My Most Promising Perspective for Cerebral Protection by Filter-Balloon

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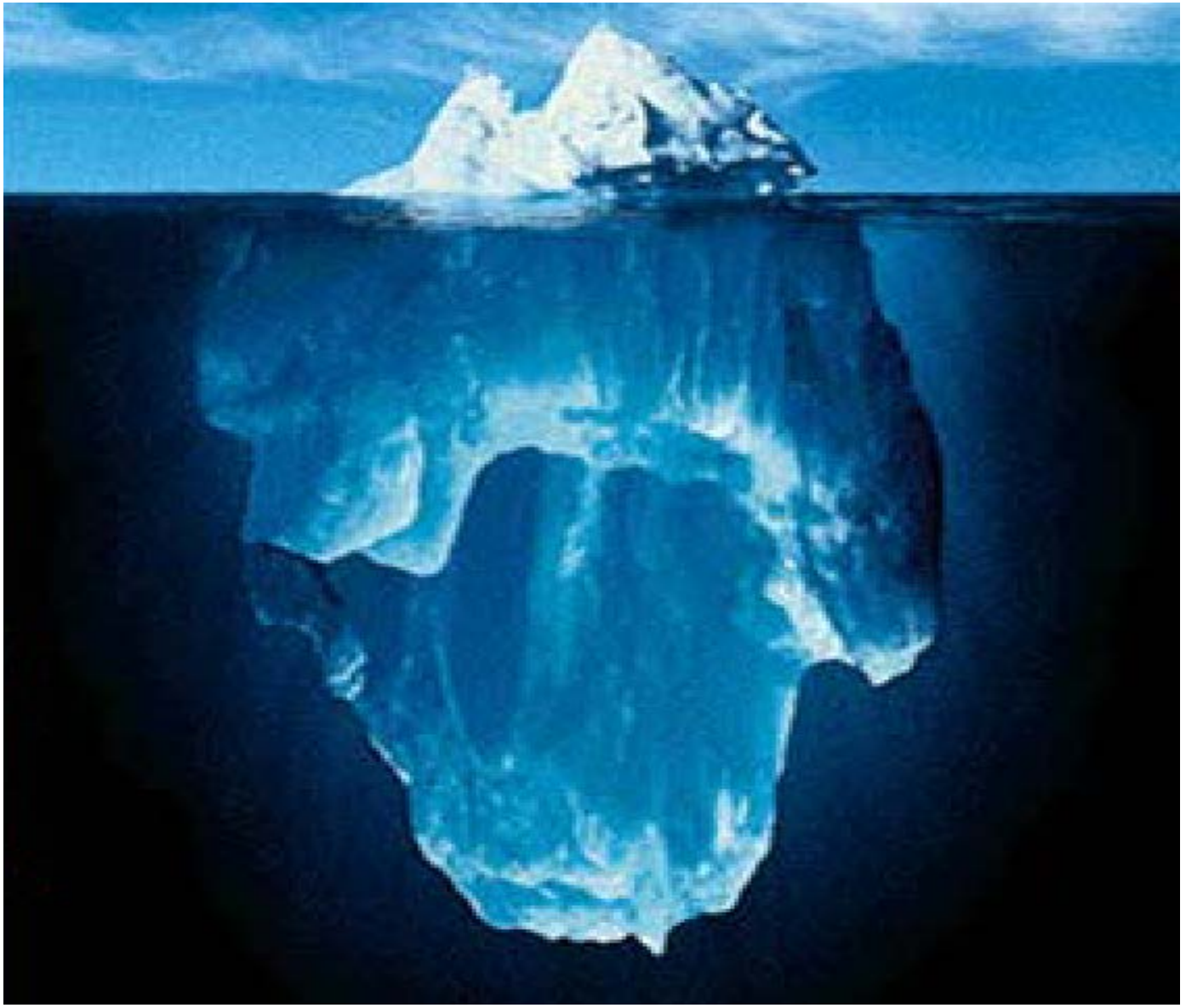
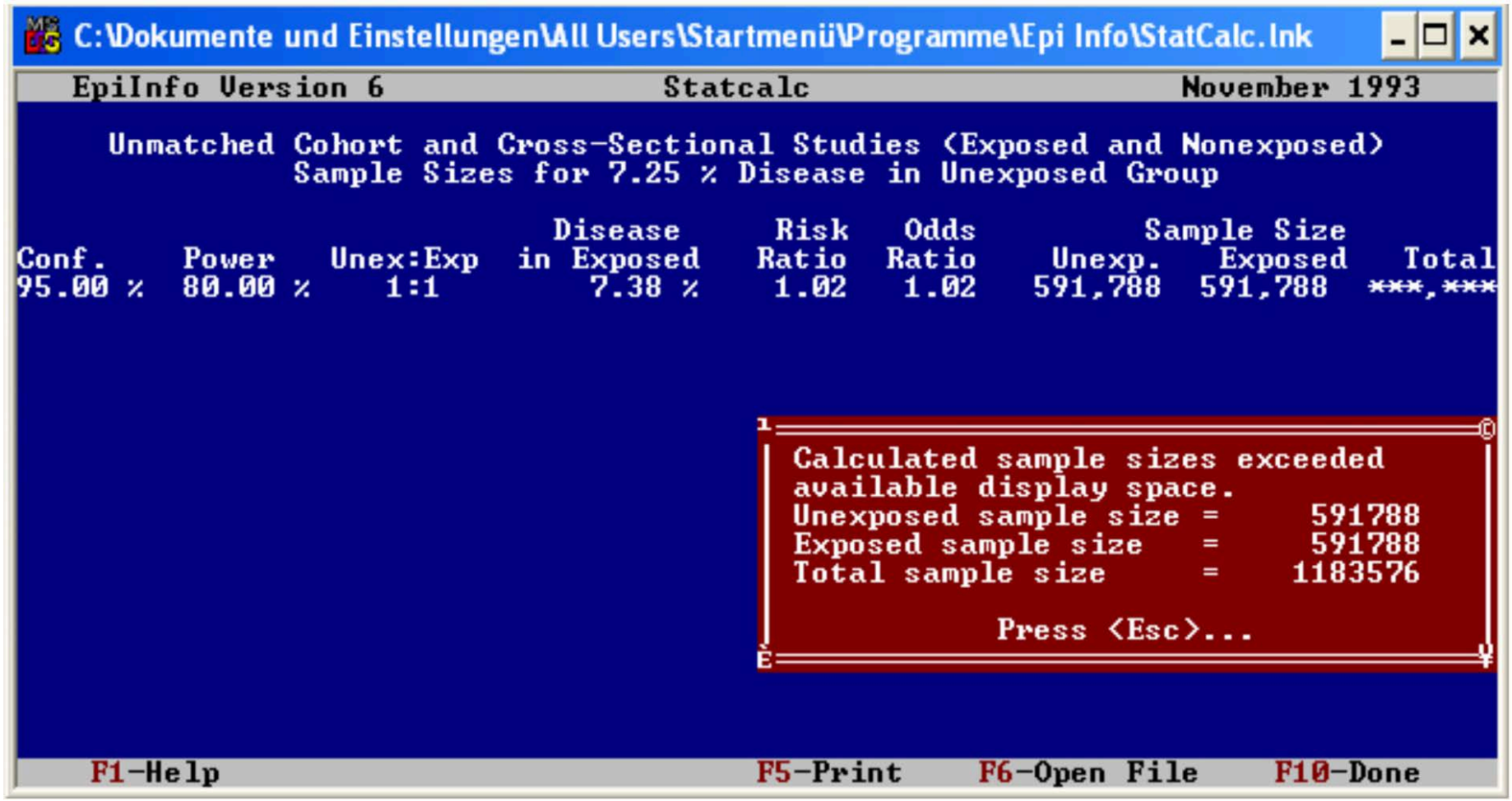
Do We Need Embolic Protection During CAS?



Protection oder no Protection -Evidence?



Acute and Long Term Results of CAS

(Stroke, MI, Death)

Depend on a 30 Second Time Frame

in Most of the Patients!

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CREST-Trial: 30 Day Outcome

Table 2. Primary End Point, Components of the Primary End Point, and Other Events, According to Treatment Group.*

End Point	Periprocedural Period				
	CAS (N=1262)	CEA (N=1240)	Absolute Treatment Effect of CAS vs. CEA (95% CI)	Hazard Ratio for CAS vs. CEA (95% CI)	P Value
	no. of patients (% ±SE)		*percentage points*		
Death	9 (0.7±0.2)	4 (0.3±0.2)	0.4 (–0.2 to 1.0)	2.25 (0.69 to 7.30)†	0.18†
Stroke					
Any	52 (4.1±0.6)	29 (2.3±0.4)	1.8 (0.4 to 3.2)	1.79 (1.14 to 2.82)	0.01
Major ipsilateral	11 (0.9±0.3)	4 (0.3±0.2)	0.5 (–0.1 to 1.2)	2.67 (0.85 to 8.40)	0.09
Major nonipsilateral‡	0	4 (0.3±0.2)	NA	NA	NA
Minor ipsilateral	37 (2.9±0.5)	17 (1.4±0.3)	1.6 (0.4 to 2.7)	2.16 (1.22 to 3.83)	0.009
Minor nonipsilateral	4 (0.3±0.2)	4 (0.3±0.2)	0.0 (–0.4 to 0.4)	1.02 (0.25 to 4.07)	0.98†
Myocardial infarction	14 (1.1±0.3)	28 (2.3±0.4)	–1.1 (–2.2 to –0.1)	0.50 (0.26 to 0.94)	0.03
Any periprocedural stroke or postprocedural ipsilateral stroke	52 (4.1±0.6)	29 (2.3±0.4)	1.8 (0.4 to 3.2)	1.79 (1.14 to 2.82)	0.01
Major stroke	11 (0.9±0.3)	8 (0.6±0.2)	0.2 (–0.5 to 0.9)	1.35 (0.54 to 3.36)	0.52
Minor stroke	41 (3.				
Any periprocedural stroke or death or post-procedural ipsilateral stroke	55 (4.				
Primary end point (any periprocedural stroke, myocardial infarction, or death or postprocedural ipsilateral stroke)	66 (5.				

20 Minor Strokes
14 Herzinfarkte

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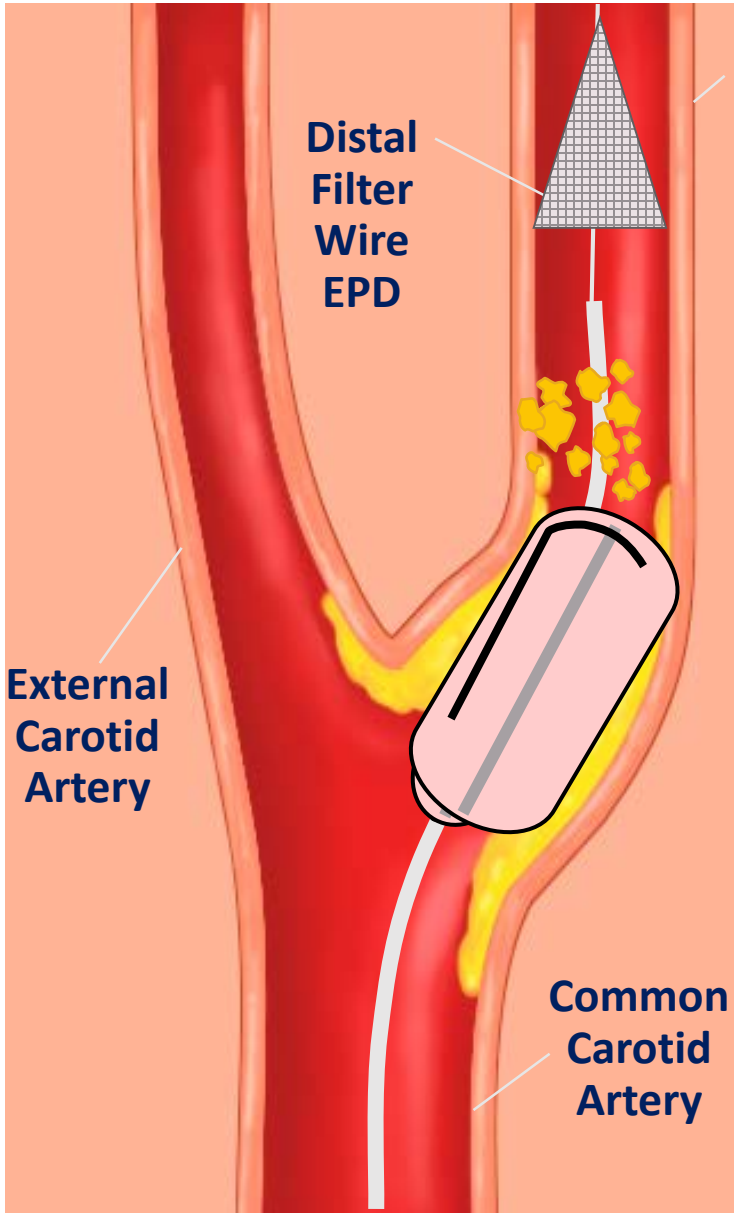

Why Do Minor Strokes Occur Despite EPD use?

- Pore Size (100-250 microns)
- Filter Malapposition
  - Improper Sizing
  - Shape Mismatch
  - Patient Movement
- Overwhelming Debris Burden

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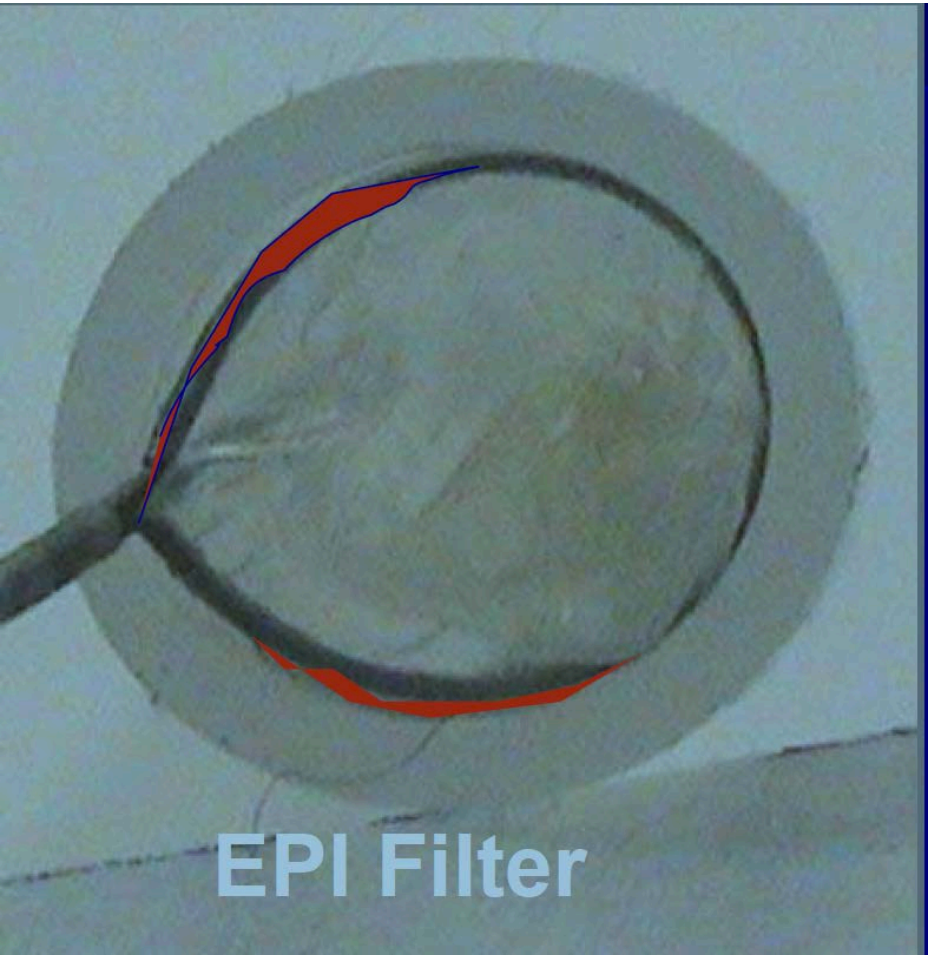
Wallapposition of Filters



Area without Protection

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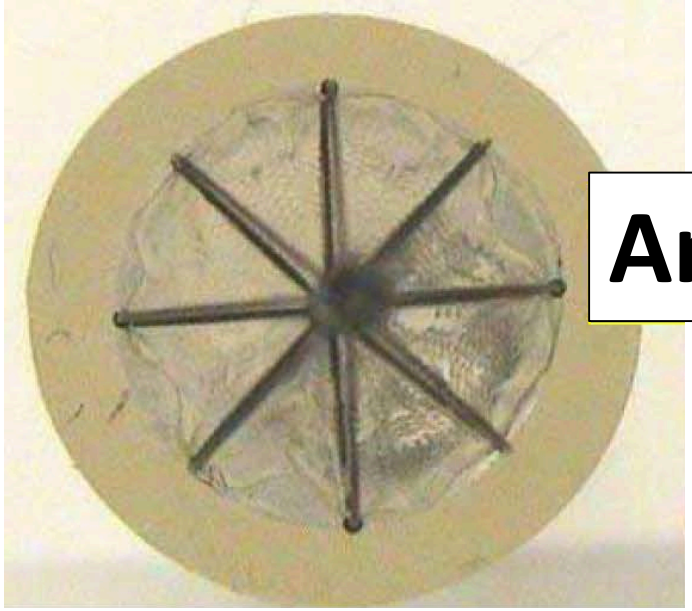
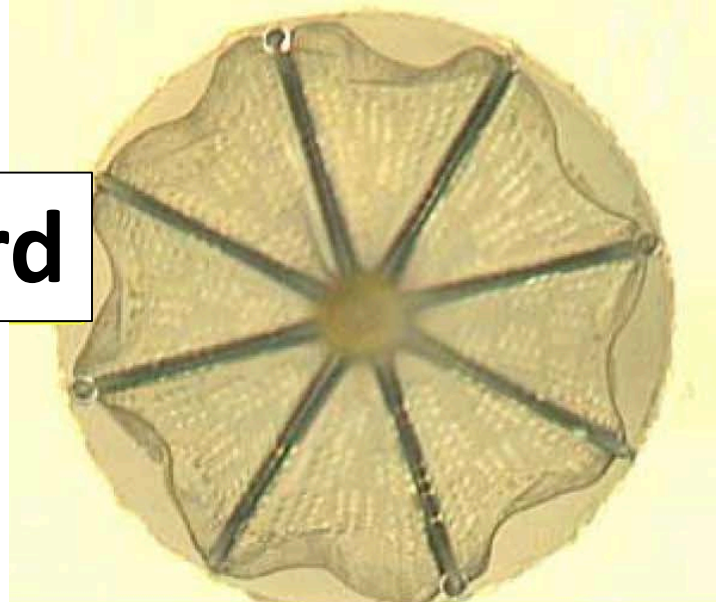
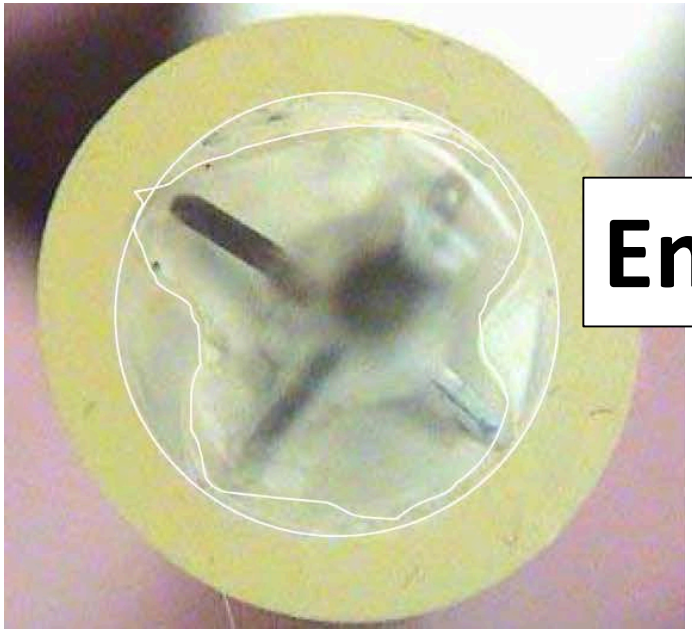


Angioguard



View of CORDIS

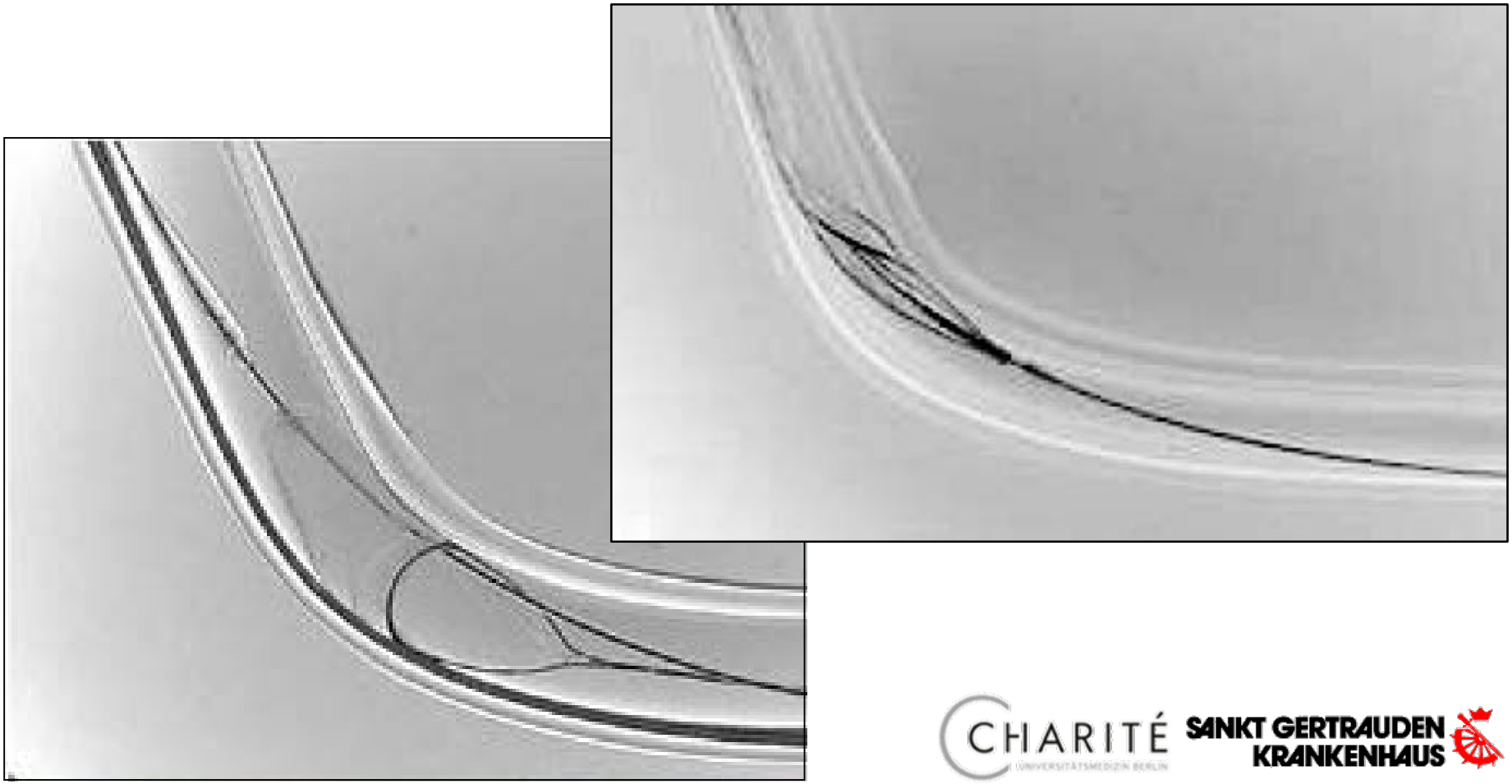
View of ABBOTT



Emboshield

Impact of Filter Design on Efficiency of EPD

concentric vs. excentric filters



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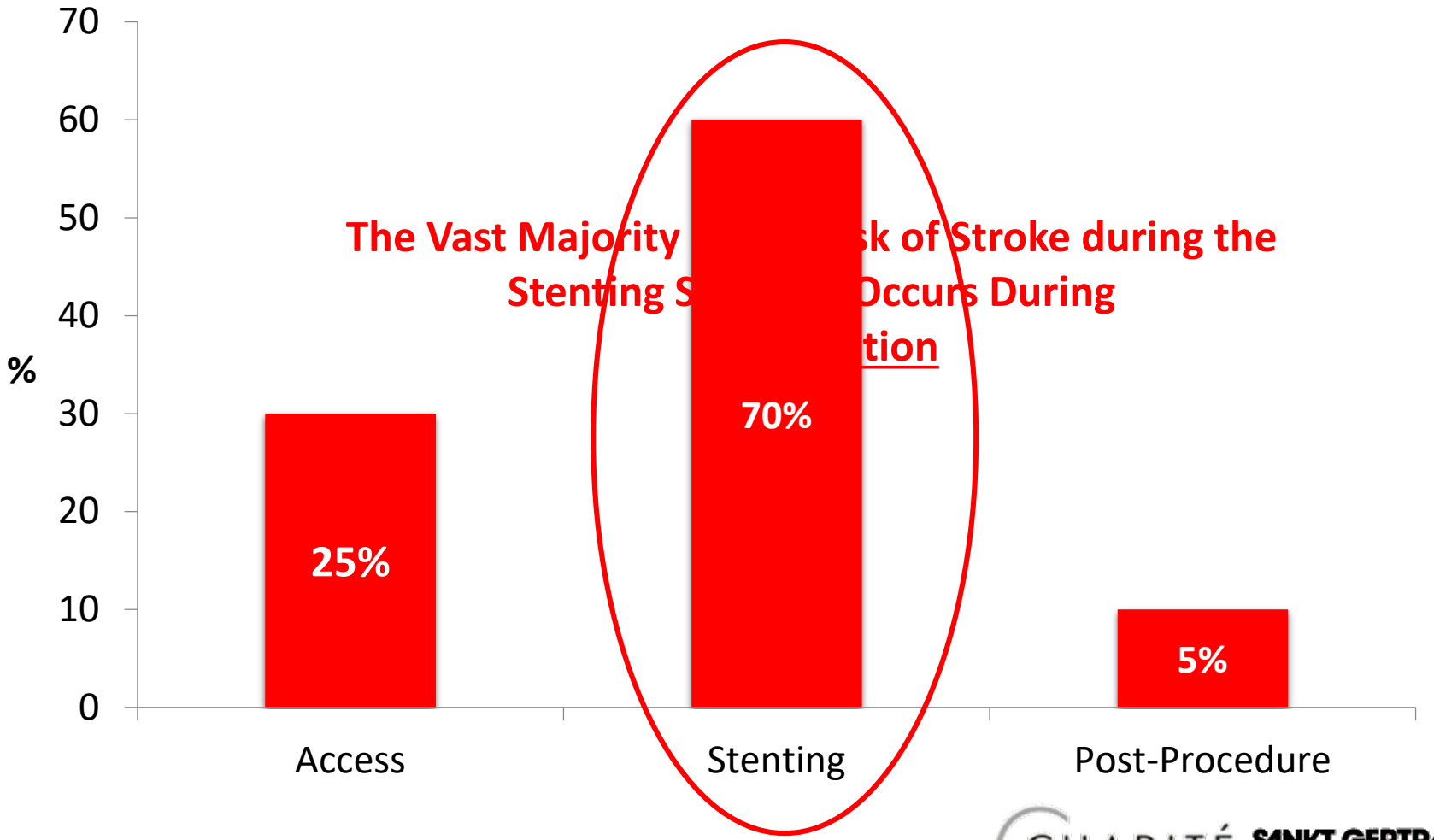
When Do Strokes Occur During Carotid Artery Stenting?



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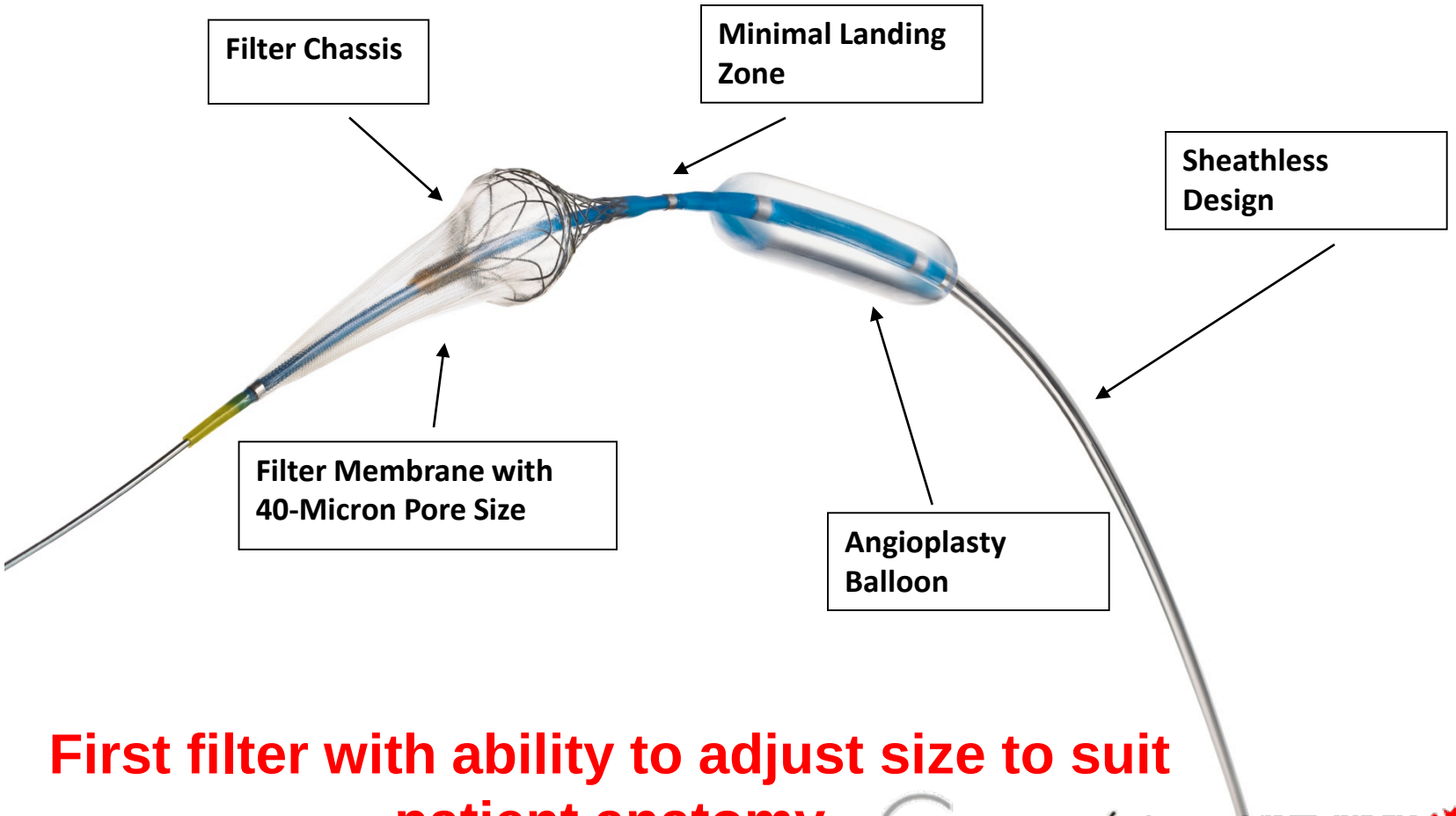
PALADIN®
Carotid Post-Dilation Balloon with Integrated Embolic Protection (IEP) Technology



First filter with ability to adjust size to suit patient anatomy

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The Paladin Study

❑ **Objective**

- To evaluate the procedural safety and technical success of the Paladin System in subjects with carotid artery stenosis

- **106 subjects enrolled at 5 sites in Germany**

Investigator	Site	# Enrolled
Dr. Ralf Langhoff	Sankt Getrauden-Krankenhaus, Berlin	45
Prof. Joachim Schofer	Mathey-Schofer Clinic, Hamburg	28
Prof. Thomas Zeller	Universitäts Herzzentrum - Freiburg - Bad Krozingen	18
Prof. Dierk Scheinert	Universitätsklinikum Leipzig	8
Prof. Horst Sievert*	Cardiovasculäres Centrum, Frankfurt	6

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PALADIN Study Patient Population

- Study Population
  - Symptomatic subjects (history of ipsilateral TIA, stroke or amaurosis fugax within the past 6 months) with carotid stenosis ≥ 50% by angiography
  - Asymptomatic subjects with carotid stenosis ≥ 70% by angiography

- Primary Endpoints
  - Acute Technical success
  - 30 day (neurological death and stroke)

Results - The Paladin Study (n=106)

- 106 Subjects Enrolled at 5 Sites in Germany
- 99% Technical Success
- No Death, Stroke, MI Through Discharge
- 1 Unrelated Stroke At Day 12, Complete Recovery

Paladin Study		
Outcome	**Outcomes at Discharge % (N/106)**	**30-Day Outcomes % (N/105[1])**
Stroke, Death and MI	**0.00**	**0.95 (1)**
Death	**0.00**	**0.00 (0)**
Stroke	**0.00**	**0.95 (1)**
Myocardial Infarction	**0.00**	**0.00 (0)**
Stroke and Death	**0.00**	**0.95 (1)**

[1] Of the 106 subjects enrolled, one (1) subject withdrew consent following discharge, and 105 were eligible for follow up at 30 days.

The Paladin Study

Two Sub-Studies:

- **MRI Study (n= 30):** Incidence of new DWI-lesions, Volume size
- **Histopathologyogical Filter-Study (n=23):** Size and counts of emboli

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Comparative Results across MRI Studies

	Paladin (n=30)	PROFI[1] Proximal group (n=31)	PROFI[1] Filter group (n=31)	ICSS[2] Filter group (n=37)	CARENET[3] CGuard (n=26)
Incidence of New Lesions	36.7%	45%	87%	73%	48%
Mean number of lesions per pt.	0.50 ± 0.7	1.0 ± 1.4	3.6 ± 3.2	NR	NR
Mean Lesion Volume (cm^3)	0.01	0.16	0.59	NA	0.04
Total number of new ischemic lesions	16	NR	NR	NR	117
Maximum lesion volume (cm^3)	0.158	0.84	2.4	NR	0.445

[1] Bijuklic K, Wandler A, Hazizi F, Schofer J. The PROFI Study. JACC 2012 Apr 10;59(15):1383-9.
[2] Bonati LH, et al, ISCC-MRI Study group. New ischaemic brain lesions on MRI after stenting or CEA for symptomatic carotid stenosis: a substudy of ICSS. Lancet Neurol. 2010 Apr;9(4):353-62.
[3] Schofer J, Musialek P, Bijuklic K, Kolvenbach R, Trystula M, Siudak Z, Sievert H. The CGuard CARENET Trial. JACC Cardiovas Interv. 2015 Aug 17;8(9):1299-34.

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Cognitive Impairment Due to Embolization

Importance of Micro-Embolization

Volume of subclinical embolic infarct correlates to long-term cognitive changes after carotid revascularization

Wei Zhou, MD,[a,b] Brittanie D. Baughman, MS,[a] Salil Soman, MD,[c] Max Wintermark, MD,[d] Laura C. Lazzeroni, PhD,[e] Elizabeth Hitchner, MS,[a] Jyoti Bhat, MS,[f] *and* Allyson Rosen, PhD,[e,f] *Palo Alto and Stanford, Calif; and Cambridge, Mass*

ABSTRACT

Objective: Carotid intervention is safe and effective in stroke prevention in appropriately selected patients. Despite minimal neurologic complications, procedure-related subclinical microemboli are common and their cognitive effects are largely unknown. In this prospective longitudinal study, we sought to determine long-term cognitive effects of embolic infarcts.

Methods: The study recruited 119 patients including 46% symptomatic patients who underwent carotid revascularization. Neuropsychological testing was administered preoperatively and at 1 month, 6 months, and 12 months postoperatively. Rey Auditory Verbal Learning Test (RAVLT) was the primary cognitive measure with parallel forms to avoid practice effect. All patients also received 3T brain magnetic resonance imaging with a diffusion-weighted imaging (DWI) sequence preoperatively and within 48 hours postoperatively to identify procedure-related new embolic lesions. Each DWI lesion was manually traced and input into a neuroimaging program to define volume. Embolic infarct volumes were correlated with cognitive measures. Regression models were used to identify relationships between infarct volumes and cognitive measures.

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Journal of the Neurological Sciences
Volume 328, Issue 1-2, 15 May 2013, Pages 58-63

Diffusion-weighted lesions after carotid artery stenting are associated with cognitive impairment

Maggio, P.a, Altamura, C.a, Landi, D.a, Migliore, S.a, Lupoi, D.b, Moffa, F.c, Quintiliani, L.a, Vollaro, S.a, Palazzo, P.a, Altavilla, R.a, Pasqualetti, P.de, Errante, Y.f, Quattrocchi, C.C.f, Tibuzzi, F.c, Passarelli, F.c, Arpesani, R.b, Di Giambattista, G.b, Grasso, F.R.f, Luppi, G.f, Vernieri, F.a

Abstract
The effect of carotid artery stenting (CAS) on cognitive function is still debated. Cerebral microembolism, detectable by post-procedural diffusion-weighted imaging (DWI) lesions, has been suggested to predispose to cognitive decline. Our study aimed at evaluating the effect of CAS on cognitive profile focusing on the potential role of cerebral microembolic lesions, taking into consideration the impact of factors potentially influencing cognitive status (demographic features, vascular risk profile, neuropsychological evaluation at baseline and magnetic resonance (MR) markers of brain structural damage). Thirty-seven patients with severe carotid artery stenosis were enrolled. Neurological assessment, neuropsychological evaluation and brain MR were performed the day before CAS (E0). Brain MR with DWI was repeated the day after CAS (E1), while neuropsychological evaluation was done after a 14-month median period (E2). Volumes of both white matter hyperintensities and whole brain were estimated at E0 on axial MR FLAIR and T1w-SE sequences, respectively. Unadjusted ANOVA analysis showed a significant CAS - DWI interaction for MMSE (F = 7.154(32), p =.012). After adjusting for factors potentially influencing cognitive status CAS â - DWI interaction was confirmed for MMSE (F = 7.092(13), p =.020). Patients with DWI lesions showed a mean E2-E0 MMSE reduction of - 3.1, while group without DWI lesions showed a mean E2-E0 MMSE of + 1.1. Our study showed that peri-procedural brain microembolic load impacts negatively on cognitive functions, independently from the influence of patients-related variables. © 2013 Elsevier B.V.

Filter Histopathology Sub-Study (n=23)

- Filters in a subset of subjects were collected for histopathological analysis to evaluate size and number of particles
- Paladin and primary EPD were retrieved from 23 subjects between Sept 2015 – Aug 2016
- Following CAS procedure, both filters preserved in 10% buffered formalin and sent to a core lab for analysis
- Upon receipt at the core lab, the filters were visibly examined
  - Samples removed from the formalin; placed in a 35 mm culture dish.
  - Visible clumps of RBCs at the edges of the culture dish removed
  - Samples scanned with SEM with 20 micron detection capability
  - Post-process images were taken using incremental high pass filter radii in Fourier space to binarize particles
  - Particle counts were determined

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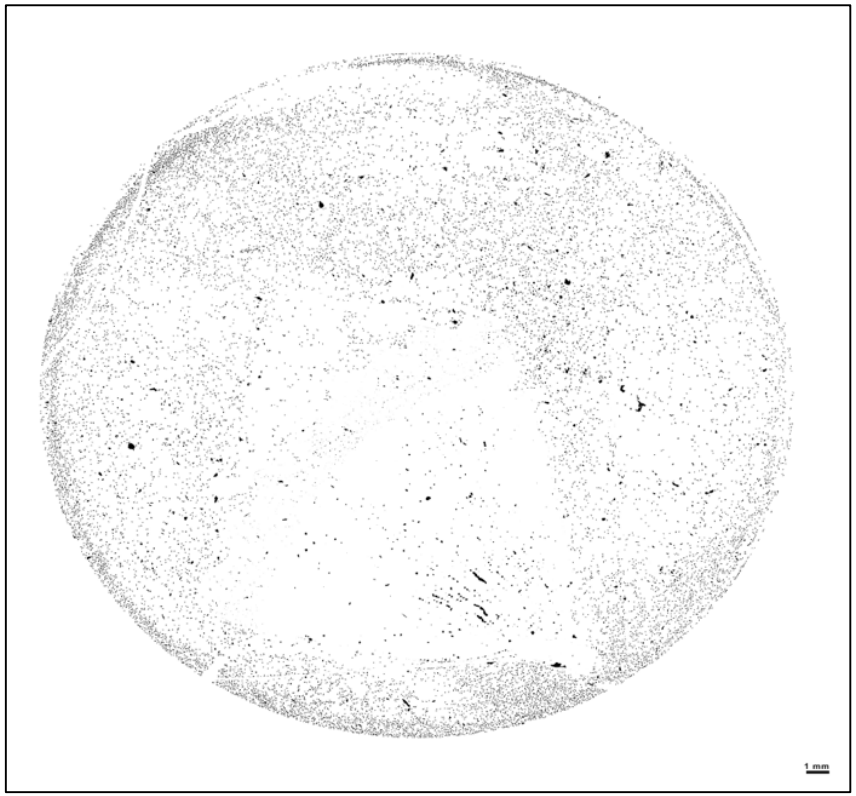
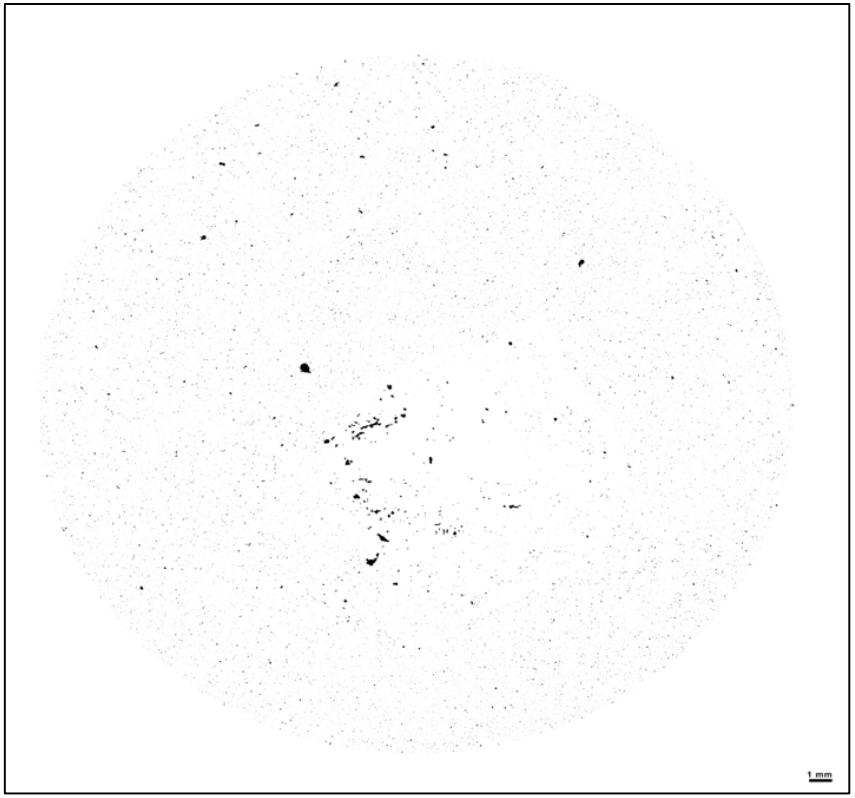
Filter Examples:

Subject 02-037, Sankt Gertrauden-Krankenhaus, Berlin
64 year old male, asymptomatic LICA
Predilation with 3x20 Maverick, BSC FilterWire + Wallstent
5.0 x 20 mm Paladin System used for post dilation



1. Post process image of Paladin filter particle scan



2. Post process image of primary filter particle scan

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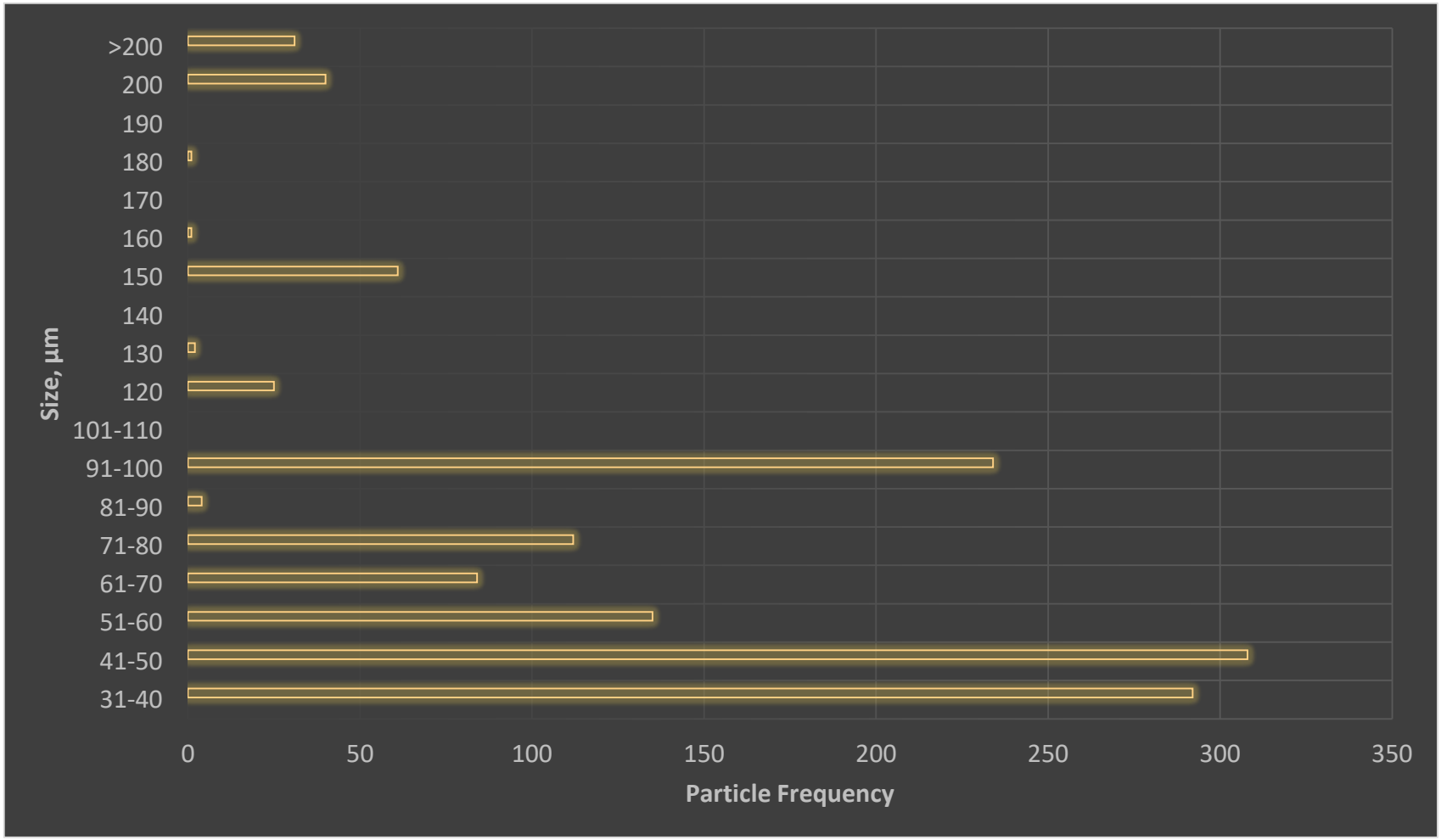
Filter Histological Analysis: Particle Size

24 filters collected for analysis of emboli count and size



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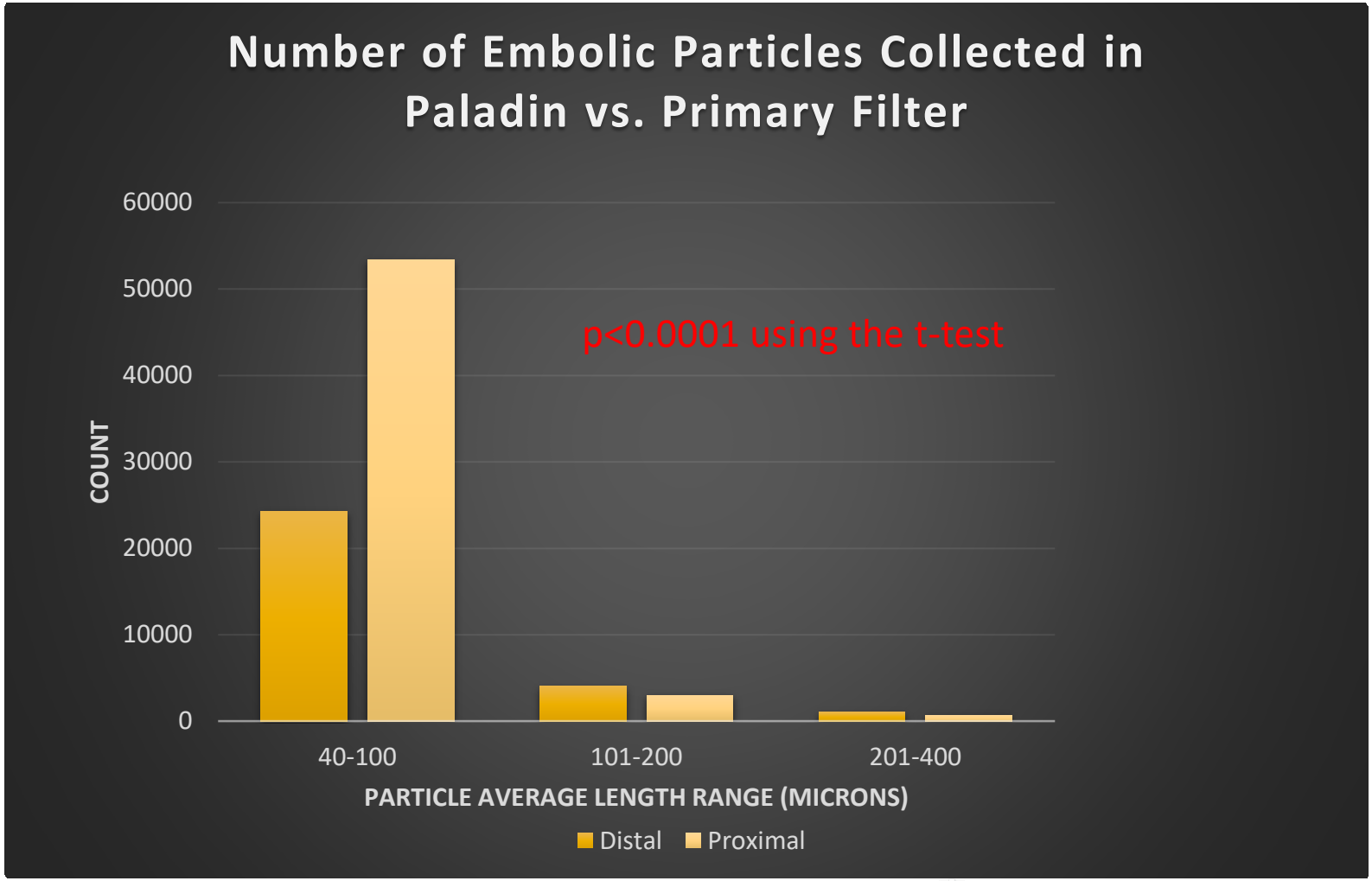
Filter Histological Analysis: Particle Count

24 paired filters collected for analysis of emboli count and size



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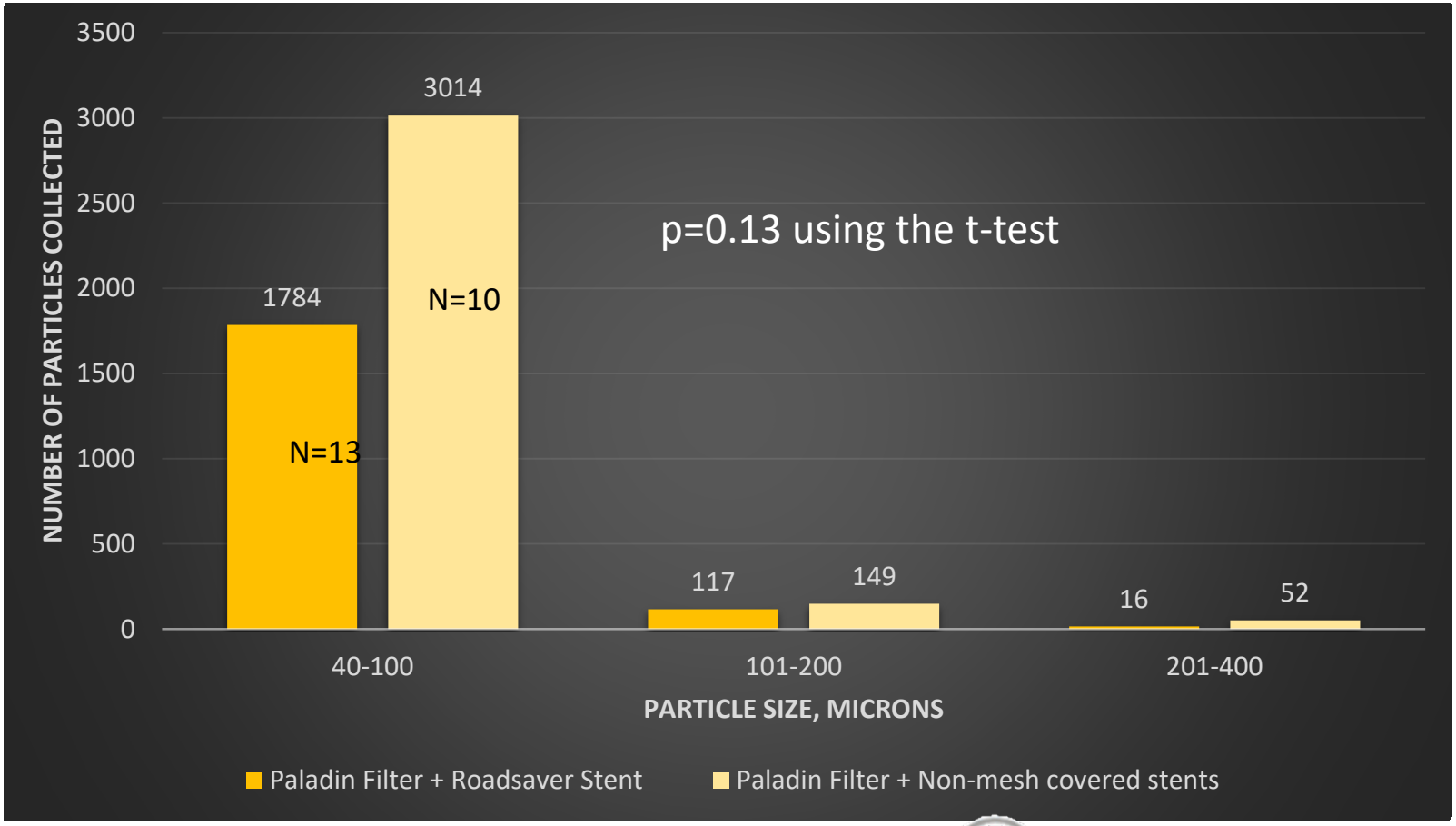
Comparison of Particle Counts in CAS with Mesh-Covered Stents vs Non-Mesh Covered Stents



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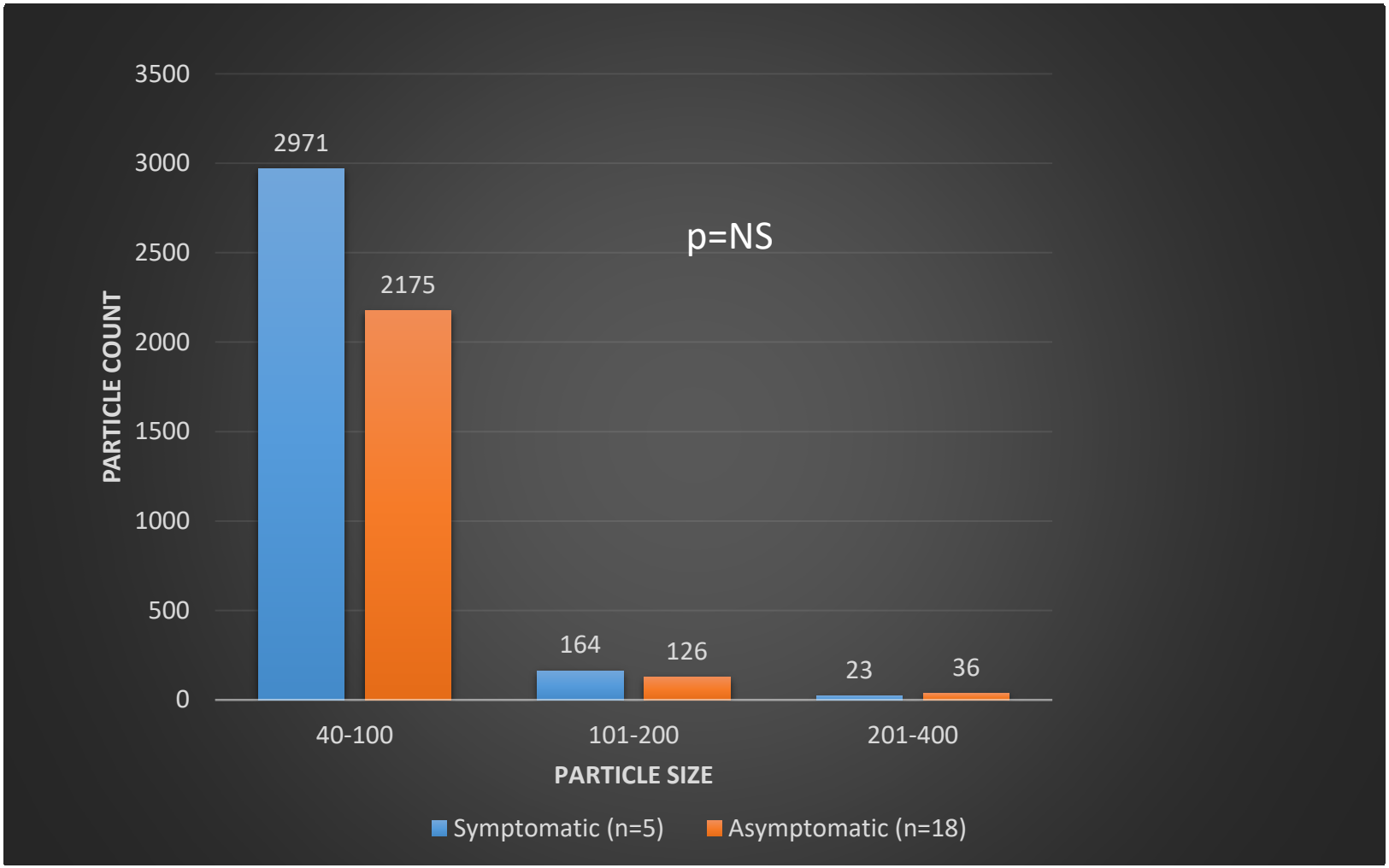
Comparison of Particle Counts in CAS in Symptomatic vs Asymptomatic Patients



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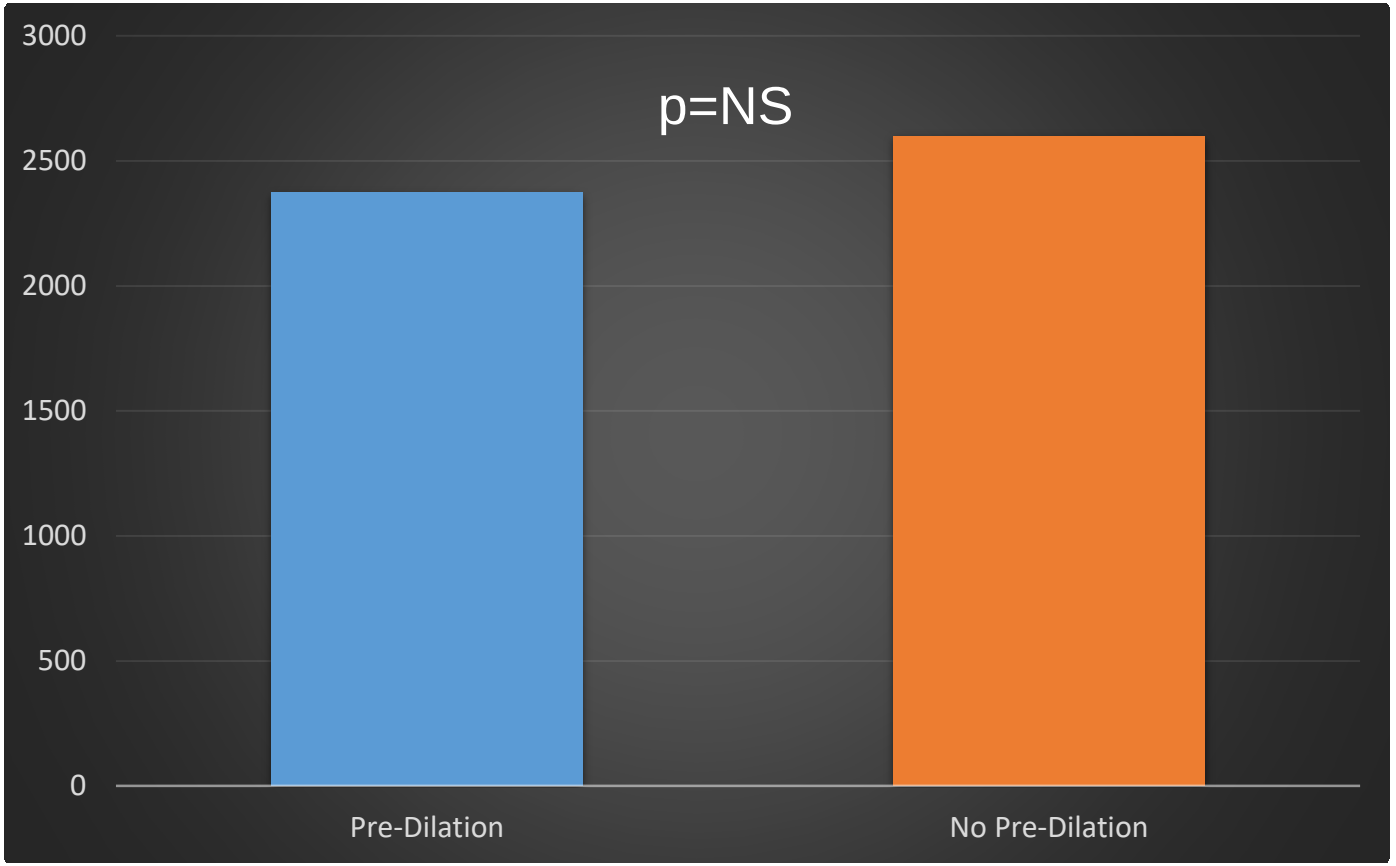
Comparison of Particle Counts in CAS performed with Pre-Dilation vs Without Pre-Dilation



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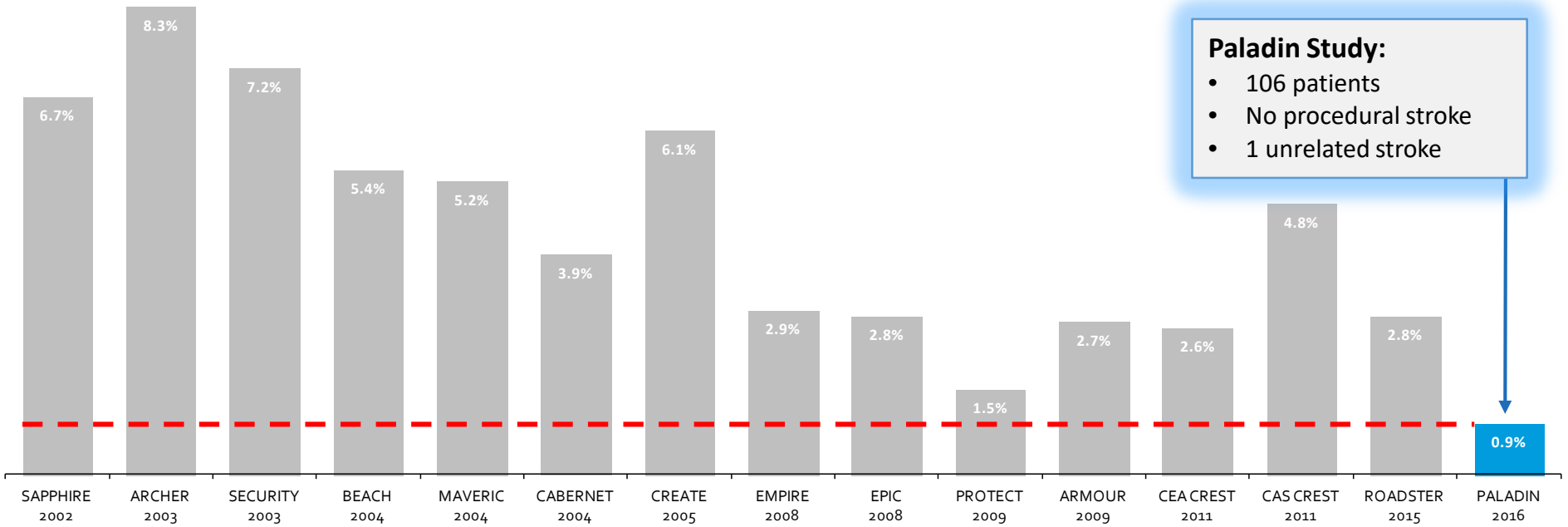
Clinical Data: Comparison of MAE Across CAS Studies

Paladin demonstrates low stroke rates compared to all other CAS studies



30-Day MAE defined as death, stroke or MI

Paladin results, 2016 study
Prospective multi-center studies with >100 patients

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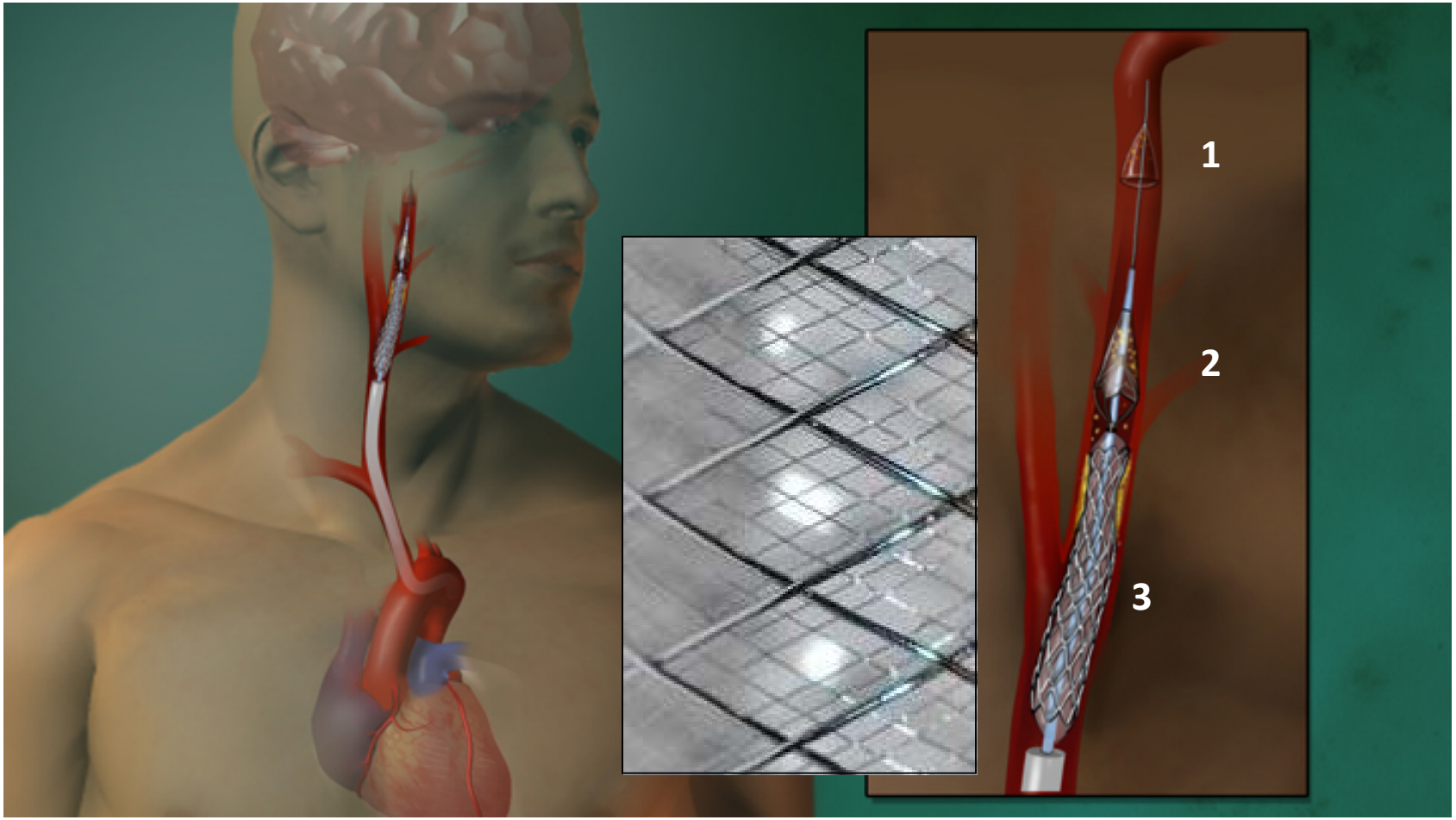
SAFETY !

Sometimes it´s really important to spot things before it finds you

‘Tripple-Protection’



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Procedures become more safe if they remain

a routine, stepwise, straight forward and

intuitive workflow

without adding any additional steps

which may cause a risk!

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SUMMARY-

Strategy to improve the outcome of CAS

- In the aera of Cerebral Protection the Stroke Risk is primarily influenced by microemboli
- Micromesh stents may prevent acute and late events (major and minor strokes)
- Paladin micropore filter for postdilation may effectively prevent minor strokes in the most critical phase of CAS
- Patient selection (soft plaques/thrombus containment) and concomittant medication will further improve acute results of CAS

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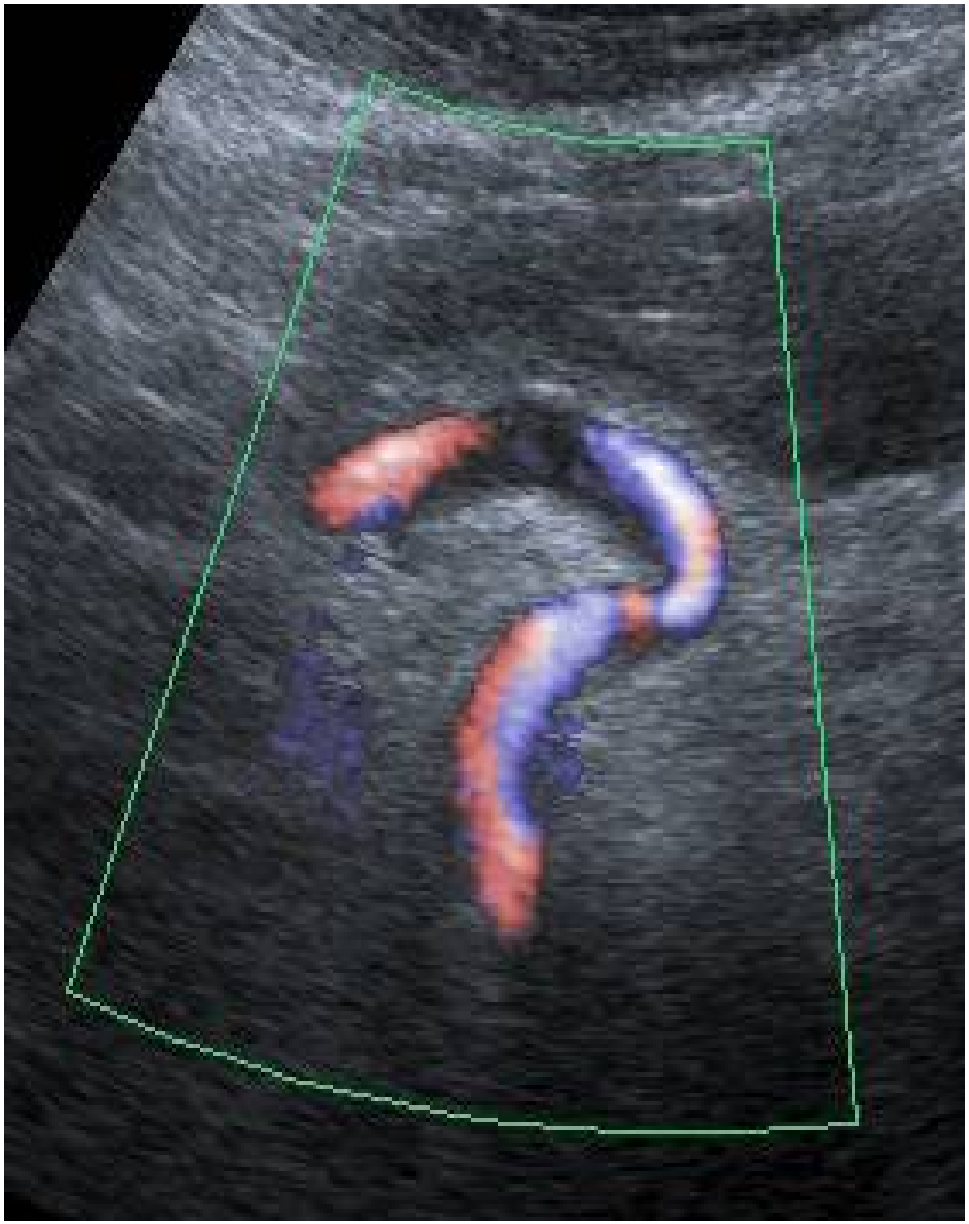

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Thank You For Your Attention!

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