenic) area[127]
MRA	• Intraplaque haemorrhage[128] • Lipid-rich necrotic core

Not (yet?) in the Guidelines
published domain evidence

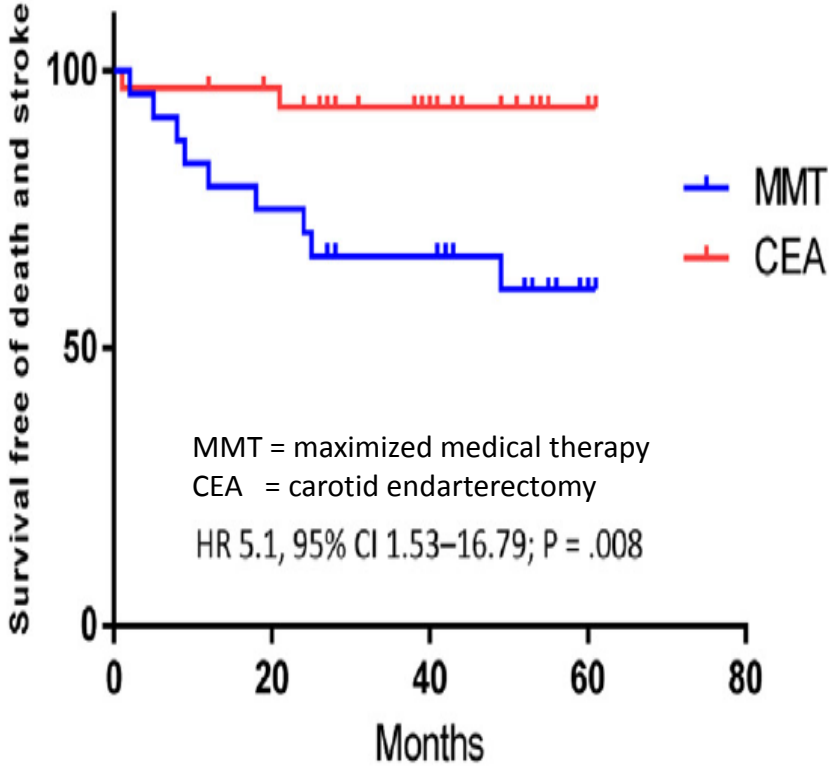
– Thrombus-containing
– Irregular and/or ulcerated
– Contralateral occlusion

Mauriello A et al. *Atehrosclerosis* 2010

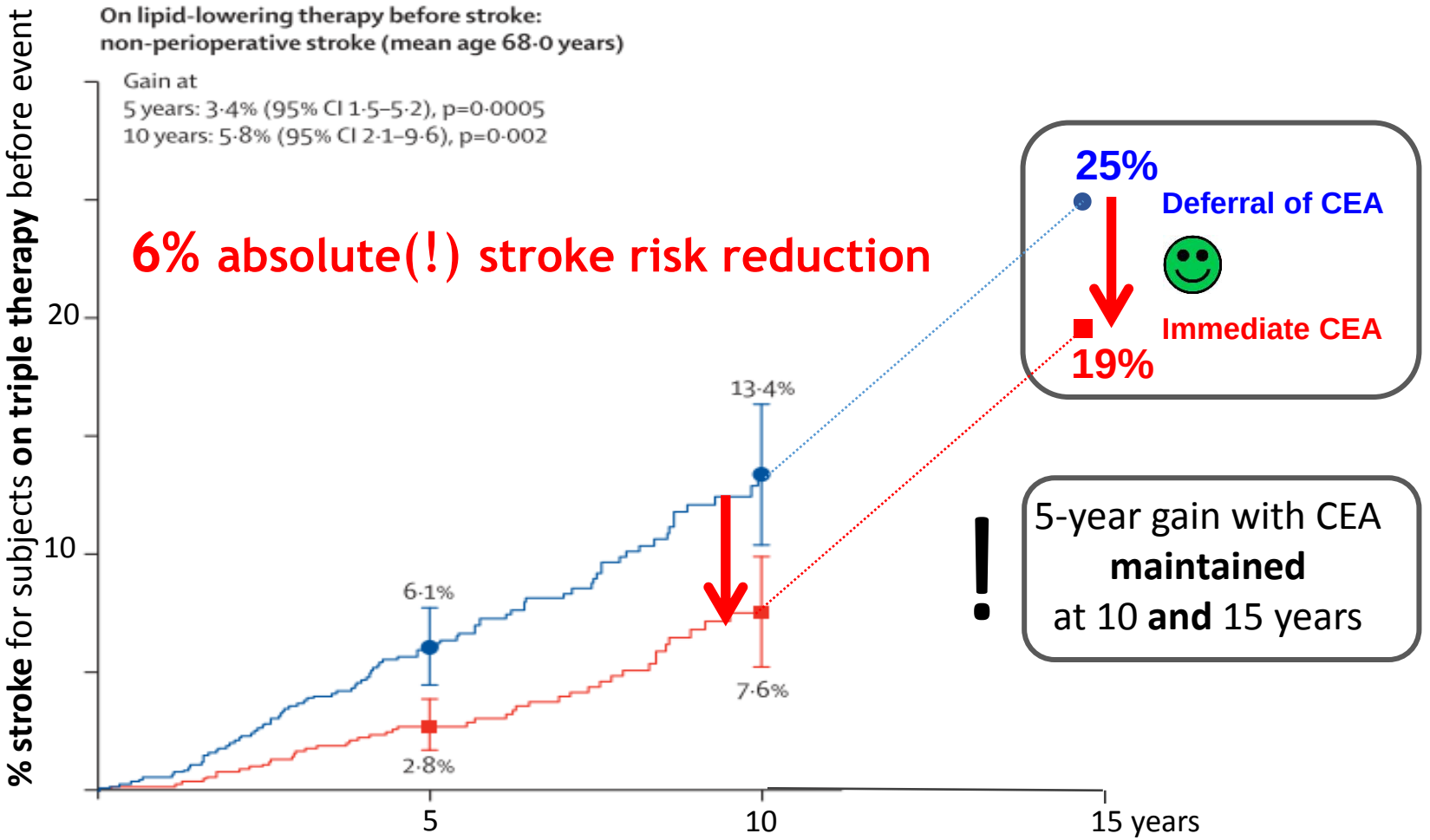
AbuRahma A et al. *Ann Surg.* 2003;238:551-562.
Ballotta E et al. *J Vasc Surg* 2007;45:516-522.
Kakkos SK et al. (ACSRS) *J Vasc Surg.* 2009;49:902-909.
Lovett JK et al. *Circulation* 2004;110:2190-97
Nicolaides AN et al. *J Vasc Surg* 2010;52:1486-96.
Taussky P et al. *Neurosurg Focus* 2011;31:6-17.

Revascularization in Asymptomatic Carotid Disease:
Reduces Stroke Risk Long-Term & Irrespective of 'Triple' Pharmacotherapy

AMTEC RCT in Asymptomatic CS:
Trial **STOPPED** by DSMB
because of harm in the OMT patients



Kolos et al. *J Vasc Surg* 2015



Asymptomatic Carotid Surgery Trial (ACST-1) data at 15 years
as per presentations by Prof. A. Halliday/Prof. R. Bulbulia, modified

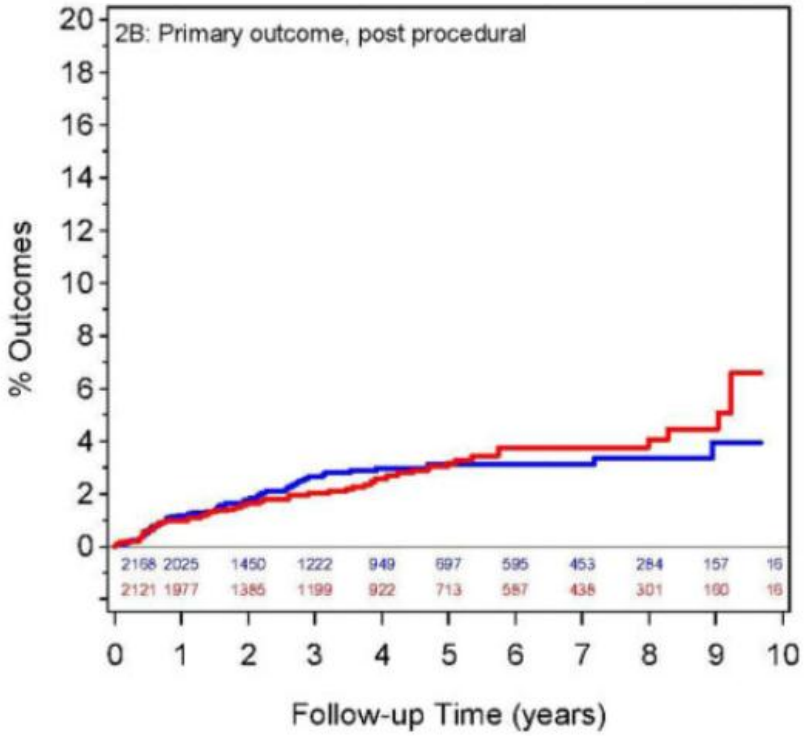
Long-term outcomes of stenting and endarterectomy for symptomatic carotid stenosis: a pre-planned pooled analysis of individual patient data Brott TG et al. *Lancet Neurol.* 2019

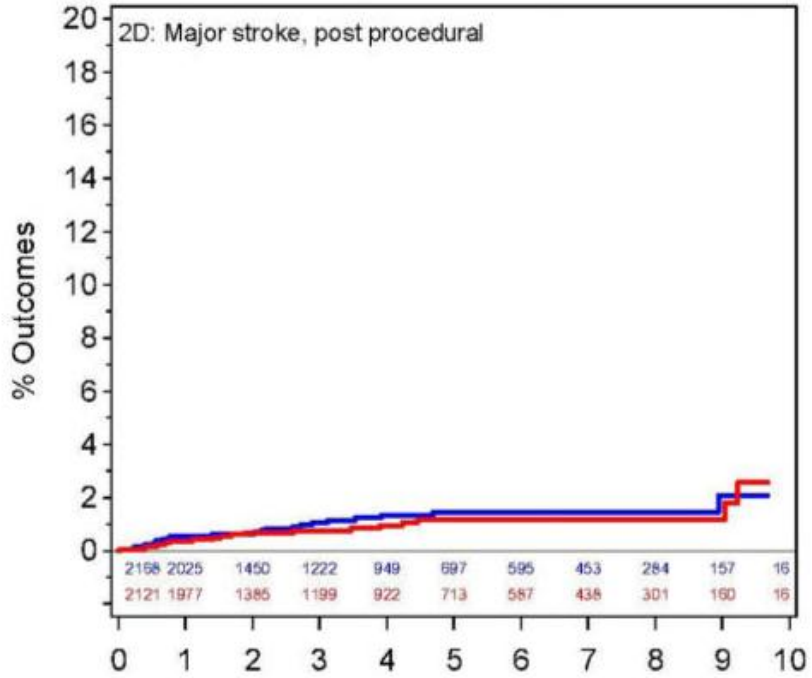
EVA-3S *plus* SPACE *plus* CREST *plus* ICSS

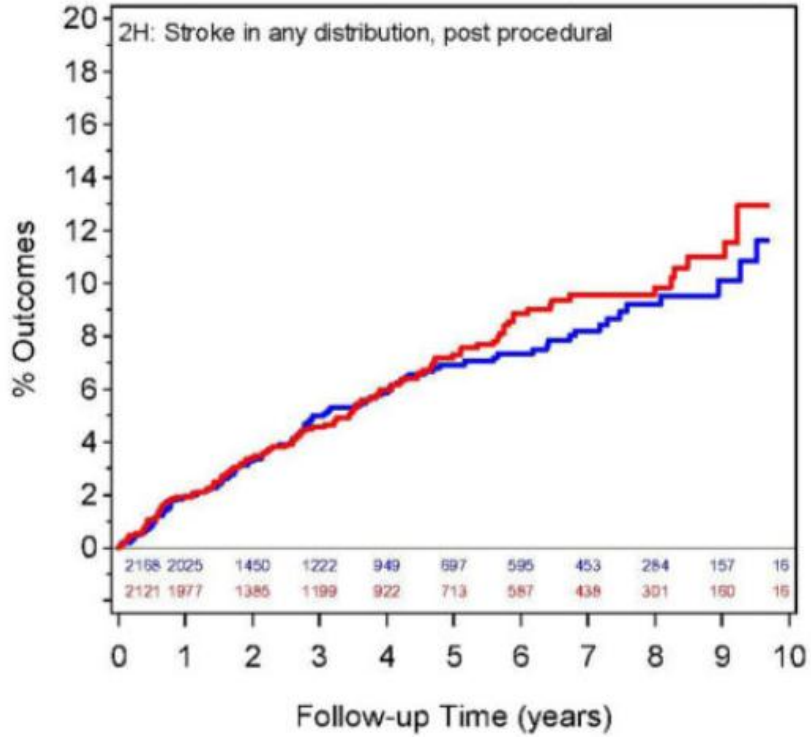
4 754 pts followed up for up to **12.4y**

Treatment — **CEA** — **CAS** (1st generation CAS, distal EPD/no EPD, single-layer stents with plaque prolapse resulting in post-proc. ↑↑ minor stroke incidence)

Post-procedural events





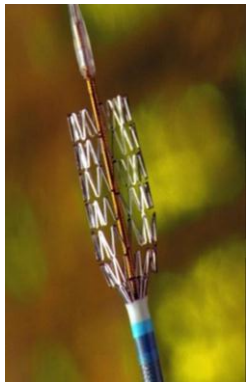


For both CEA and CAS, if performed safely, most revascularised patients can anticipate freedom from stroke up to 10y

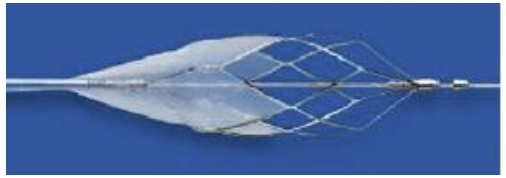
'Improvements in the peri-procedural safety of CAS could provide similar outcomes of the two procedures in both the short and long-term' – ***or CAS outcomes might be BETTER/pm !!***

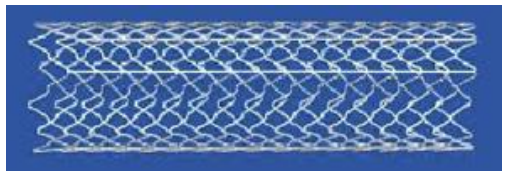
Today's CAS ≠ CREST-era 'CAS' that had determined the Guidelines

Conventional Carotid Stents Do Have A Problem



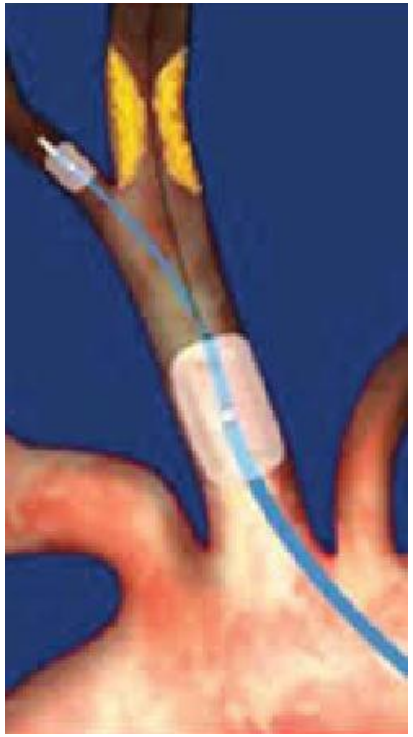
Plaque Prolapse translates into ↑peri-procedulal stroke risk (in conjunction with subotimal intraprocedulal cerebral protection) *and* ↑↑post-procedural stroke in relation to CEA (CAPTURE, CREST, ICSS)

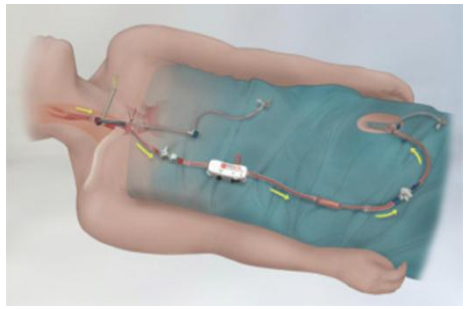


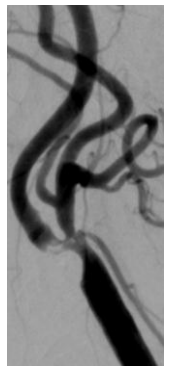


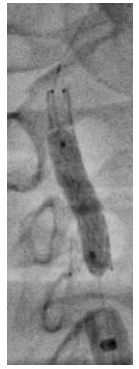
OPTIMIZED INTRA-PROCEDURAL Cerebral Protection

(incl. '**PROXIMAL**' systems)

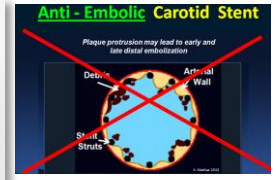


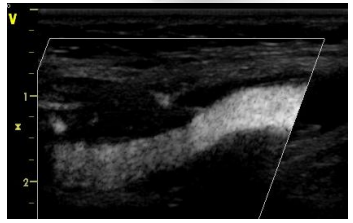


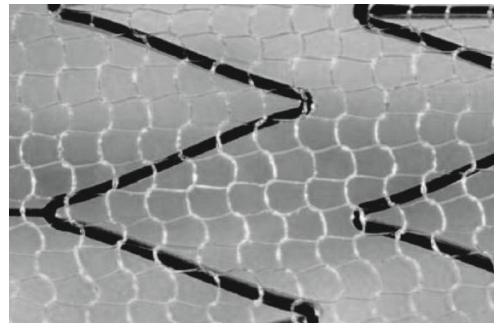


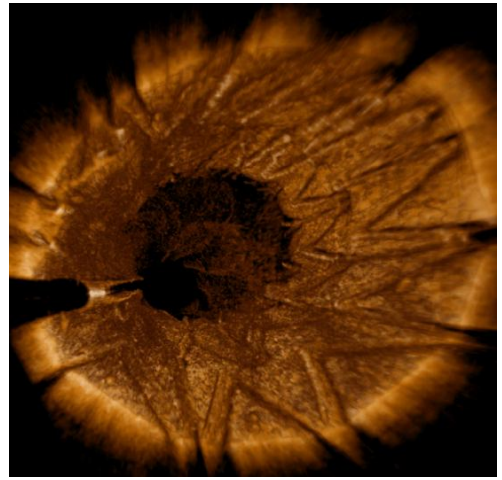


2nd GENERATION (dual-layered) Carotid STENTS









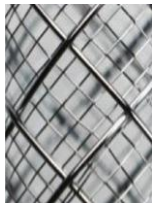
↓↓ intra-procedural embolism + abolished post-procedural cerebral injury

enabling safe, routine endovasc treatment of standard-risk and high-risk patients/lesions with OPTIMAL long-term clinical outcomes

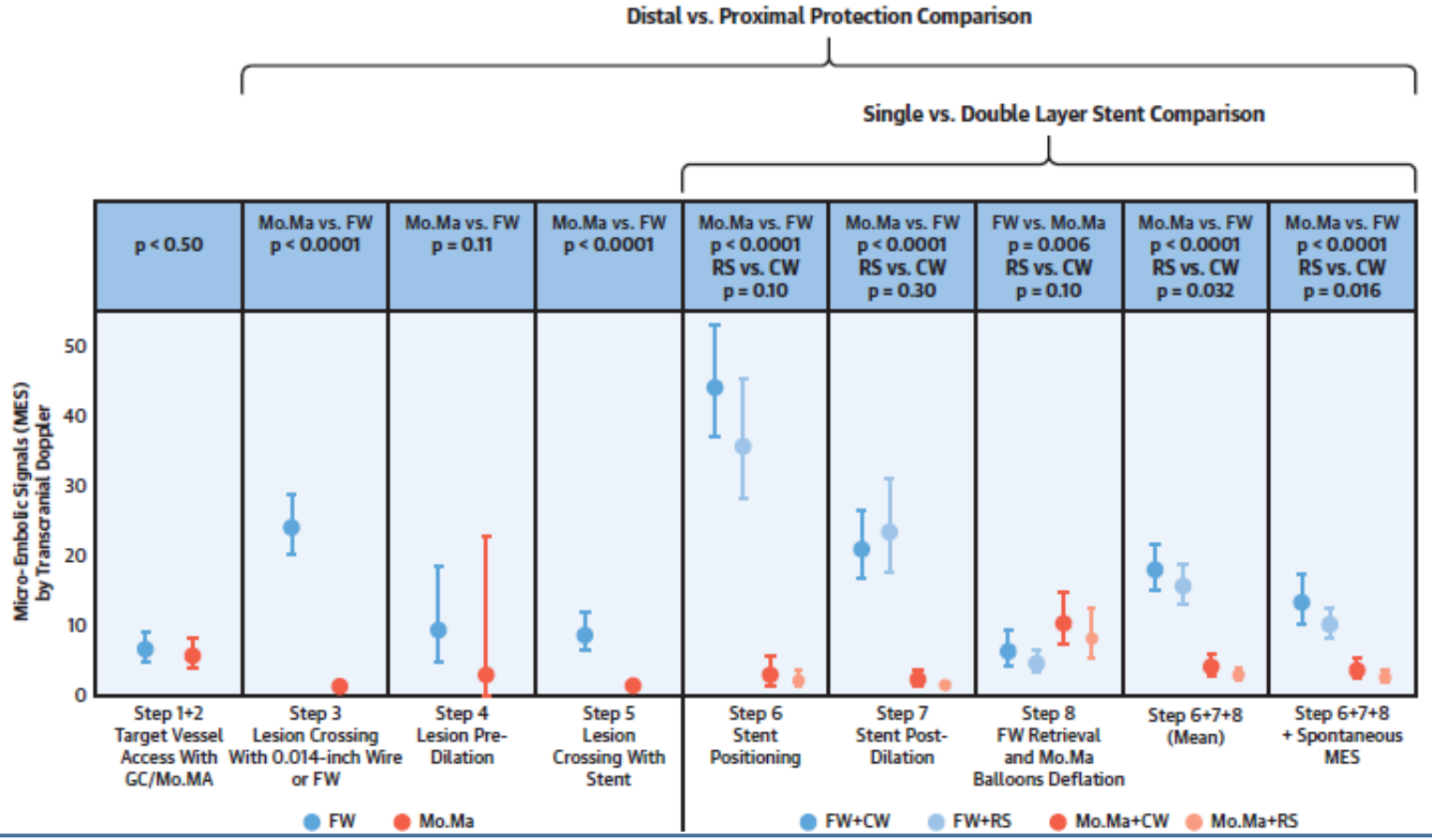
Carotid Wallstent Versus Roadsaver Stent and Distal Versus Proximal Protection on Cerebral Microembolization During Carotid Artery Stenting

104 consecutive patients with lipid-rich carotid artery stenosis

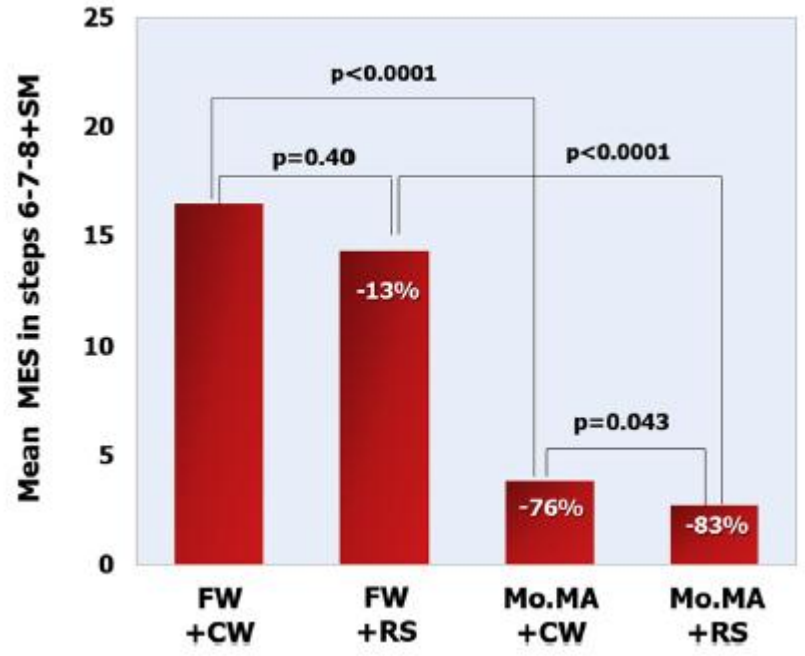
randomized 1:1:1:1 to CAS with FilterWire + **RoadSaver Stent**
FilterWire + Carotid Wallstent
MoMa + Carotid Wallstent
MoMa + **RoadSaver Stent**


RoadSaver

CENTRAL ILLUSTRATION Microembolic Signals Throughout Carotid Artery Stenting Steps According to Type of Brain Protection (Distal vs. Proximal) and the Carotid Stent Used (Single vs. Double Mesh)



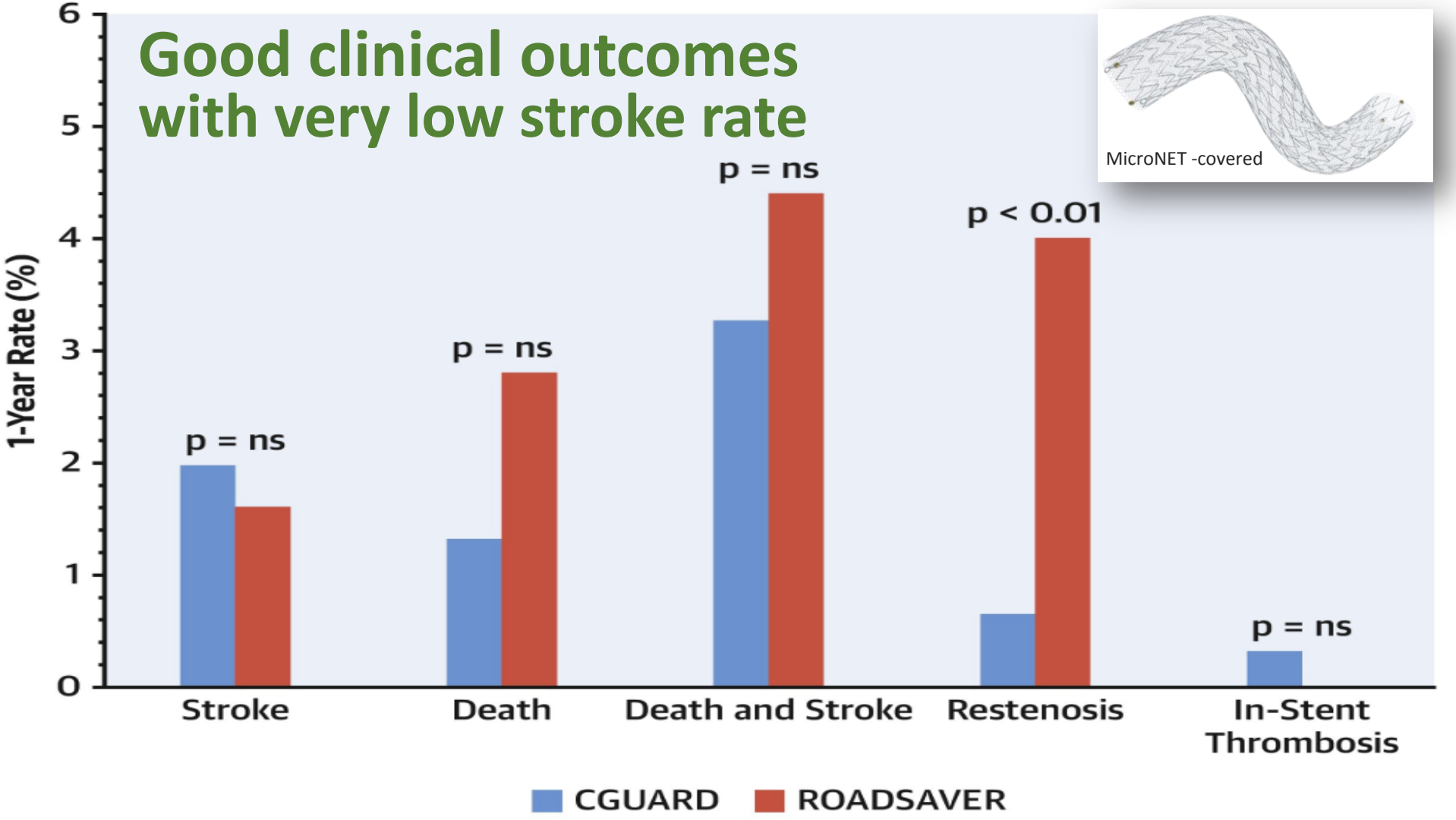
Primary endpoint = number of microembolic signals (MES) on transcranial Doppler during the CAS steps

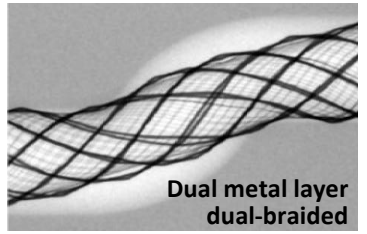


Use of Proximal cerebral protection (Mo.Ma)+ Dual-layer mesh stent (RoadSaver) resulted in lowest microembolic signals count

Use of Dual-Layered Stents for Carotid Artery Angioplasty: 1-Year Results of a Patient-Based Meta-Analysis (CGuard - 306; RoadSaver - 250)

Good clinical outcomes with very low stroke rate

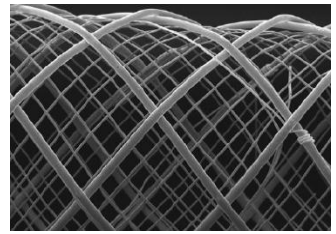




cf., Wissgott *J Endovasc Ther.* 2015

NO class effect in ISR

RoadSaver use



= the only independent predictor of ISR

Stabile E et al.
JACC Cardiovasc Interv.
2020;13:1709-1715

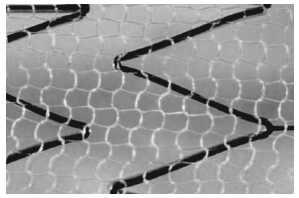
Randomized controlled trial of conventional versus micronet-covered stent use in percutaneous neuroprotected carotid artery revascularization:

Peri-procedural and 30-day **diffusion-weighted magnetic resonance (DWI) imaging** and clinical outcomes

HEAD-TO-HEAD 100 consecutive patients (25% symptomatic) **RANDOMIZED 1 : 1**

Distal EPD (Emboshield) in all

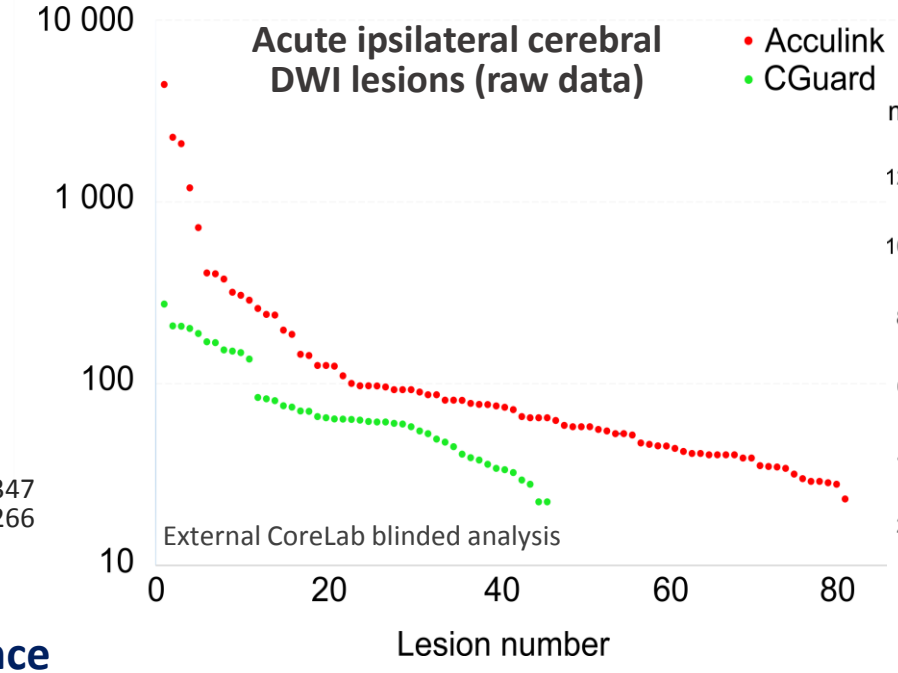
MicroNET-Covered
open-cell nitinol frame
2nd generation stent



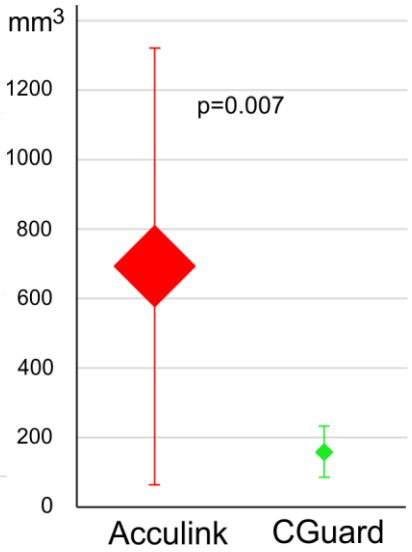
vs.

Conventional (workhorse)
open-cell nitinol
1st generation stent

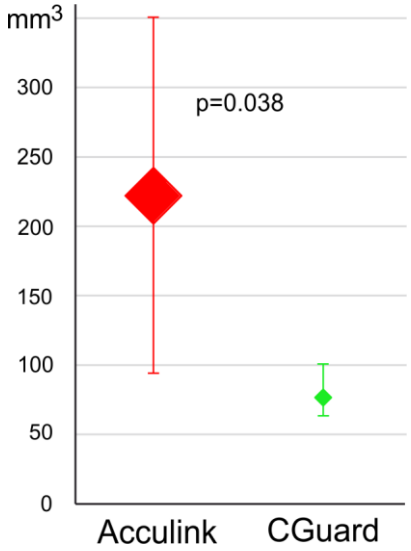
EuroIntervention 2017;13:1347
EuroIntervention 2017;13:1266



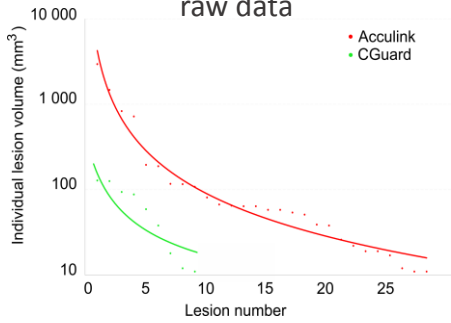
Total lesion volume
(per affected patient)



Average lesion volume
(per lesion)



PERMANENT Lesions
(FLAIR, 30d)
raw data



NEW DWI lesions @30d
6 vs. 0 (p=0.03)

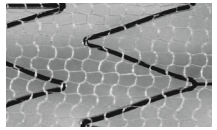
Stroke @30d
2 vs. 0

NOW
Level-1 Evidence
for the MicroNET prevention of plaque prolapse embolism, translating into cerebral protection with MicroNET extending by 30 days

Karpenko A et al. **ePCR 2020 Late-Breaking Clinical Trial** *(manuscript ar review)*

MicroNET-covered stent: clinical and duplex 5-year outcomes

PARADIGM-Extend Study



n = 480

59.8% symptomatic

	12 mo	24 mo	36 mo	48 mo	60 mo
	n = 354	n= 248	n= 173	n=106	n=46
Ipsilateral stroke	1*§ (device unrelated)	0	0	0	1* (device unrelated)
Any stroke	1	2 (1-cerebellum)	1 (brain stem)	1 (contralateral)	1
Stroke related death	0	0	0	0	1
MI or other non - cerebral VA	1	3	2	2	0
Restenosis	1 (after RTh)	1 **(DEB treated)**	0	0	0
Any death	13 (CHF – 4, Ca–3, PE–1, urosepsis – 1, MI-2, COPD-1, surg-1)	10 (CHF – 3, Ca -2, MI -2, intracranial bleed -1, surg-2)	7 (Ca – 2, CHF -3, MI – 1, pneumonia/ sepsis - 1)	6 (CHF -2, MI – 2, Ca -2)	1 (stroke) **(contralateral)**

30-day TOTAL death/stroke **0.83%**

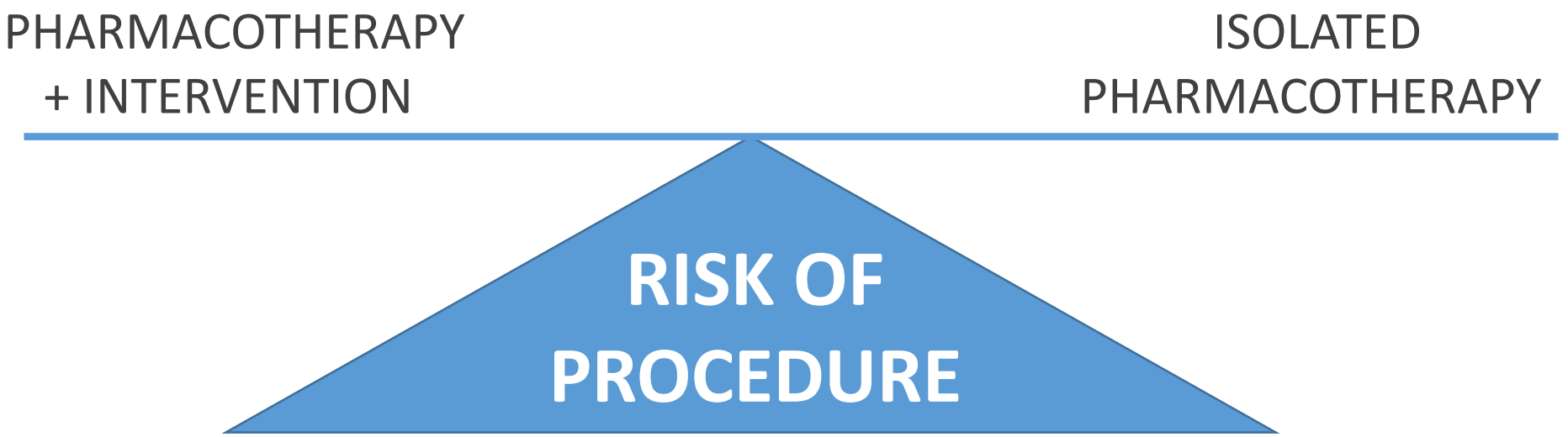
*normal-healed stent on duplex Doppler, § *de novo* Atrial Fibrillation, "n" indicates patients who crossed the follow-up window

in-stent PSV / EDV (m/s)

0.78±0.40/0.21±0.11 **0.76**±0.36/0.20±0.09 **0.75**±0.34/0.20±0.09 **0.75**±0.41/0.20±0.08 **0.78**±0.50/0.20±0.10

Mazurek A et al. ESC 2020 BEST POSTER

A/S Carotid Stenosis
Decision-making



Conclusions

- Carotid artery stenosis is **not** a 'benign' disease; it remains an important –and modifiable– risk factor of ischaemic stroke.
- Prevalence of 'significant' ("≥50%") carotid stenosis is similar to non-valvular paroxysmal AFib; in pharmacologically-treated patients the annual stroke risk is similar to the stroke risk in paroxysmal AFib on ASA (≈ 2.0-2.5% per year).
- Optimized Medical Therapy (**OMT**, including a high-dose statin titrated to the **guideline-indicated** target LDL-cholesterol level) is **the fundament of treatment**.
- OMT may reduce and/or delay the stroke risk, but **there is no evidence today that OMT alone would be generally sufficient to prevent carotid-related strokes**; quite opposite: carotid stenosis-related strokes do continue to harm OMT patients.
- Stroke risk in "asymptomatic" cardiovascular clinic patients may be –for a number of reasons including symptomatic disease status in other territory/ies– greater than that in general population.

Conclusions *(cont'd)*

- Lumen stenosis severity is a poor marker of stroke risk; the disease is in the wall (!)
- Several clinical (such as diabetes), plaque/stenosis-level (lesion morphology, contralateral occlusion or symptoms), and cerebral MRI/CT imaging (clinically-silent infarct) increased stroke risk characteristics have been identified and some are already listed in the 2017 ESC/ESVS/ESO Guidelines – **these should be routinely employed today in clinical decision-making on revascularization indication on top of OMT**, until (and unless) there is different evidence.
- Large-scale research is needed to determine a combined role of stroke risk factors and risk markers in clinically 'asymptomatic' carotid stenosis, and to develop and validate user-friendly risk assessment scales to ease decision-making, similar to those already available in *e.g.* AFib
- Carotid revascularization, on top of pharmacotherapy, continues to effectively prevent strokes in 'asymptomatic' carotid stenosis many years after the procedure – note continued curve separation of immediate vs. deferred CEA in ACST-1 after 15years despite triple medical Tx.
- Novel endovascular revascularization technologies (optimized intra-procedural protection including the proximal systems, micronet-covered stents for sustained embolic prevention) are associated with a low/v. low risk of revascularization-related cerebral injury (note recent RCT data); evidence is increasing today for their long-term safety & stroke prevention efficacy, leading to a change in the treatment paradigm in patients with ↑risk features in particular.