Klinikum Stuttgart

Intracranial Atherosclerosis Life after SAMMPRIS

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NeuroNews

The international newspaper for neurointerventionists

November 2011 **Issue 4**

Charles Strother: Future stroke units

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Toshio Hyogo: Profile

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Trevo: Product news

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SAMMPRIS results find intracranial stents linked to more strokes and death

FROM WASID TO SAMMPRIS

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The goal was to show the superiority of intracranial stenting. The initial idea to use a coronary *drug eluting stent* was rejected by the FDA.

Against the advise of the inventors of the *Wingspan System* (a conventional old balloon and a self-expanding [aneurysm] stent with enhanced radial force) the „**S**tenting versus **A**ggressive **M**edical **M**anagement for **P**reventing **R**ecurrent stroke in **I**ntracranial arterial **S**tenosis" (SAMMPRIS) study was initiated.

SAMMPRIS

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451 patients in the acute phase after TIA or cerebral ischemia due to a high grade stenosis of a large intracranial artery

50 US centers

aggressive medical treatment (AMT)

vs.

AMT + Stent-PTA (*Wingspan*)

(AMT = 325 mg ASA, 75 mg Clopidogrel for 90 days, Rusovastatin, blood pressure normalizing, life-style modification)

Chimowitz 2011

Klinikum Stuttgart

Primary endpoints

- stroke or death **within** the first 30 days after enrollment

or after Stent-PTA during the follow-up period

- stroke in the territory of the target artery **after** 30 days
- for cross overs (from AMT to Stent-PTA): stroke or death within 30 days

N = 451

AMT = 227

AMT + Stent-PTA = 224

Chimowitz 2011

SAMMPRIS

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	AMT	Stent
Primary endpoint **30 days**	5.8%	**14.7%**
Primary endpoint **1 year**	**12.2%**	20%

Chimowitz 2011

SAMMPRIS

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complications in Stent-PTA arm: 33 out of 224 (**14.7%**) patients

30 complications due to Stent-PTA
3 complications of diagnostic DSA

those **30 procedural complications** included

19 ischemic (12 perforator strokes, 3 embolic, 2 perforator & embolic, 2 stent occlusions)

11 hemorrhagic (6 ICH, 5 SAH) !!!!!!!!!!!!

Chimowitz 2011

SAMMPRIS

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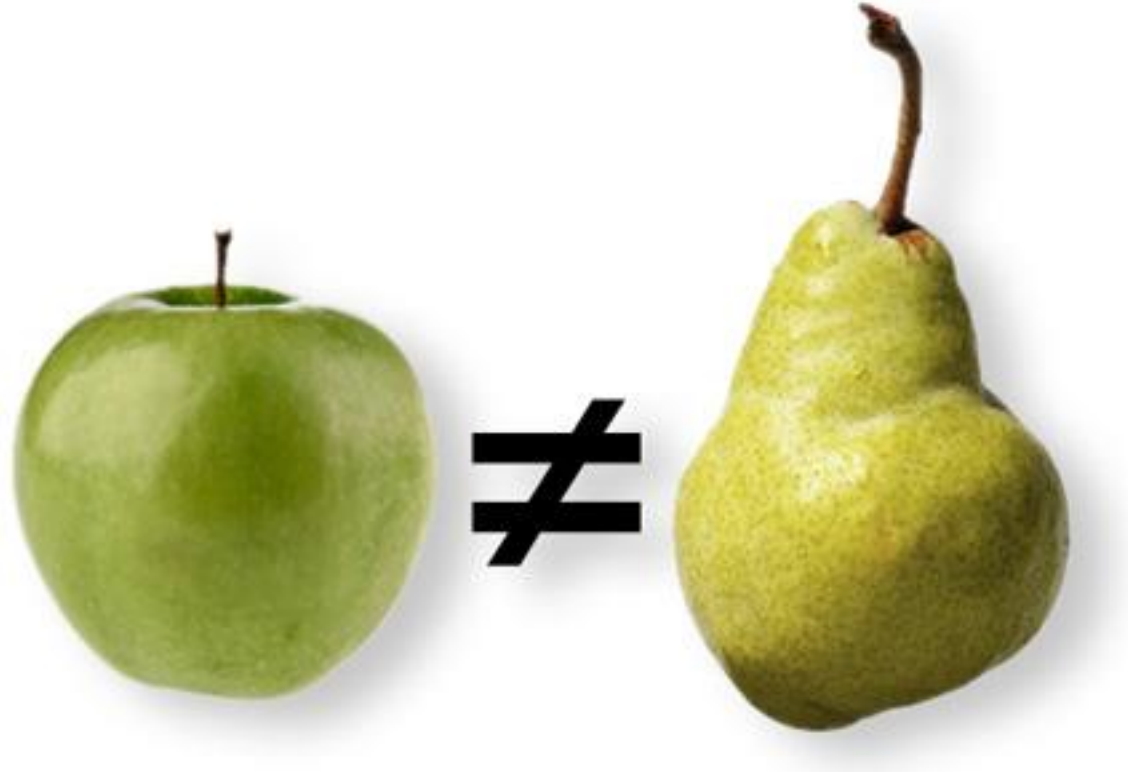
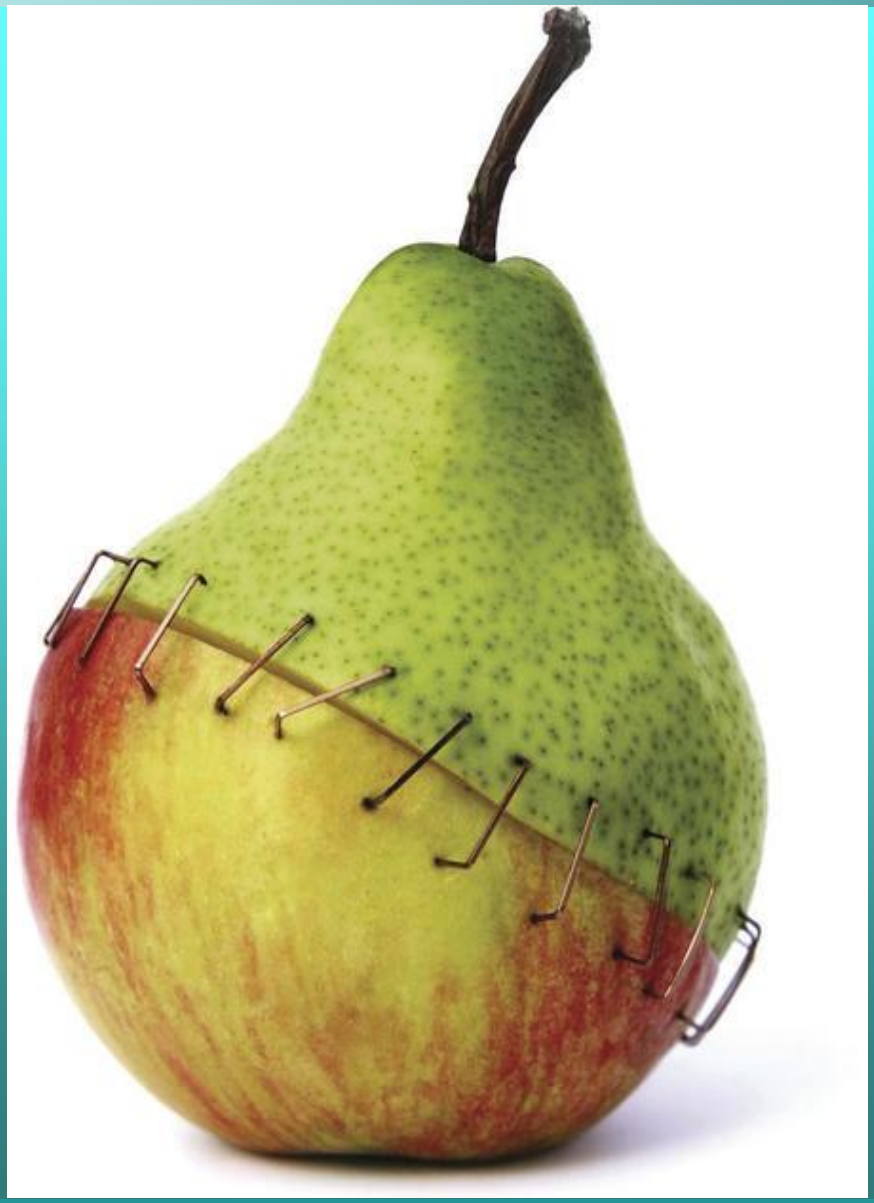
In SAMMPRIS the wrong physicians treated the wrong stenoses with the wrong device:

- many intracranial stenoses are not equally suitable for AMT *and* Stent-PTA
- the qualification criteria for the physicians performing the procedures in the stent arm were inadequate
- the enrollment rate per center was way too low
- the Wingspan system was already outdated
- the (high) in-stent re-stenosis rate after Wingspan was not addressed

However: SAMMPRIS confirms the high stroke rate under AMT **(12% primary endpoint in 1 year under AMT)**





ARGUMENT #1

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Clinical trials concerning the treatment of intracranial atherosclerotic arterial stenoses, comparing **ONE** medical regime with **ONE** surgical or endovascular procedure can not properly reflect the clinical reality and the medical demands; the structure of these studies rather creates an „artefact" than allowing a reasonable comparison of different treatment modalities.

EXAMPLE EC-IC BYPASS

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ARGUMENT #2

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The atherosclerotic stenoses of an intracranial artery is a progressive disease. Any known medical treatment (either antiaggregation or anticoagulation) will not remove an atherosclerotic stenosis. It may prevent distal emboli and may allow leptomeningeal collaterals to develop; the efficacy of this process is essentially unpredictable.

After a „maturation" of several months or years, many stenoses will simply be untreatable by endovascular means, mainly due to an inabilty of microwire or balloon passage distal to the stenosis.

EXAMPLE STENOSES NOT ACCESSIBLE

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ARGUMENT #3

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Arguments for a ***medical*** treatment

- less than 50% stenosis
- asymptomatic while under (dual) platelet function inhibition
- sufficient leptomeningeal collaterals
- „only" perforator ischemia, no infarcts due do hemodynamic compromise

ARGUMENT #4

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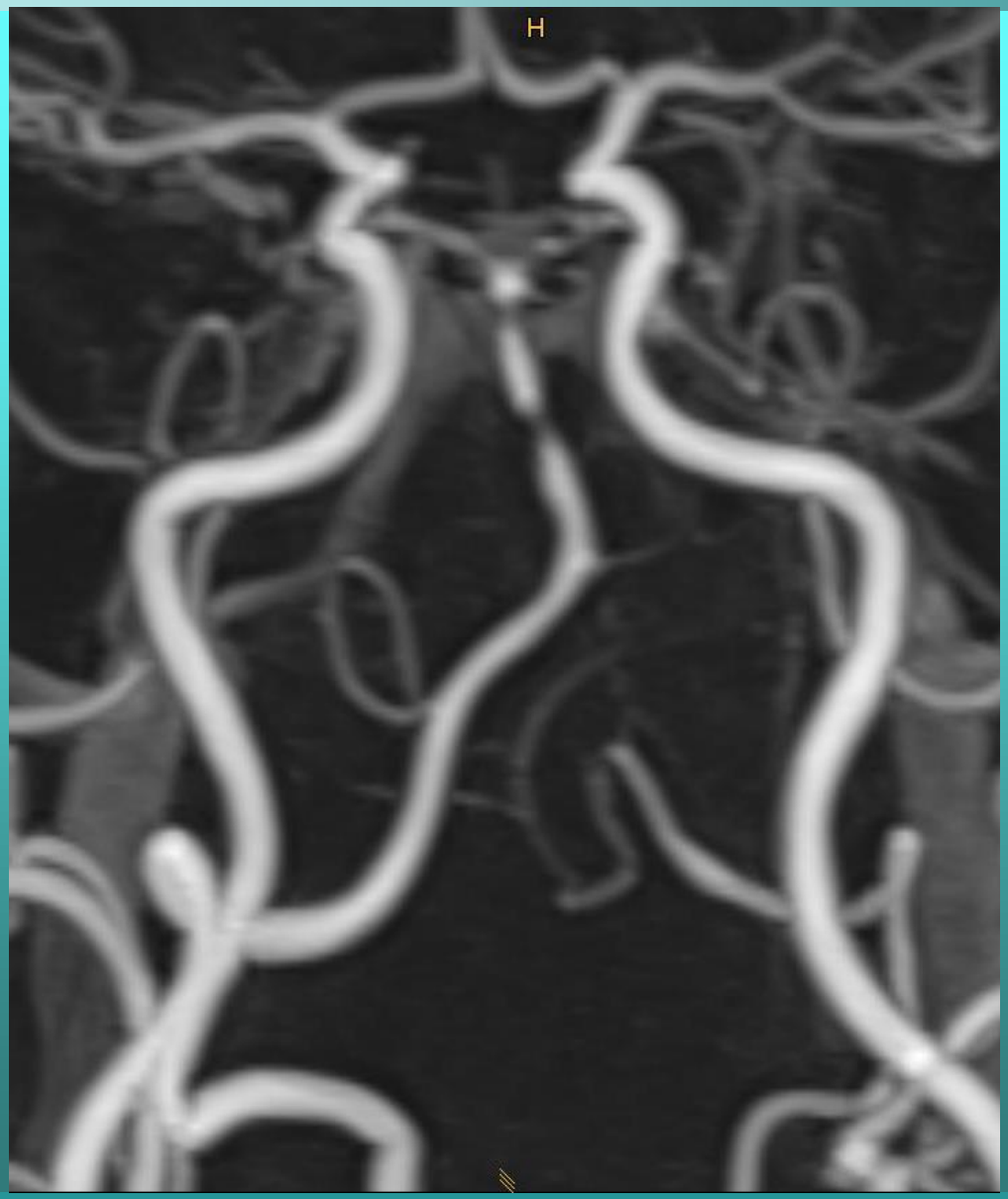
Arguments for an ***endovascular*** treatment

- more than 70% stenosis
- TIA or cerebral ischemia despite dual antiaggregation or anticoagulation
- progessive stenosis with poor or missing collaterals
- hemodynamic compromise due to stenosis

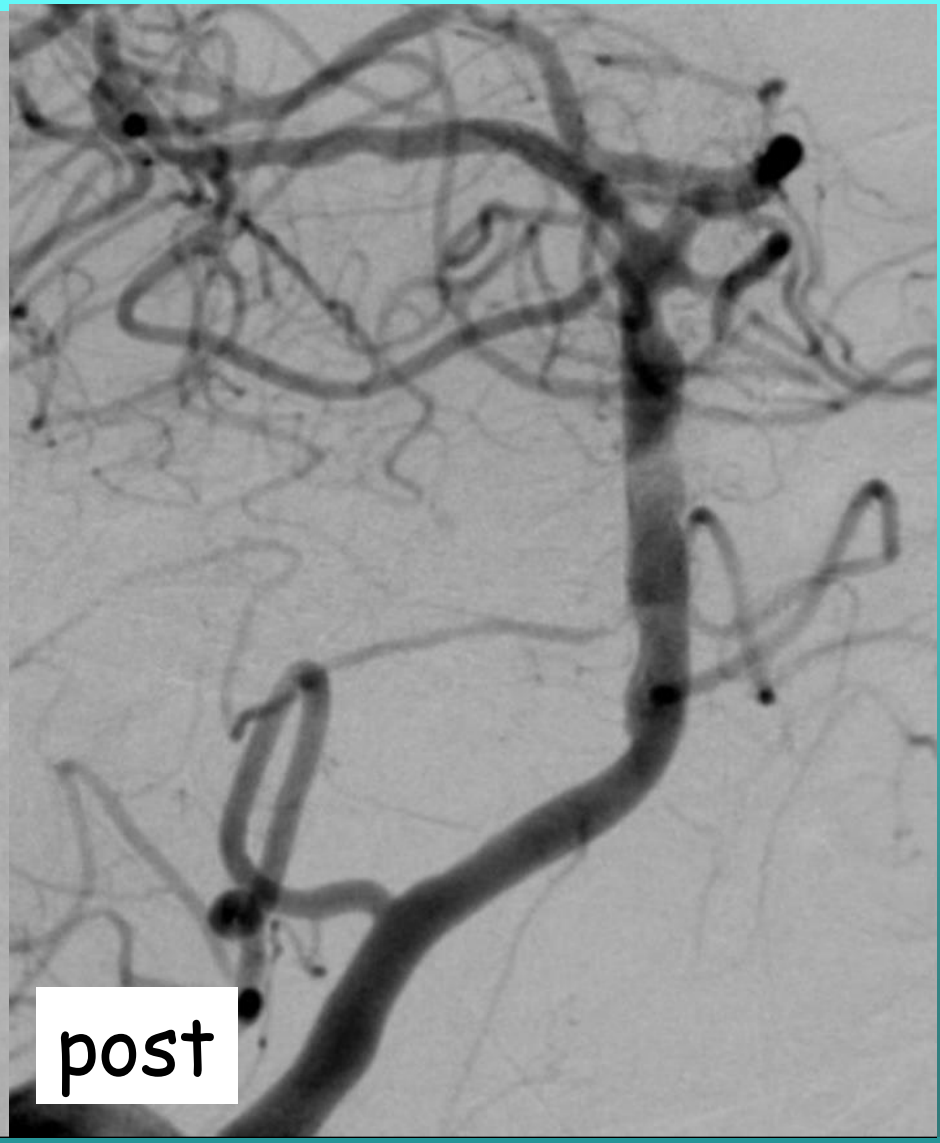
HEMODYNAMIC COMPROMISE

Klinikum Stuttgart



HEMODYNAMIC COMPROMISE

Klinikum Stuttgart



ARGUMENT #5

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Treatment options for intracranial atherosclerotic stenoses

ASA

ASA + Clopidogrel or Prasugrel or Ticagrelor

DOAC + ASA, DOAC + Clopidogrel

Balloon angioplasty only

Balloon angioplastie + selfexpanding stent

Selfexpanding stent only

Balloonexpandible bare metal stent

Balloonexpandible drug eluting stent

Direct bypass

Indirect bypass

ARGUMENT #6

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The endovascular treatment of intracranial stenoses

- can be a technically demanding procedure
- can be associated with significant risks
- is hardly ever a standardized treatment
- must be weight against treatment alternatives on an individual basis
- the documented rate of permanent morbidity and mortality related to intracranial stent PTA procedures in a given center and for a given operator has to be **below 10%**

ARGUMENT #7

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Intracranial stent PTAs should only be performed in specialized neurovascular centers, including

- vascular Neurology

- vascular Neurosurgery

- Neuroanesthesiology

- infrastructure (e.g., Multiplate, ICU, Stroke Unit, etc.)

- to be discussed: procedure frequency or case load, institutional experience, operator experience… (qualification issues)

RESULTS (M&M)

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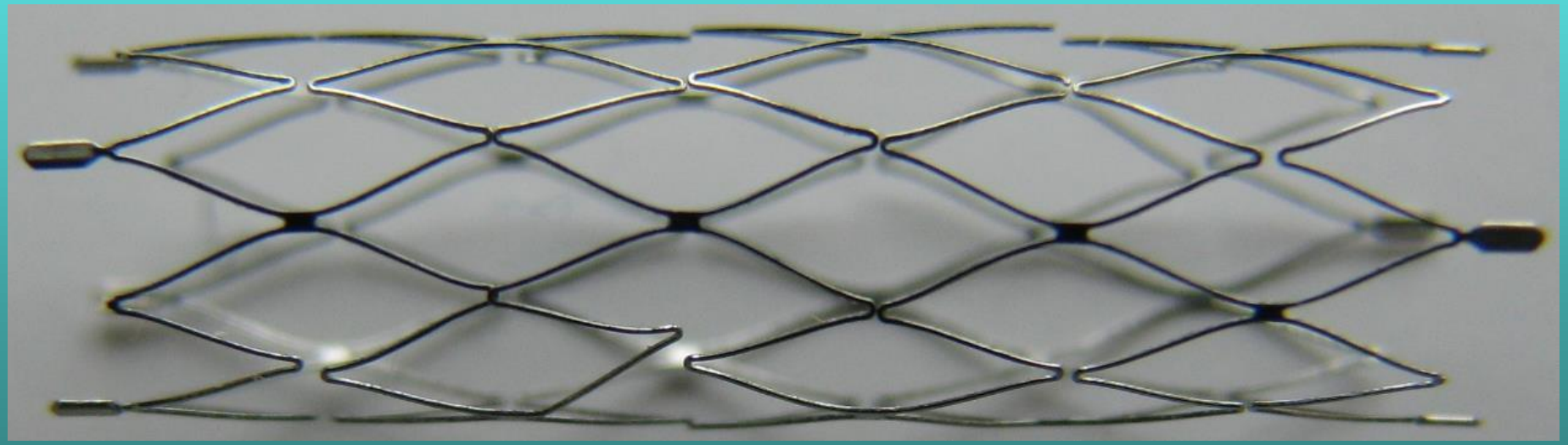
Kurre 2010	Intrastent	severe complications	7%
Dorn 2012	Various	severe complications	8%
Vajda 2012	Enterprise	severe complications	8%
Vajda 2012	DEB & Enterprise	severe complications	5%
Vajda 2012	Coroflex Please	severe complications	4 %

WHICH STENT?

Klinikum Stuttgart

Wingspan?



WHICH STENT?

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Wingspan has a higher radial force than Neuroform

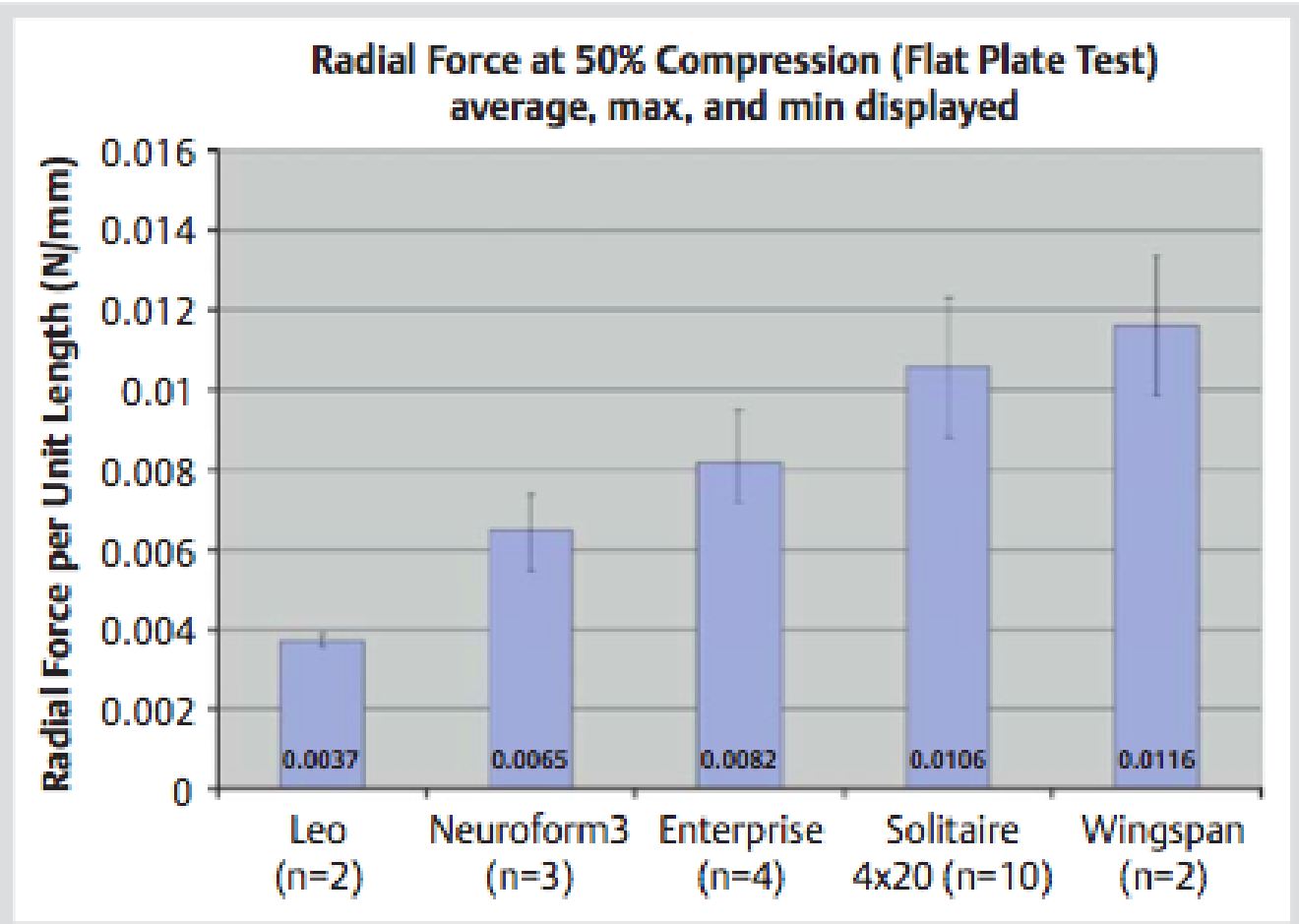

Fig. 3 Comparison of the stents' radial force at 50 % compression using a "Flat Plate Test".

WINGSPAN

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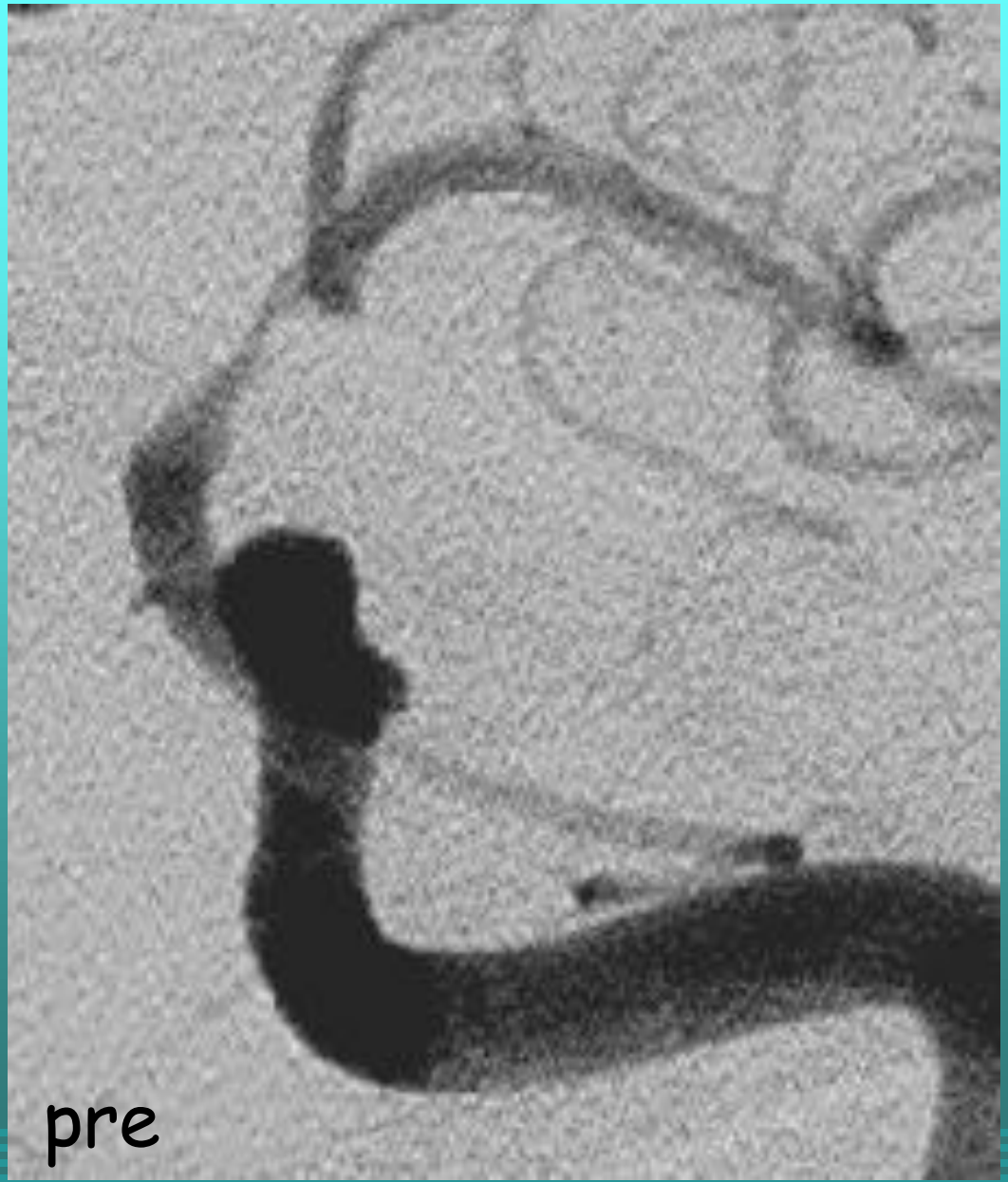

WINGSPAN

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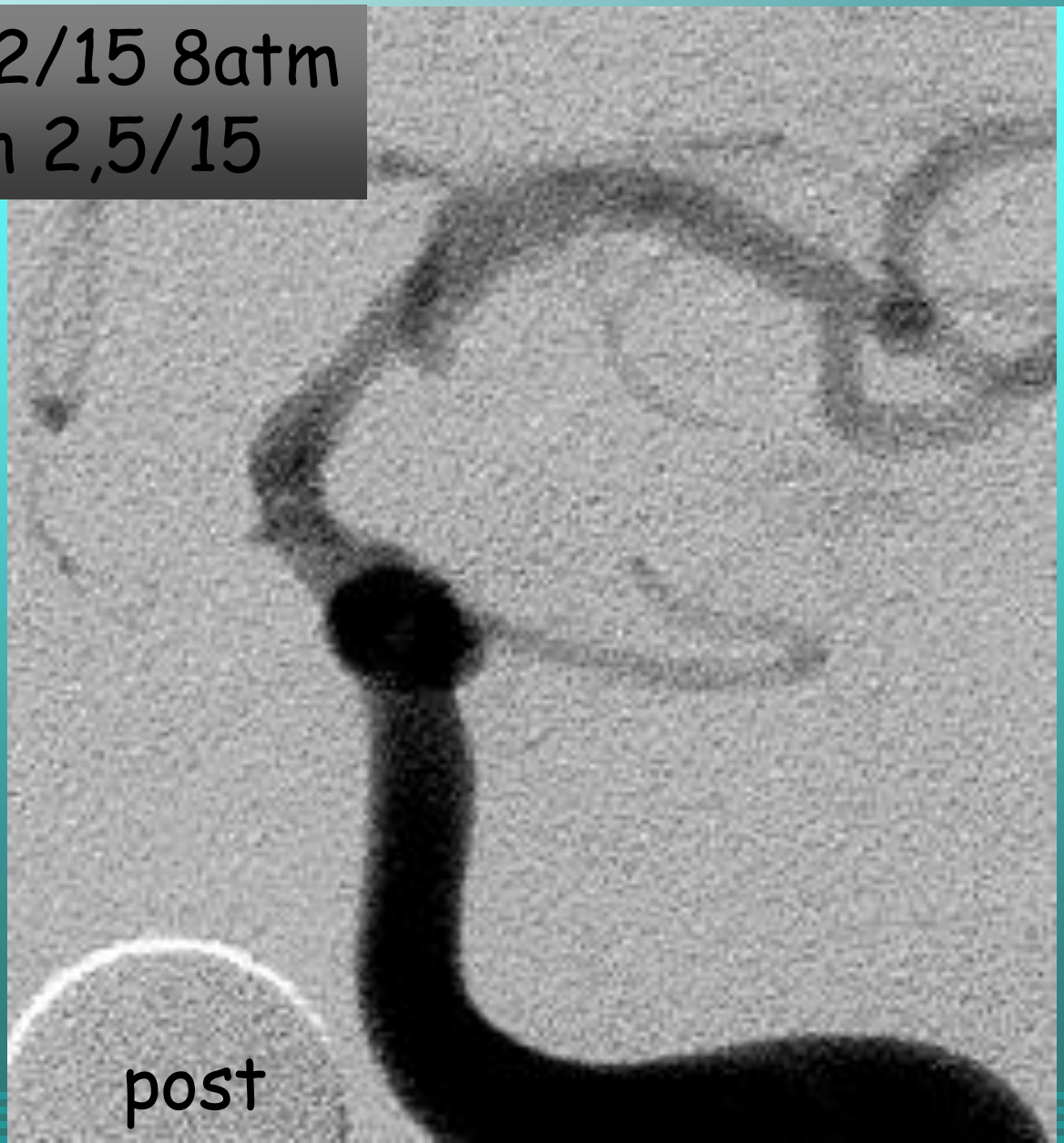
Gateway 2/15 8atm
WingSpan 2,5/15



WINGSPAN

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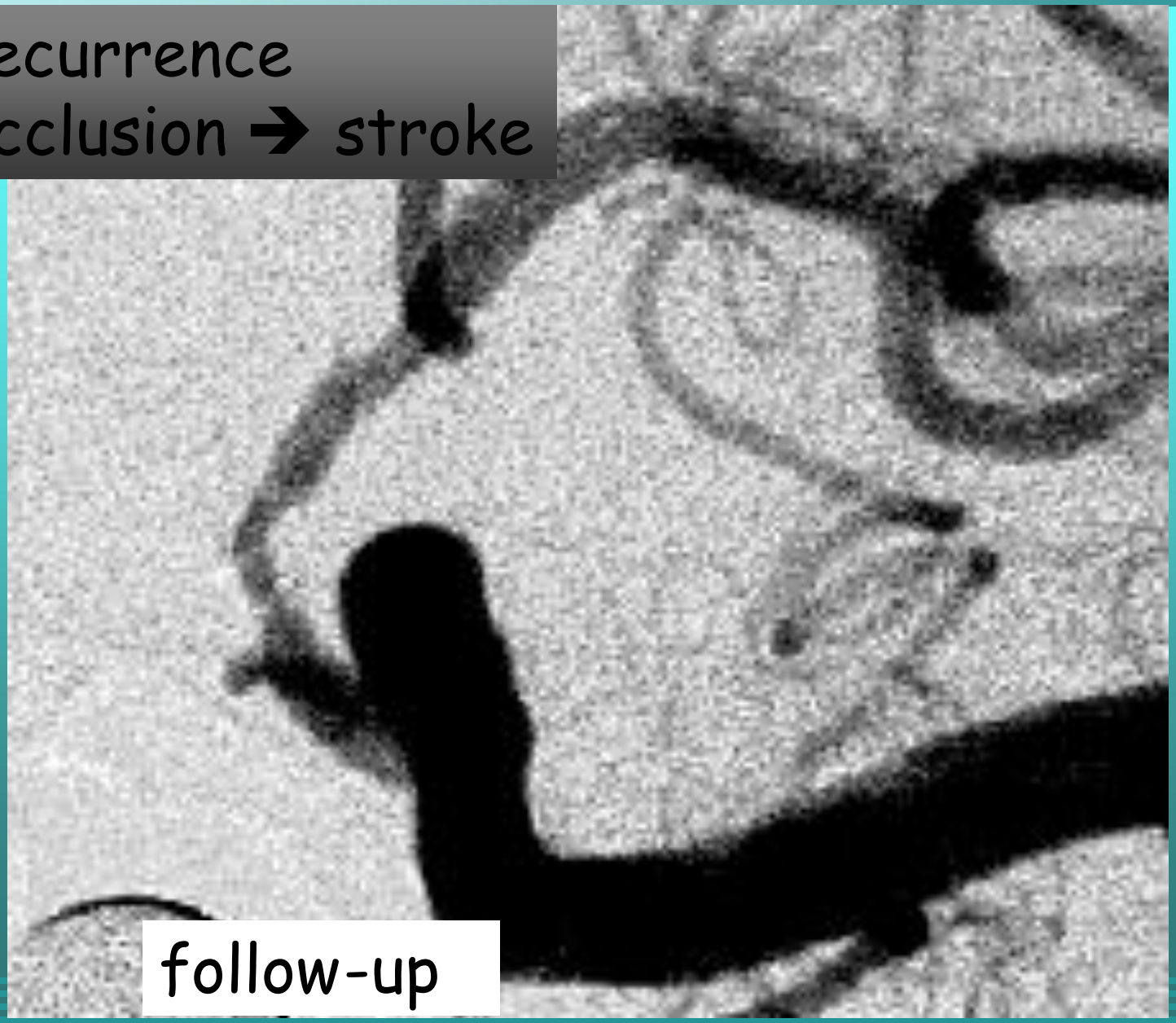
5 Mo: recurrence
6 Mo: occlusion ➔ stroke



AFTER THIS POINT:
ALMOST EVERYTHING IS OFF LABEL

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WHICH STENT?

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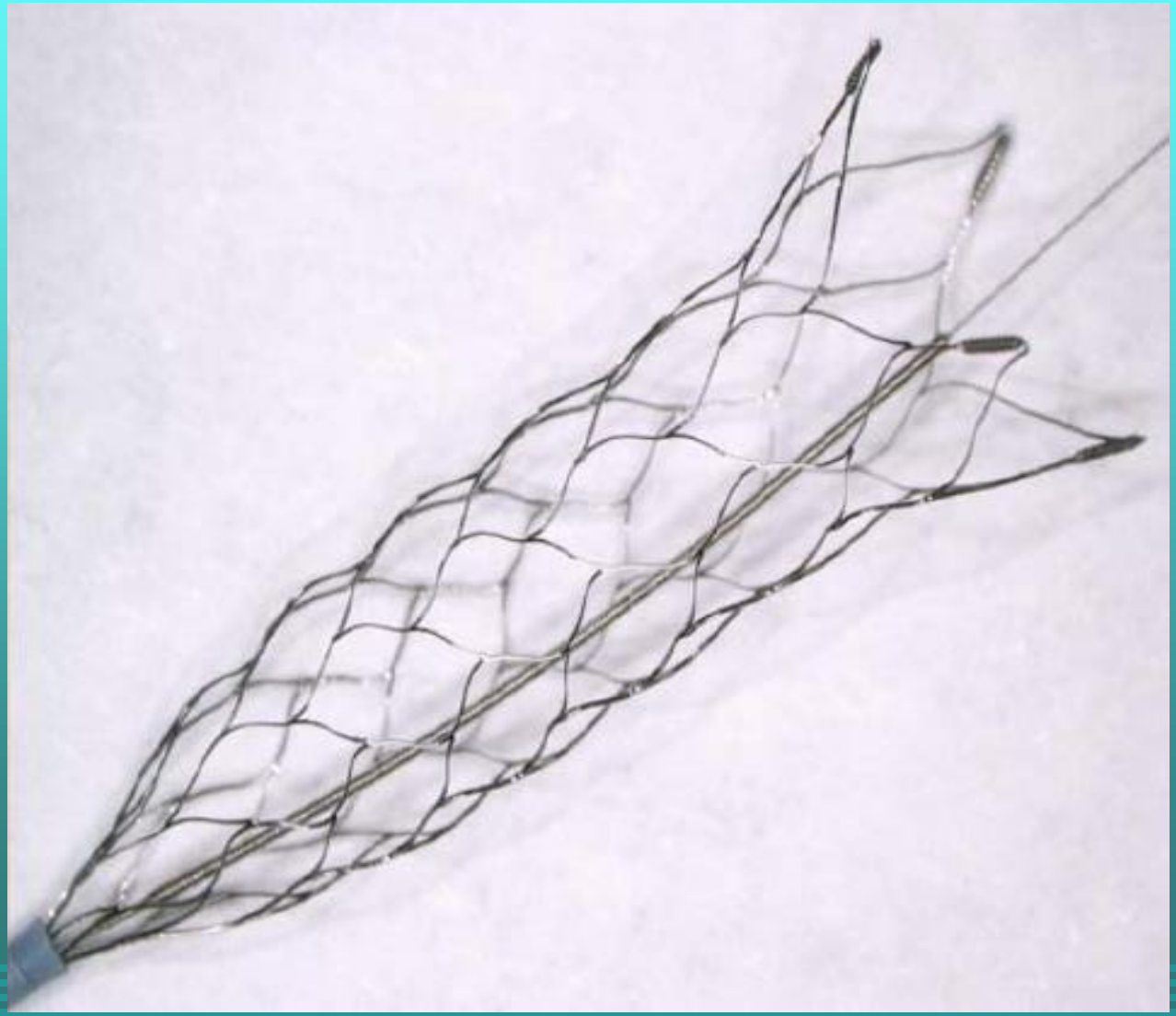
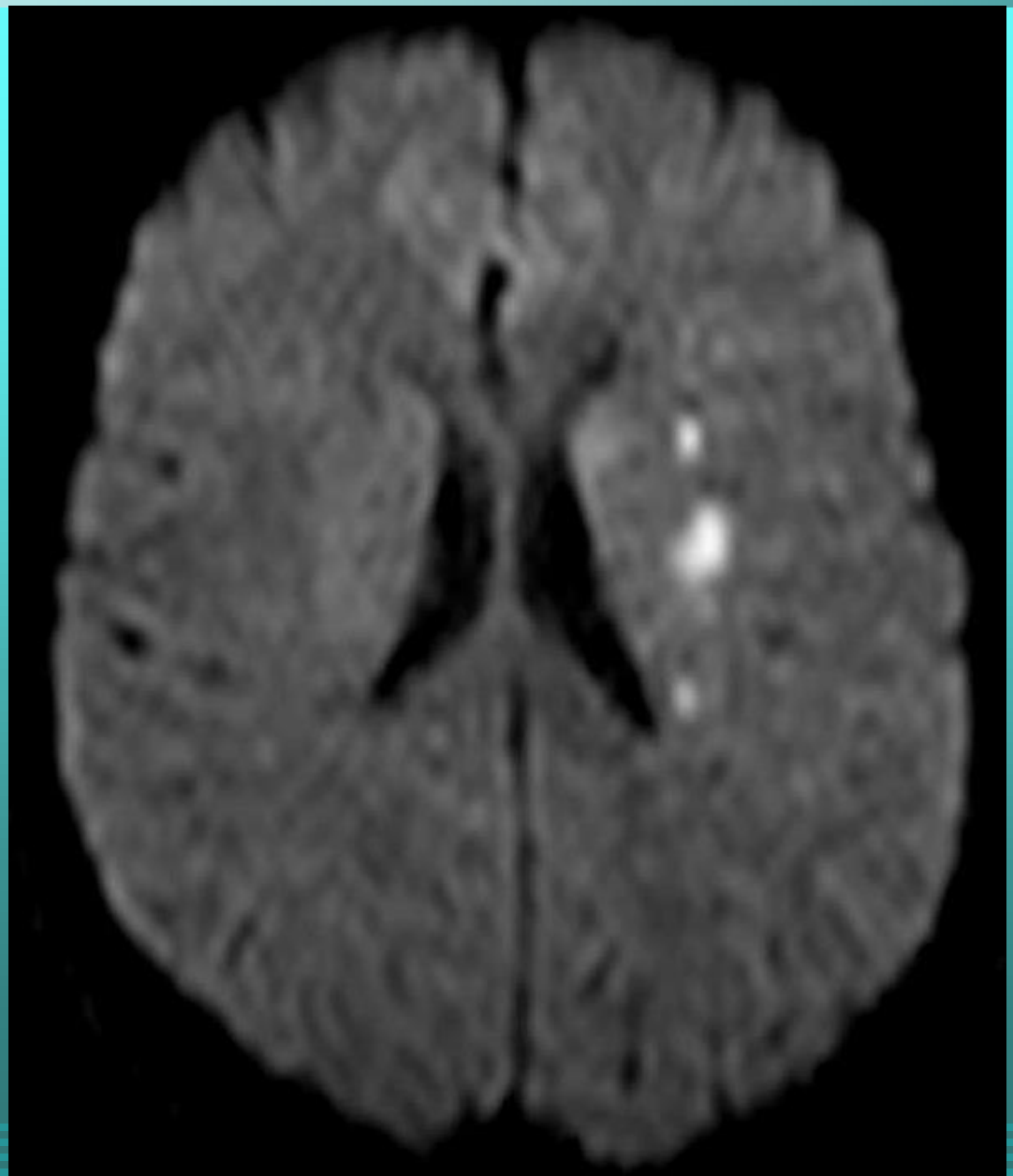
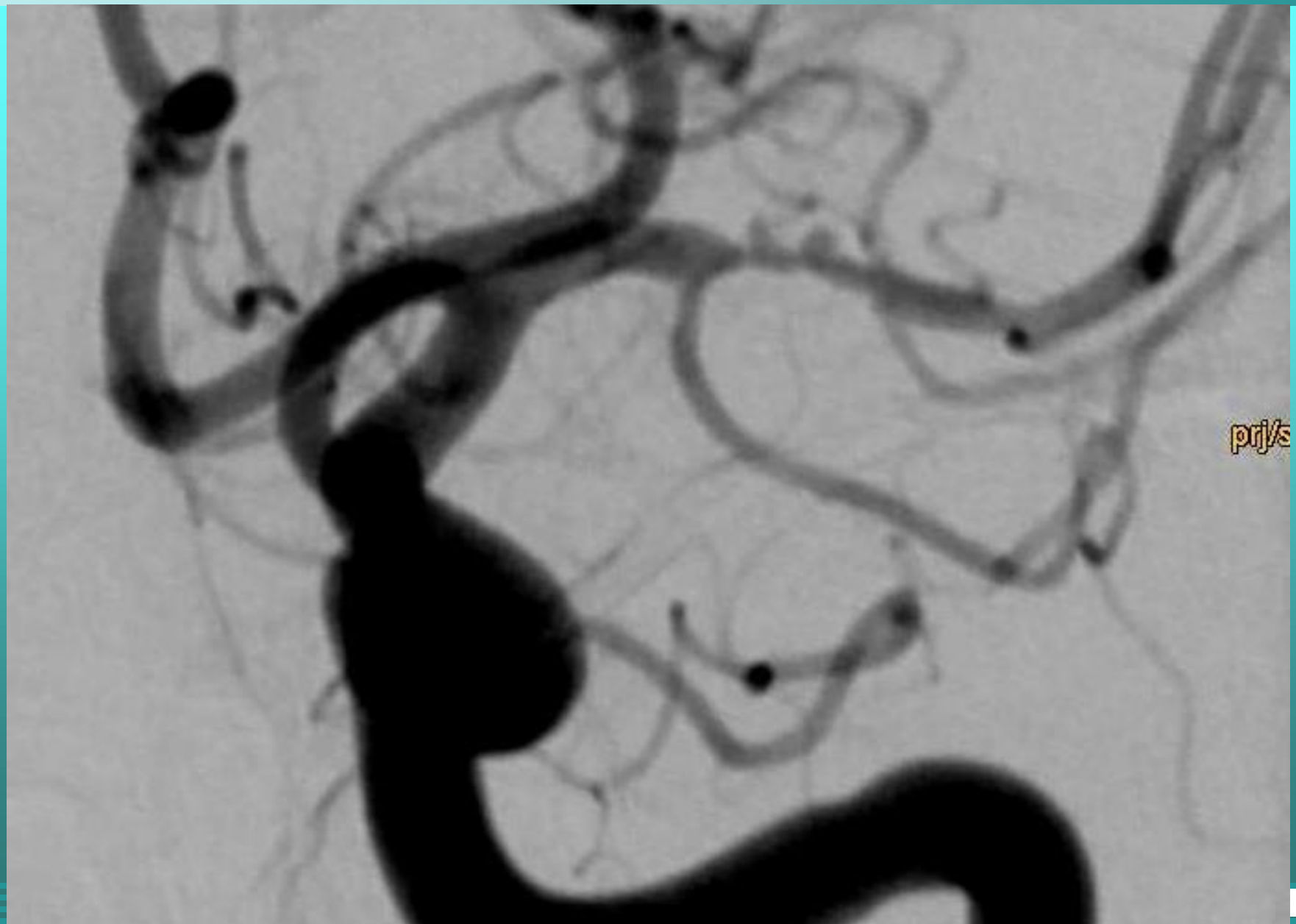
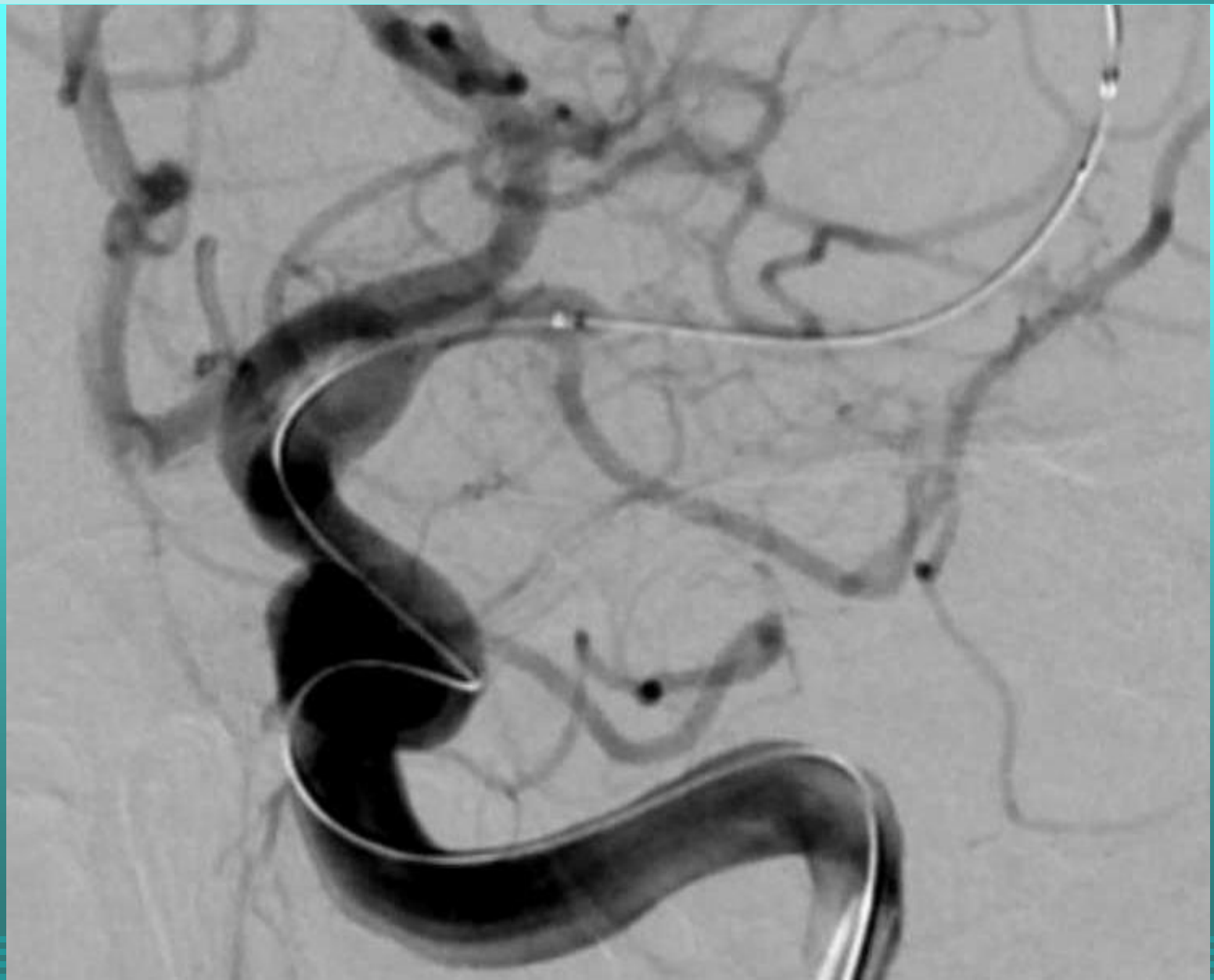
Enterprise1






prj/s




29.11.2007
10:19
11 IMA 300
RM Angio
4mm
prj/schätz
Angulierung 1: 0.2
Angulierung 2: 20.3
kV/mA: 86.0/100
BV (cm): 110.0
WL: 256/128

m Stuttgart


*14.02.1954
29.11.2007
10:19
12 IMA 300
AXIOM-Artis
RM Angio
4mm
prj/schätz
Angulierung 1: 0.2
Angulierung 2: 20.3
kV/mA: 86.0/100
BV (cm): 110.0
WL: 256/128


29.11.2007
10:20
13 IMA 300
RM Angio
4mm
prj/schätz
Angulierung 1: 0.2
Angulierung 2: 20.3
BV (cm): 110.0

Stuttgart


*14.02.1954
29.11.2007
10:30
16 IMA 300
AXIOM-Artis
RM Angio
4mm
prj/schätz
Angulierung 1: 0.2
Angulierung 2: 20.3
kV/mA: 86.0/100
BV (cm): 110.0
W/L: 256/128

n Stuttgart

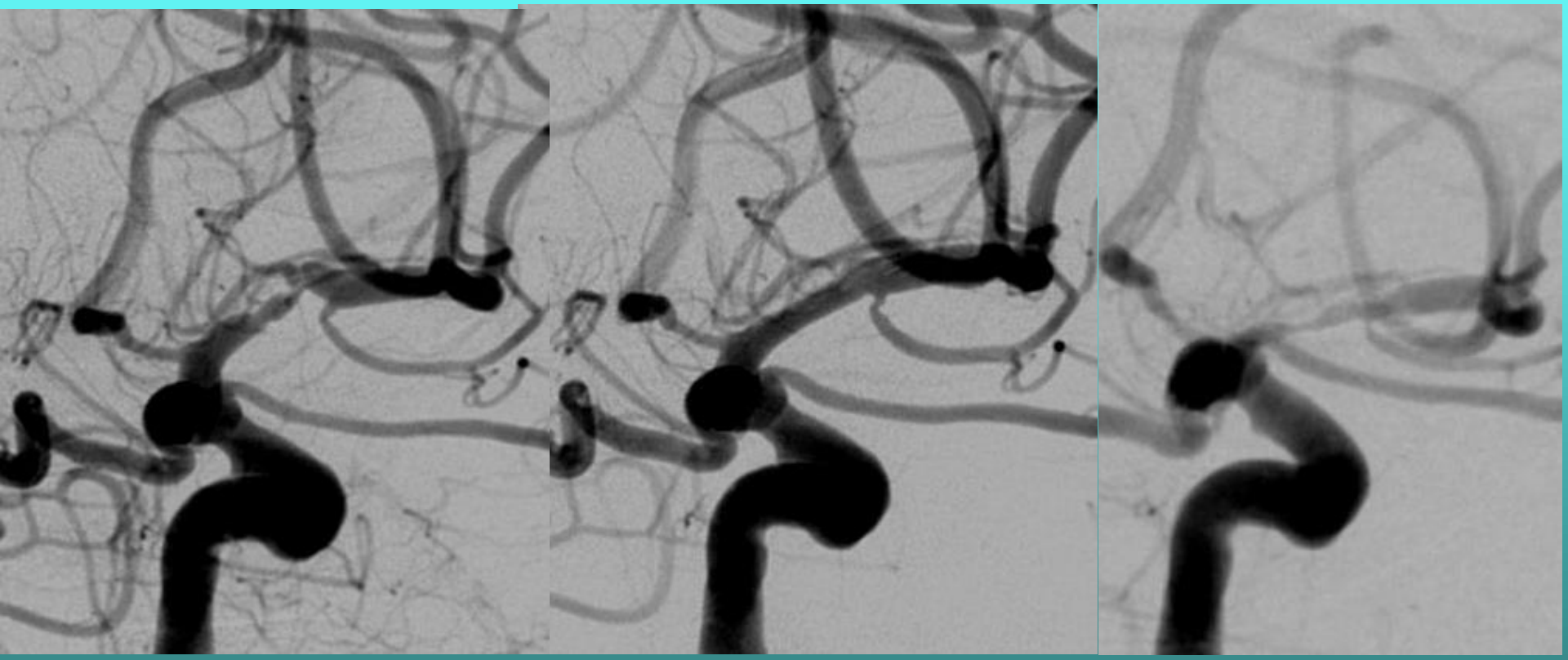

*14.02.1954
29.11.2007
10:31
17 IMA 300
AXIOM-Artis
RM Anglo
4mm
prj/schälz
Angulierung 1: 0.2
Angulierung 2: 20.3
kV/mA: 86.0/100
BV (cm): 110.0
VW: 256/128

n Stuttgart


BAUMGART, RAINER (M)
*14.02.1954
29.11.2007
10:36
19 IMA 301
Neuroradiologie KH Stuttgart
AXIOM-Artis
DSA cerebral
4mm
prj/schätz
Angulierung 1: 0.2
Angulierung 2: 20.3
kV/mA: 77.0/474
BV (cm): 110.0
W/L: 256/128


4mm
prj/schätz
29.11.07


20.02.2008
12:09
3 IMA 300
DSA cerebr.2B/s
4mm
prj/schätz
20.2.08



Intracranial ISRS

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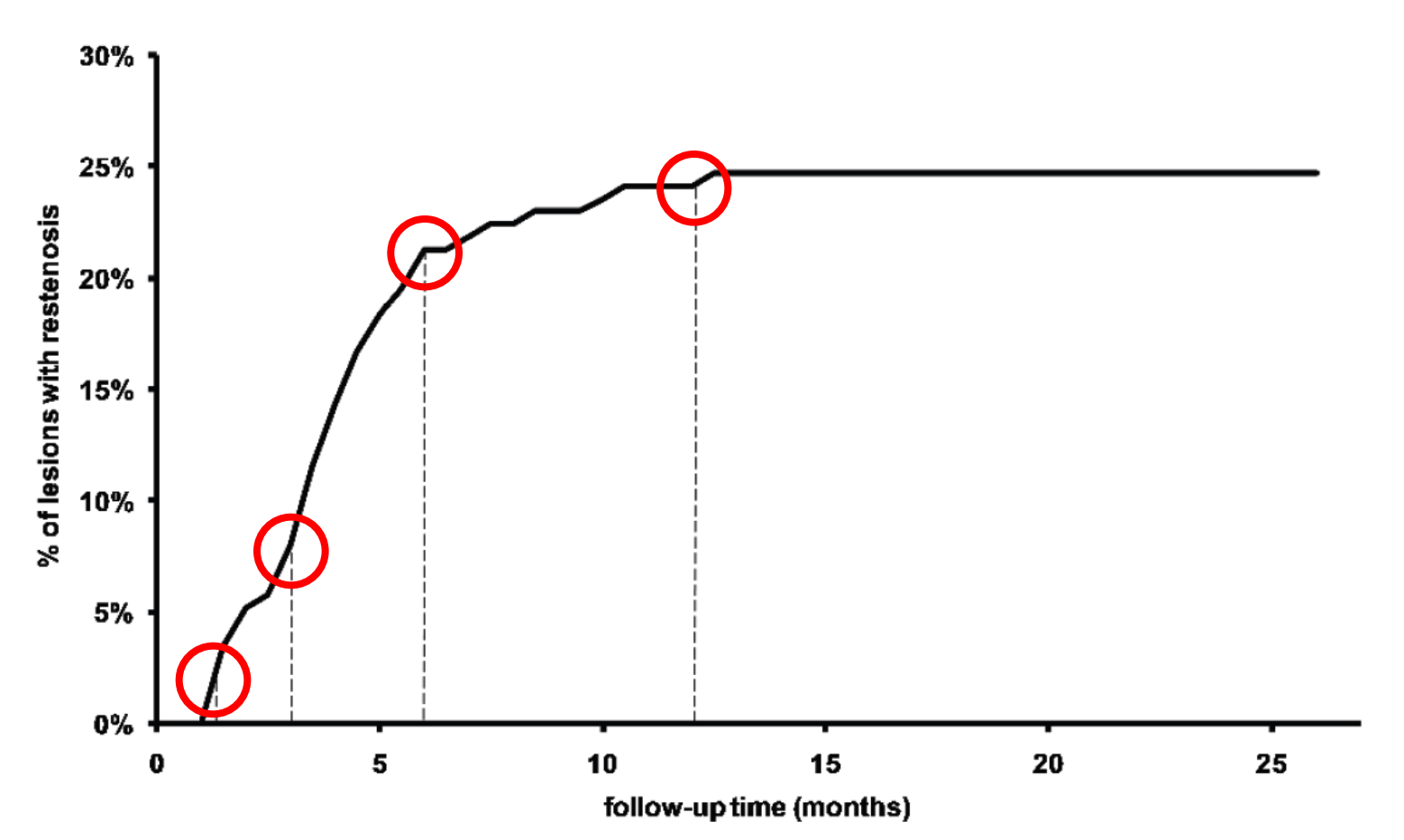
Autor	N=	Stent-Typ	restenosis occlusion	ipsilateral TIA stroke
Jiang (2012)	454 216	balloon expandible selfexpanding	20% 28%	11%
Vajda (2012)	209	Enterprise	→25%	→9.3%
Jiang (2012)	100	Wingspan	27% (45 angio FU)	11%
Costalat (2011)	60	Wingspan	17%	6%
Zhu (2010)	61	balloon expandible	30%	n.a.
Miao (2009)	79	balloon expandible	20%	25%
Levy (2007)	78	Wingspan	36%	27.6%
Jiang (2007)	94	balloon expandible	20%	26%

ISRS – over time



Vajda et al. Neurosurgery 2012

Drug Eluting Stents

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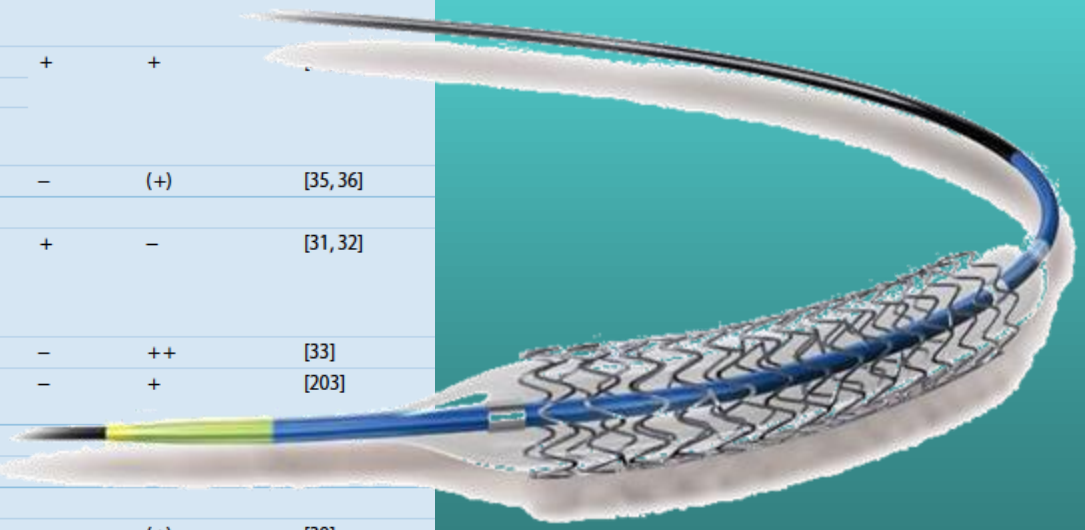
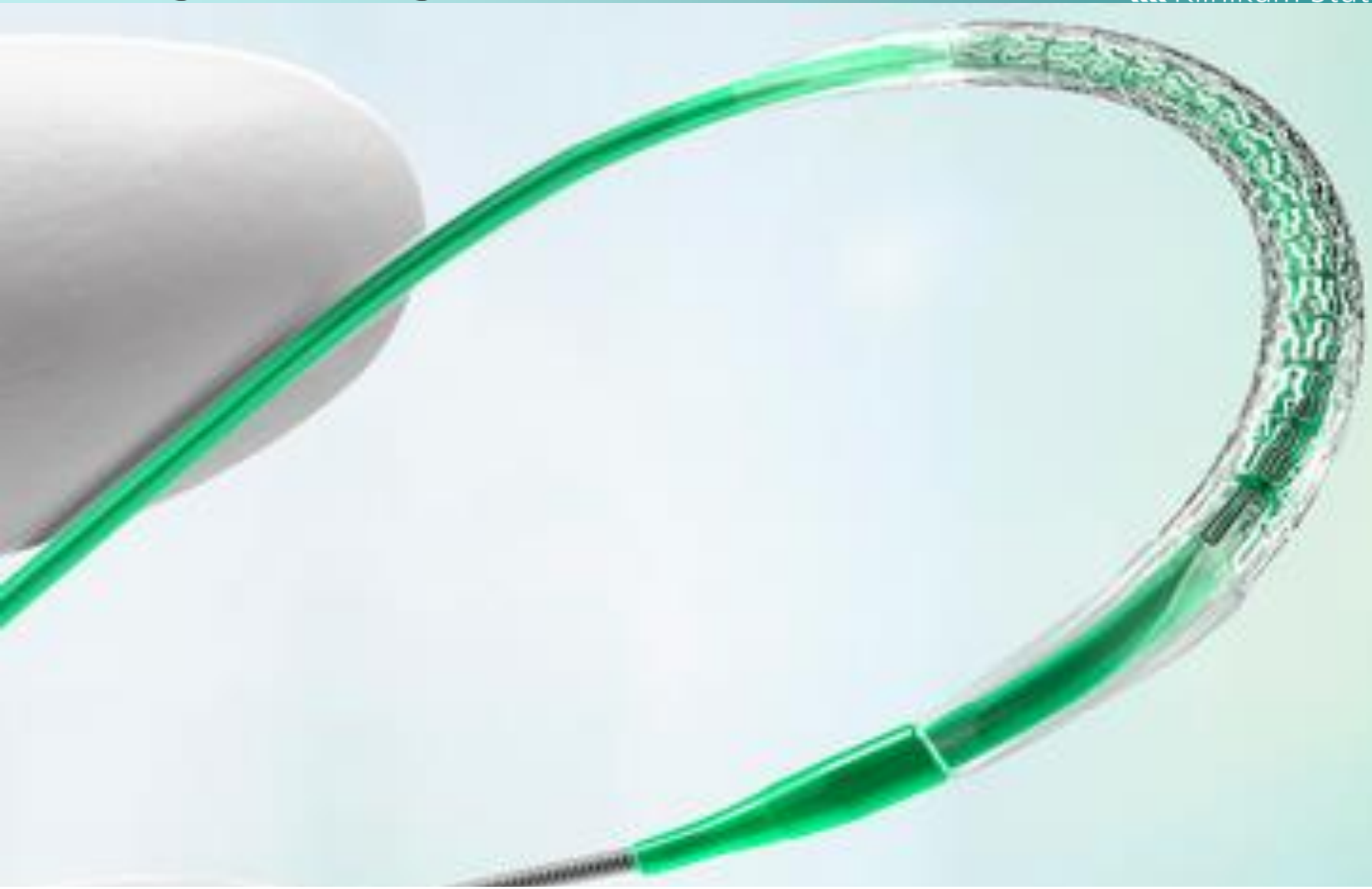
Stentsystem/ Stentfamilie	Hersteller	Wirkstoff	Trägerbeschichtung	Stentgerüst	Endpunkt klinisch	Endpunkt angiographisch	Literatur
Biostabile Polymerbeschichtung							
Cypher-Familie Cypher Cypher Select	Cordis	Sirolimus	Polyethylen-co-vinylacetat (PEVA), Poly-n-butyl-Methacrylat (PBMA)	Stainless steel	++	++	[2, 16, 17, 31, 32, 200, 201]
Taxus-Familie Taxus Nir/Express/Express² Taxus Liberte	Boston Scientific	Paclitaxel	Poly-Styren-b-isobutylen-b-styren (SIBS)	Stainless steel	++	++	[15, 20, 21, 25, 33, 202]
Taxus Element				Platin-Chrom			
Xience/Promus-Familie Xience V Xience Prime	Abbott	Everolimus	Poly-Vinyliden-Fluorid-Hexafluoro-Propylen (PVDF-HFP)	CoCr	++	++	[16, 20, 21, 201]
Promus Promus Element	Boston Scientific			CoCr Platin-Chrom			[14, 16, 20, 21, 201]
Endeavor-Familie Endeavor Sprint	Medtronic	Zotarolimus	Phosphorylcholin (ABT 578)	CoCr	++	++	[17, 25, 28]
Resolute-Familie	Medtronic		3 Komponenten Biolinx		+	+	
Resolute				CoCr			
Resolute Integrity				CoCr			
Coroflex Please	B. Braun	Paclitaxel		Stainless steel	–	(+)	[35, 36]
Biodegradierbares Polymer							
Biomatrix-Familie Biomatrix Biomatrix Flex	Biosensors	Biolimus A9	PLA	Stainless steel	+	–	[31, 32]
Nobori	Terumo	Biolimus A9	PLA	Stainless steel	–	++	[33]
Nevo	Cordis	Sirolimus	Resorbierbares Polymer	CoCr	–	+	[203]
Polymerfreie Beschichtung							
Yukon (ISAR)	Translumina	Sirolimus	Kein Polymer	Stainless steel			
Bioabsorbierbare Stents							
Absorb	Abbott	Everolimus	PLDA	PLLA (bioabsorbierbarer Stent)	–	(+)	[39]

Datenlage: ++ mehrere positive randomisierte Studien, + eine positive randomisierte Studie, (+) Registerdaten, – keine klinischen Daten; Publikation jeweils in „peer-reviewed journals". Literaturzitate relevanter klinischer Studien seit der letzten Aktualisierung des Positionspapiers.



Drug Eluting Stents

Klinikum Stuttgart



SeQuent ISAR (Sirolimus)

Indications and Results

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Efficacy

- **All** DES reduce the likelihood of re-intervention at the target vessel compared to BMS
- **EVEROLIMUS, SIROLIMUS, ZOTAROLIMUS- Resolute** are the most efficatious

Safety

- **No** difference in procedural mortality compared to BMS
- **All DES (but not Paclitaxel DES)** reduced the risk of MI
- **EVEROLIMUS** has the best safety profile concerning stent thrombosis

Drug Eluting Balloons

Klinikum Stuttgart

Ballonsys-tem	Hersteller	Zusatz zur Beschichtung	Wirksubstanz	Angiogra-phische End-punktstudien	Literatur
SeQuent Please	B. Braun	Kontrastmittel (Iopromid)	Paclitaxel 3 µg/ mm^2	++ (ISR, de novo mit Stent)	[41, 43, 44, 45, 46, 96, 118]
Dior II	Eurocor	Schellack	Paclitaxel 3 µg/ mm^2	–	[47]
Pantera Lux	Biotronik	Butyryl-trihexyl Zitrat	Paclitaxel 3 µg/ mm^2	–	
Elutax	AachenReso-nance		Paclitaxel 2 µg/ mm^2	–	
In.Pact Falcon	Medtronic Invatec	Harnstoff	Paclitaxel 3 µg/ mm^2	(+)	[204]

ISR Therapie der Instentstenose.
Studienlage (publiziert in „peer-reviewed journals"): ++ mehrere positive randomisierte
+ eine positive randomisierte Studie, (+) Registerdaten, – keine klinischen Daten.

Drug Eluting Balloons

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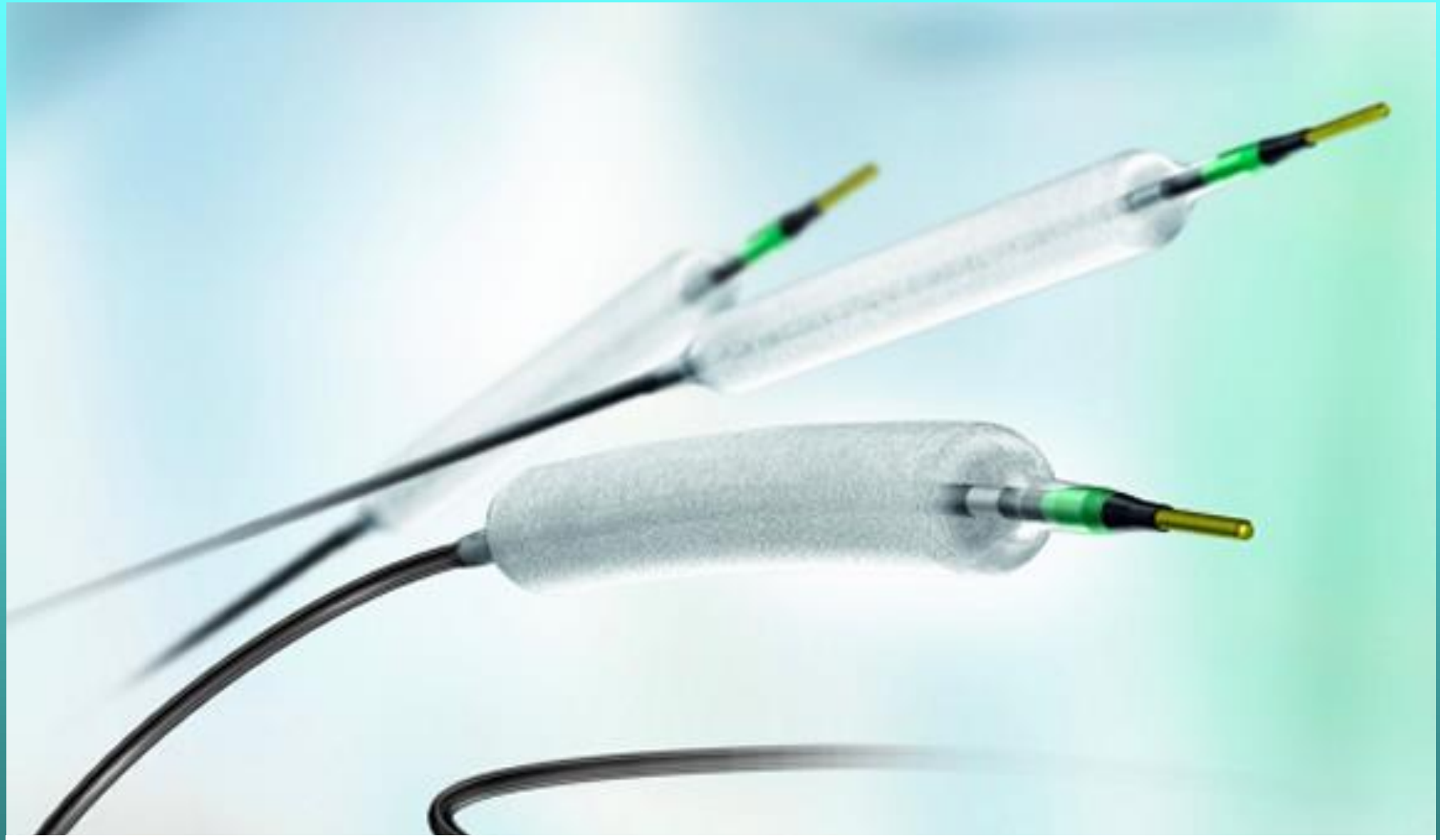

SeQuent Please, Sequent Please NEO

Results and Indications

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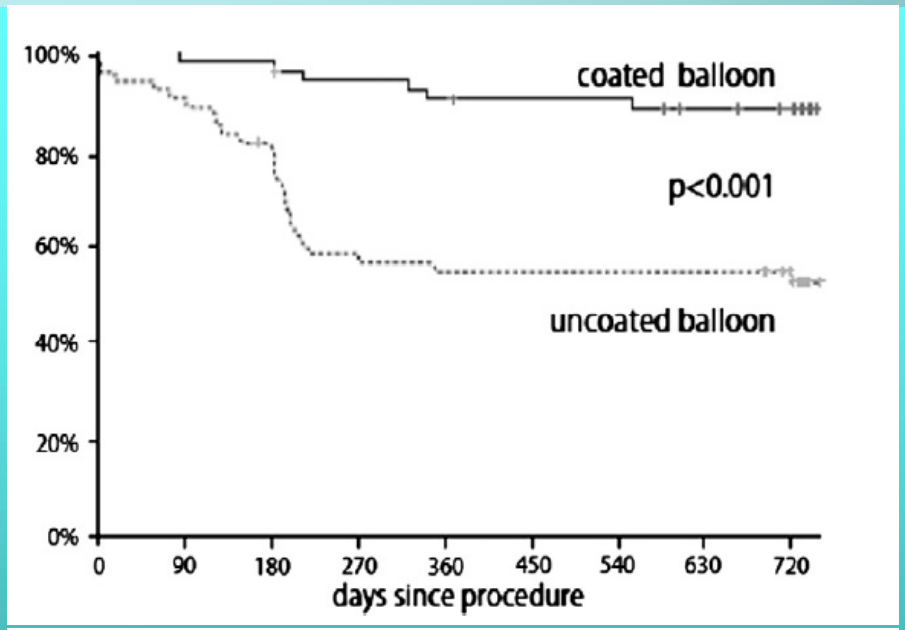


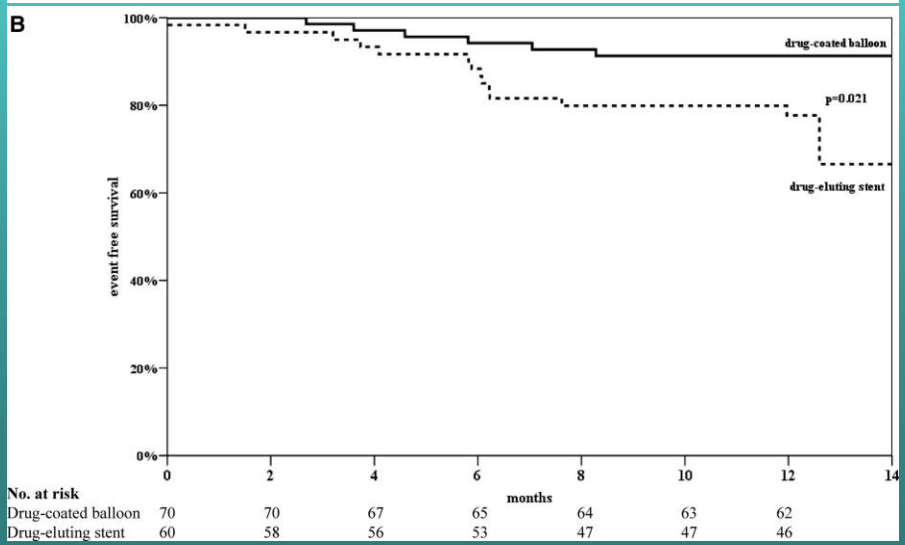
ISRS

DEB vs. uncoated PTA

Event free survival at 2 years

(Stent thrombosis, TLR, MI, Stroke, death)

Scheller 2008

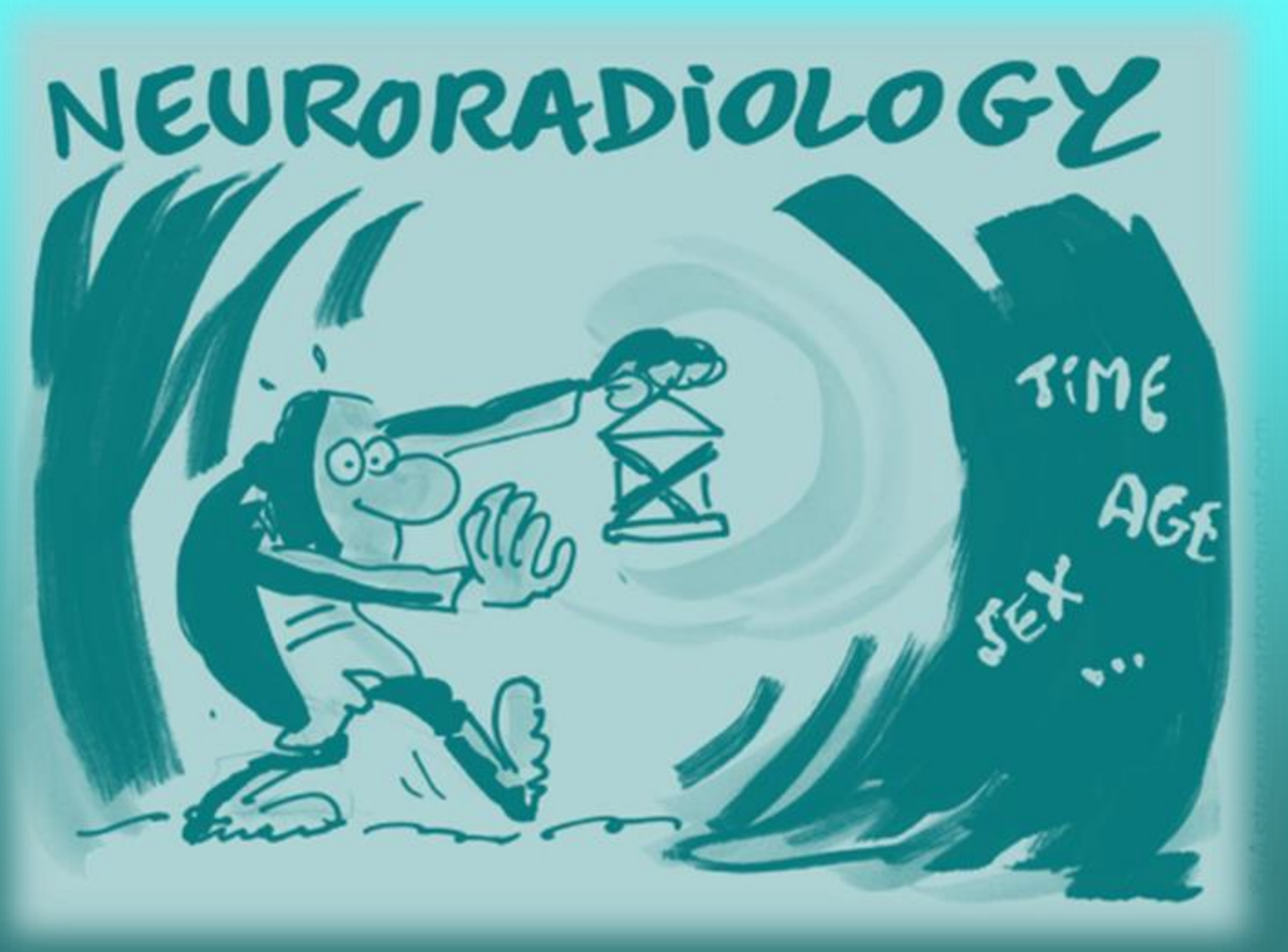


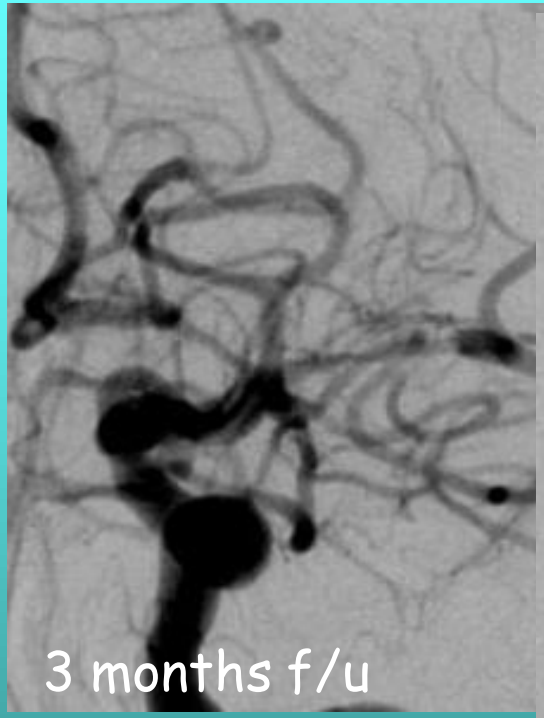
DEB vs. DES (Paclicatxel)

Event free survival at 2 years

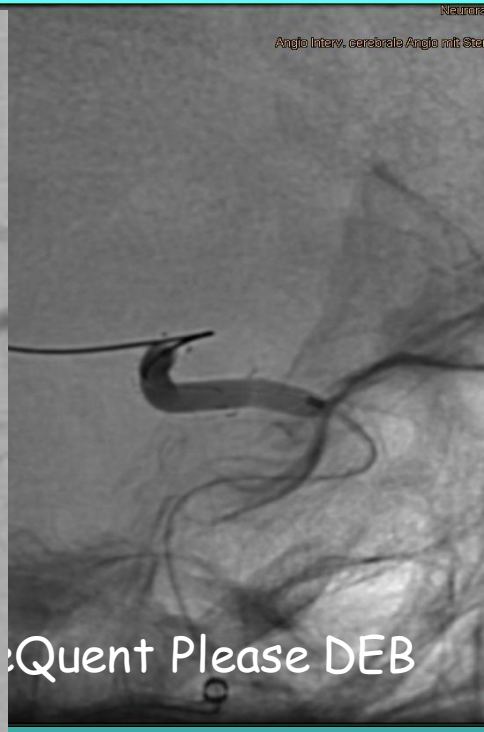
(Stent thrombosis, TLR, MI, death)

Unverdorben 2009)


NEURORADIOLOGY
TIME
AGE
SEX
...


3 months f/u


12 months f/u


Quent Please DEB

ISRS treatment with DEB

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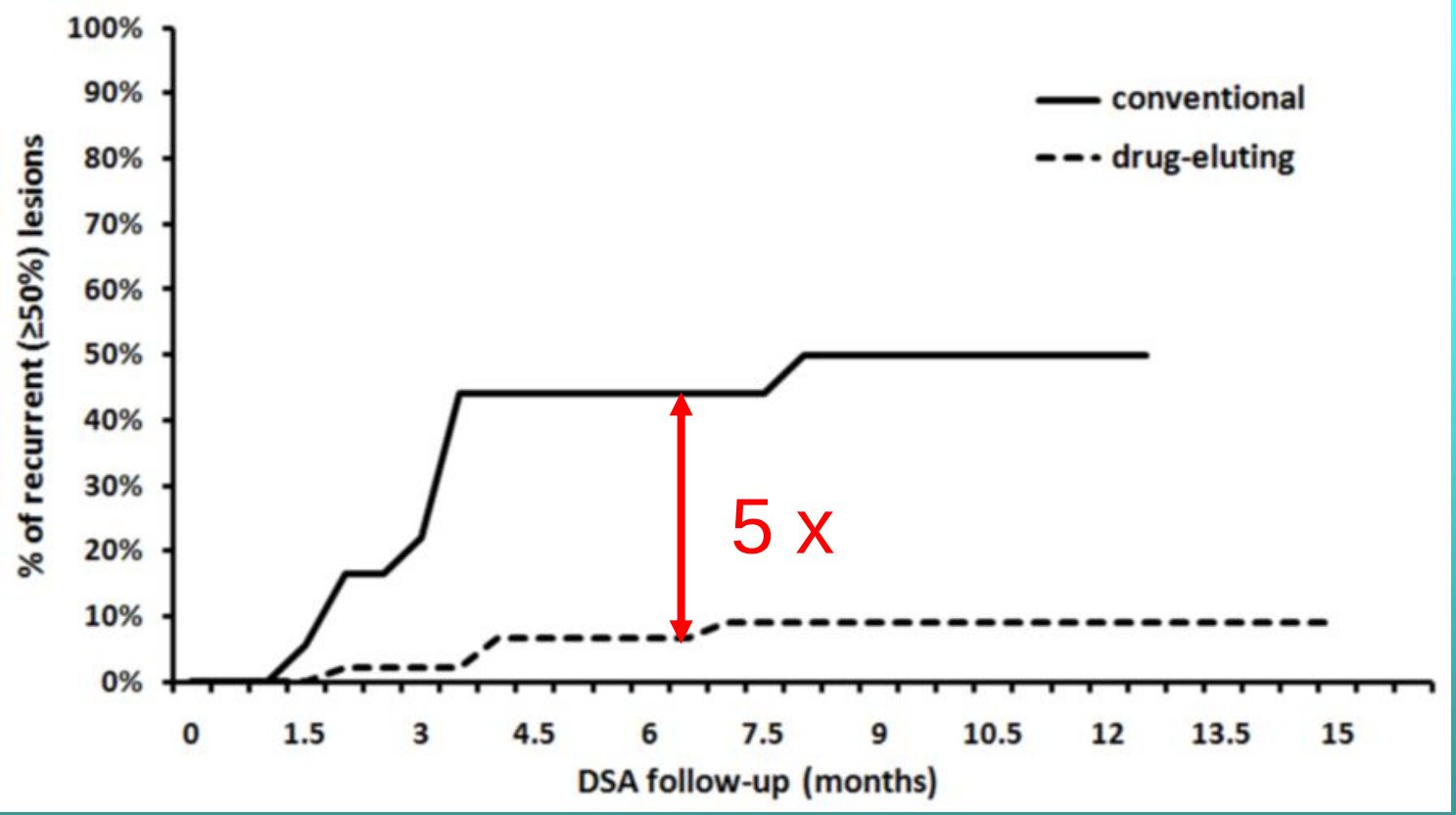

Vajda et al. AJNR 2011

20 conventional balloons– 43 SeQuent Please DEBs

6 % „failed attempts" with SeQuent Please!

DEB and Enterprise

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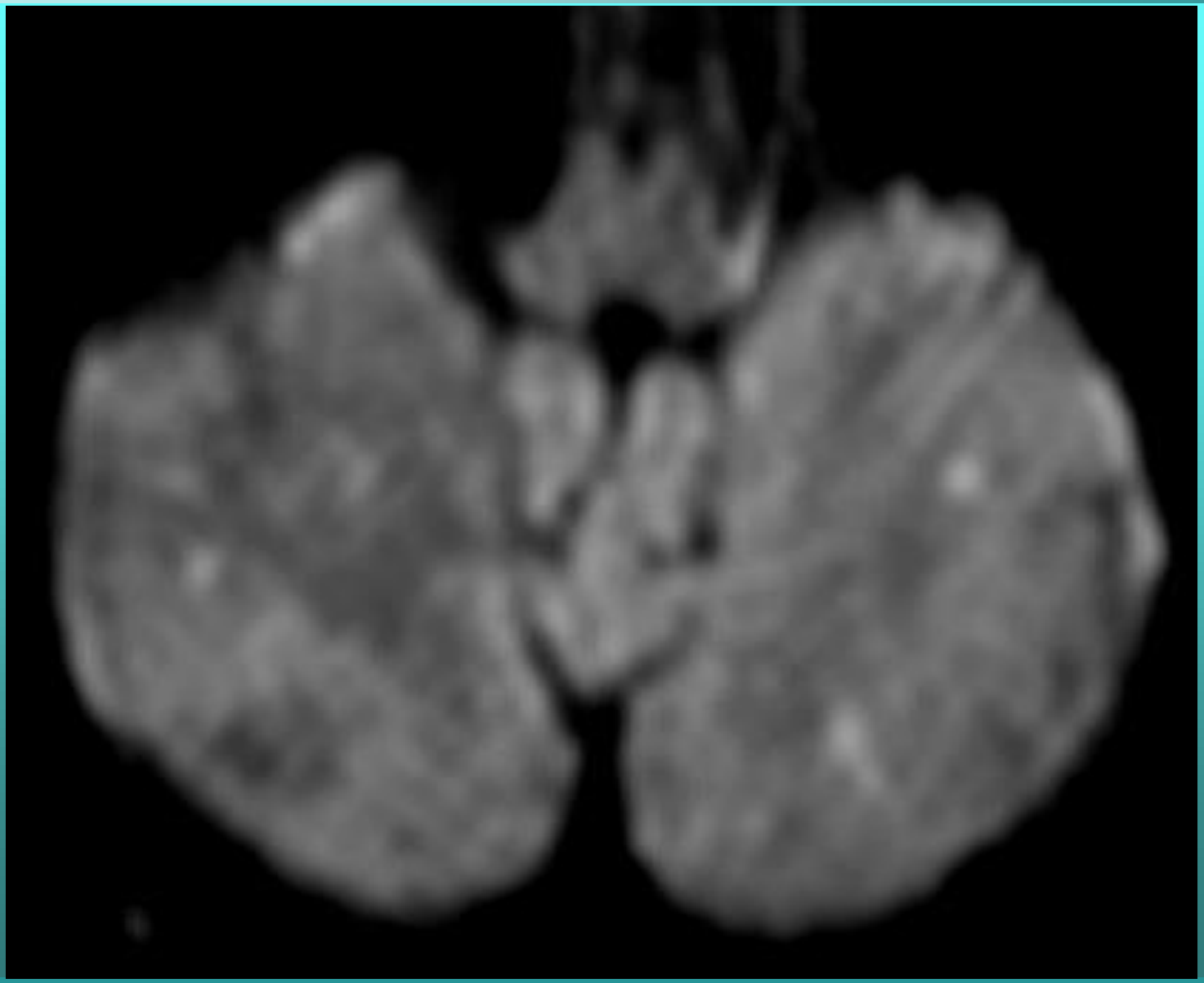

DEB and Enterprise

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DEB and Enterprise

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DEB and Enterprise

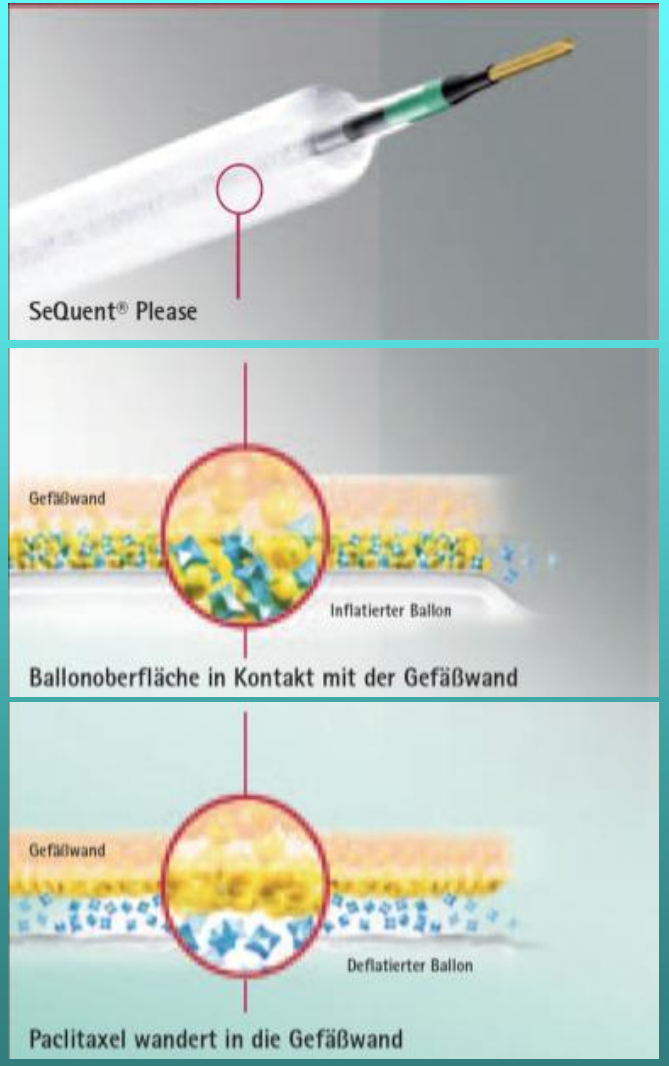
Klinikum Stuttgart

DEB and Enterprise

Klinikum Stuttgart

54 stenoses (52 patients)	
technical failure	**19 %**
30 d Stroke, death	8.8 %
8.9 months FU	0%
restenoses	**3 %**

Vajda et al. Cardiovasc Intervent Radiol 2012



DES in Neuroradiology

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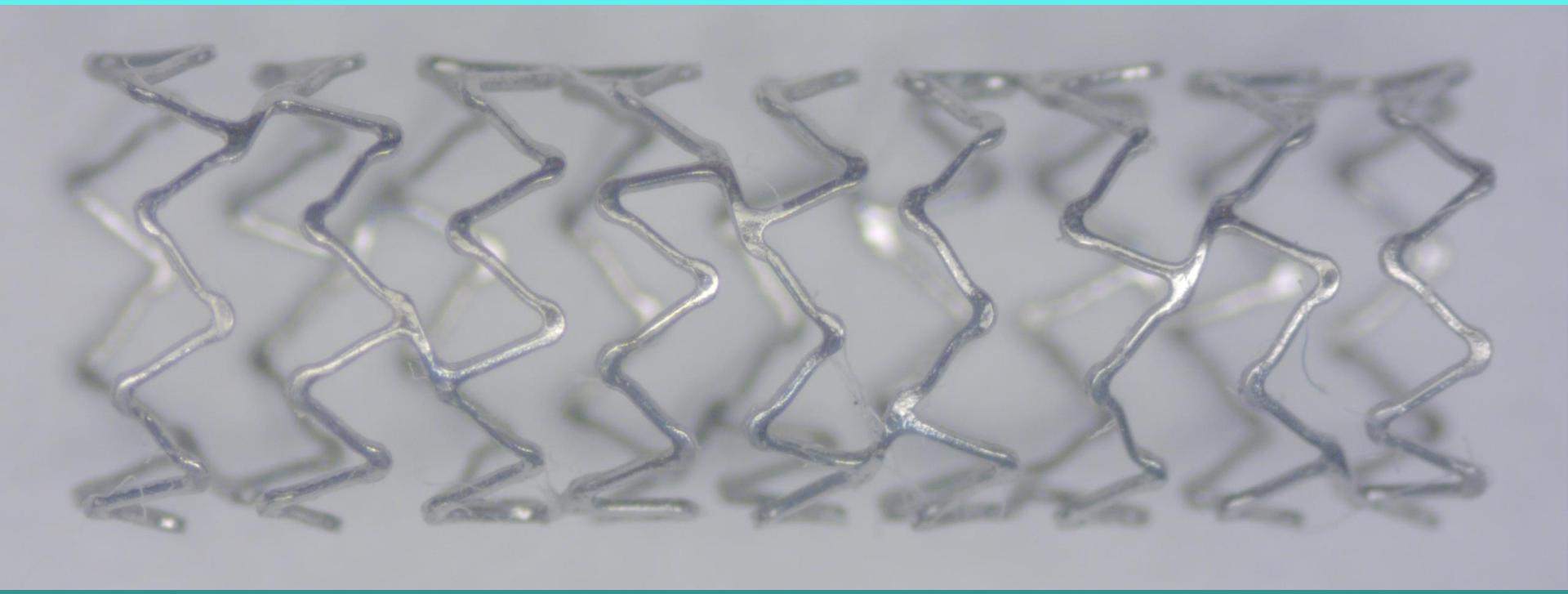
author	n=	type of stent	failure	restenosis	occlusion
Vajda (2012)	106	Coroflex Please	7%	3.8%	0.9%
Lu (2012)	24	Taxus Express Excell Firebird	0%	0%	0%
Steinfort (2007)	13	Taxus	0%	0%	0%
Qureshi (2006)	21	Cypher Taxus express	14%	14%	0%
Gupta (2006)	29	Cypher	10%	5%	0%
Abou-Chebl (2005)	8	Cypher Taxus	0%	0%	0%

TAXUS™ Element™ Stent

Klinikum Stuttgart



Recoil – flexibility – wall apposition

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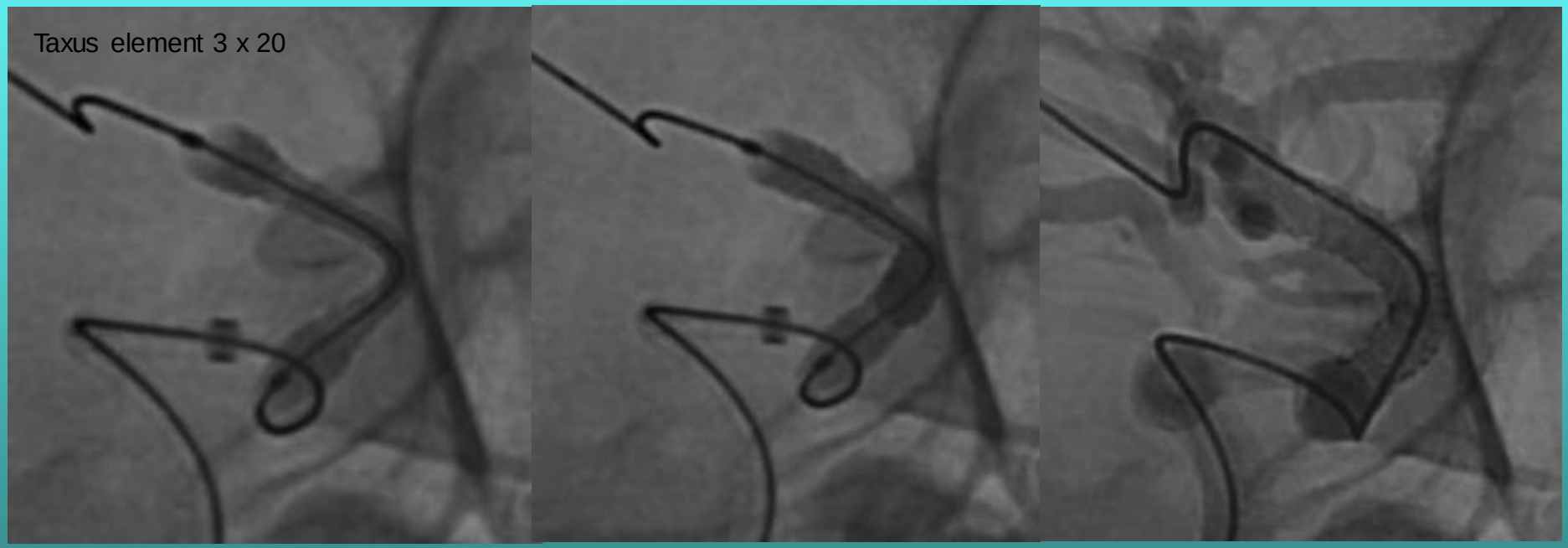
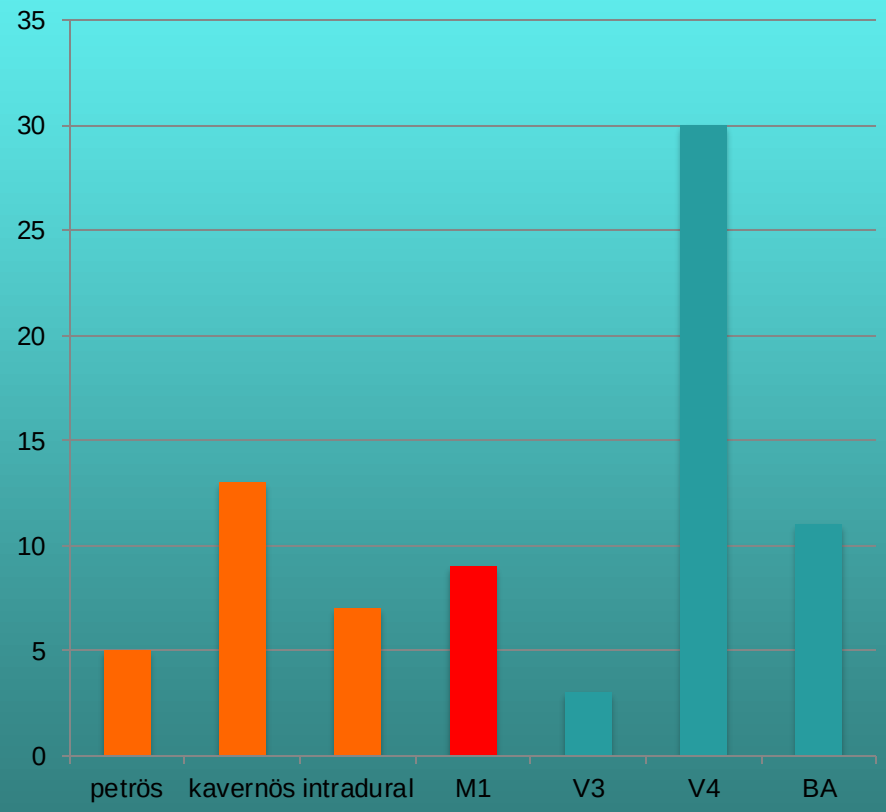


Results with Taxus Element

Klinikum Stuttgart

N= 78 stenoses



Length of stenoses

Median 6.4 mm (4-14 mm)

Stent dimensions

diameter:

slightly undersized

length:

as short as possible (8 mm)

(6x Taxus > 8 mm)

Results with Taxus Element

Klinikum Stuttgart

Technical success

In 68 / 78 stenoses successful **(87%)**

10 failures **(13%)**

- 3 conventional PTA
- 1 DEB
- 1 DEB & Enterprise
- 3 PTA & Enterprise
- 1 treated with a smaller Taxus Element
- 1 transbrachial approach, success with Taxus Element

Results with Taxus Element

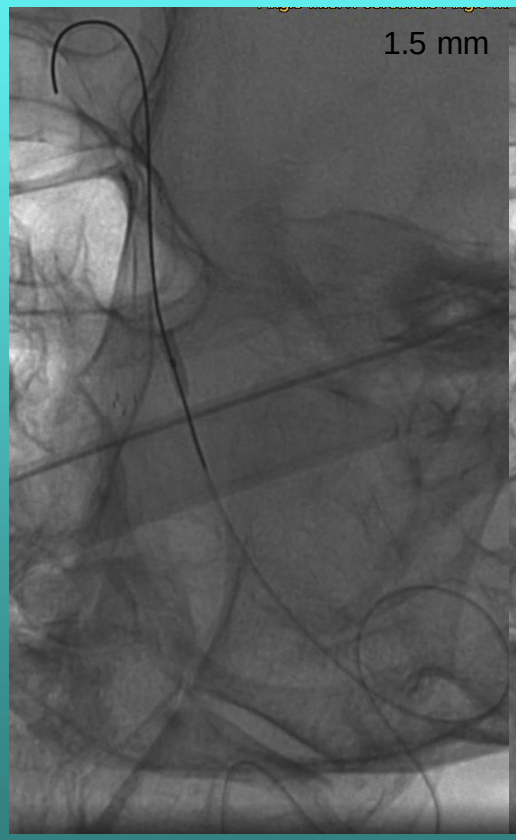
Klinikum Stuttgart

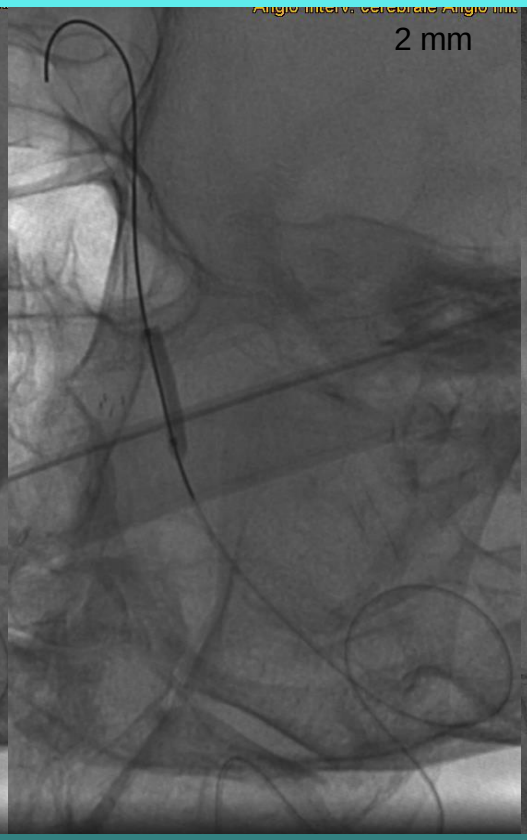
Taxus Element – technical failure

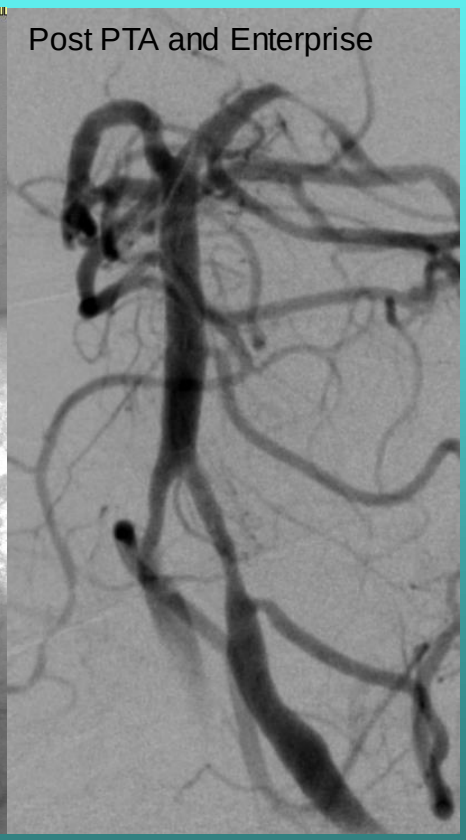
Results with Taxus Element

Klinikum Stuttgart

Taxus Element – technical failure



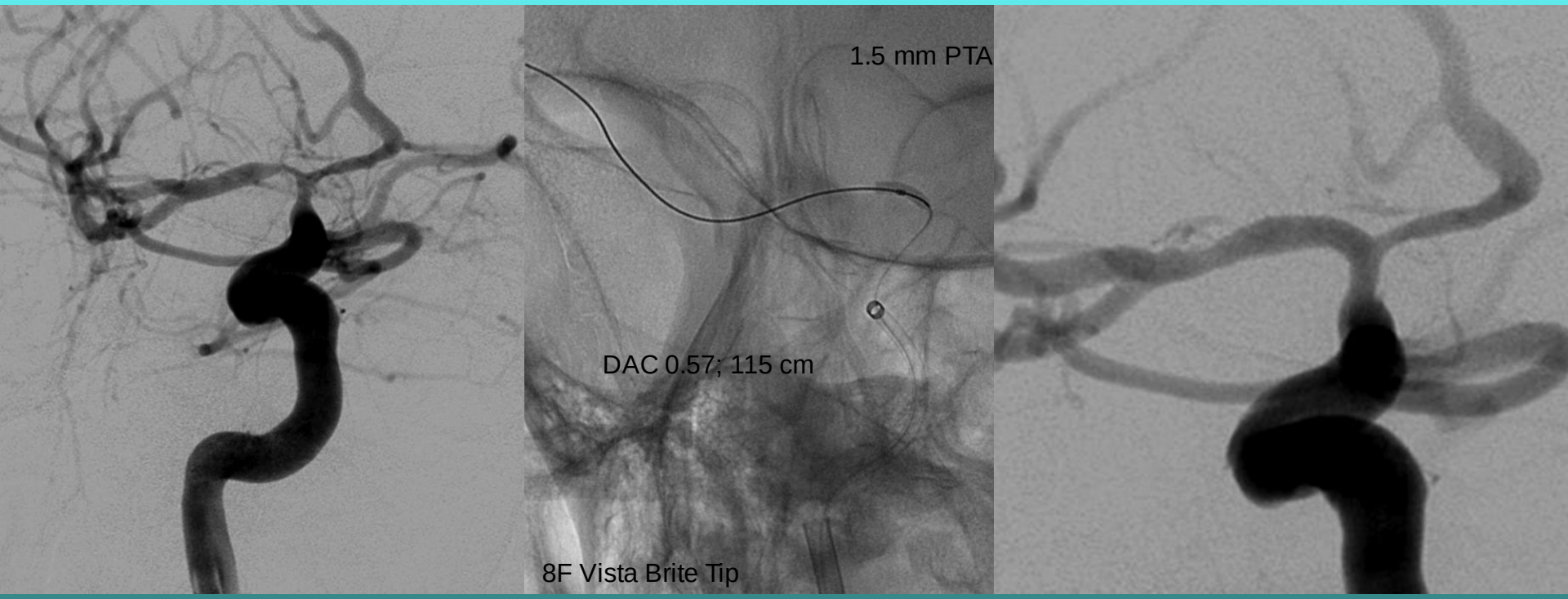




Results with Taxus Element

Klinikum Stuttgart

Robust access required



Results with Taxus Element

Klinikum Stuttgart

Robust access required

Anterior circulation

- 8 F Vista Brite Tip
- 0.57 DAC or
- 0.58 NavienA+
  - **115 cm!**
- Traxcess EX

Posterior circulation

- 6 F Vista Brite Tip

Results with Taxus Element

Klinikum Stuttgart

ISRS

57 stenoses with F/U DSA

Results with Taxus Element

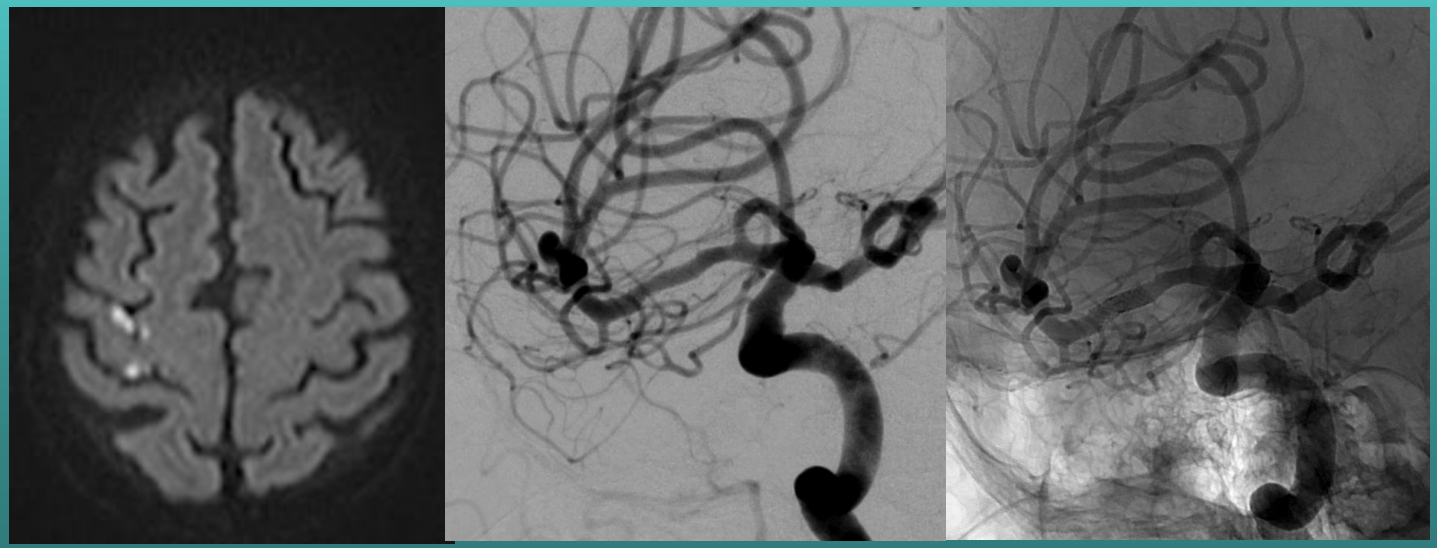
Klinikum Stuttgart

Clinical results

1 **(1.8%)** ipsilateral stroke

- Clopidogrel was stopped after 9 months

1 **(1.8%)** stroke in another vascular territory



Results with Taxus Element

Klinikum Stuttgart

Acute stroke

n= 8

Loading with 600 mg Clopidogrel and 500 mg ASA

prior to transport

or via gastric tube prior to the procedure

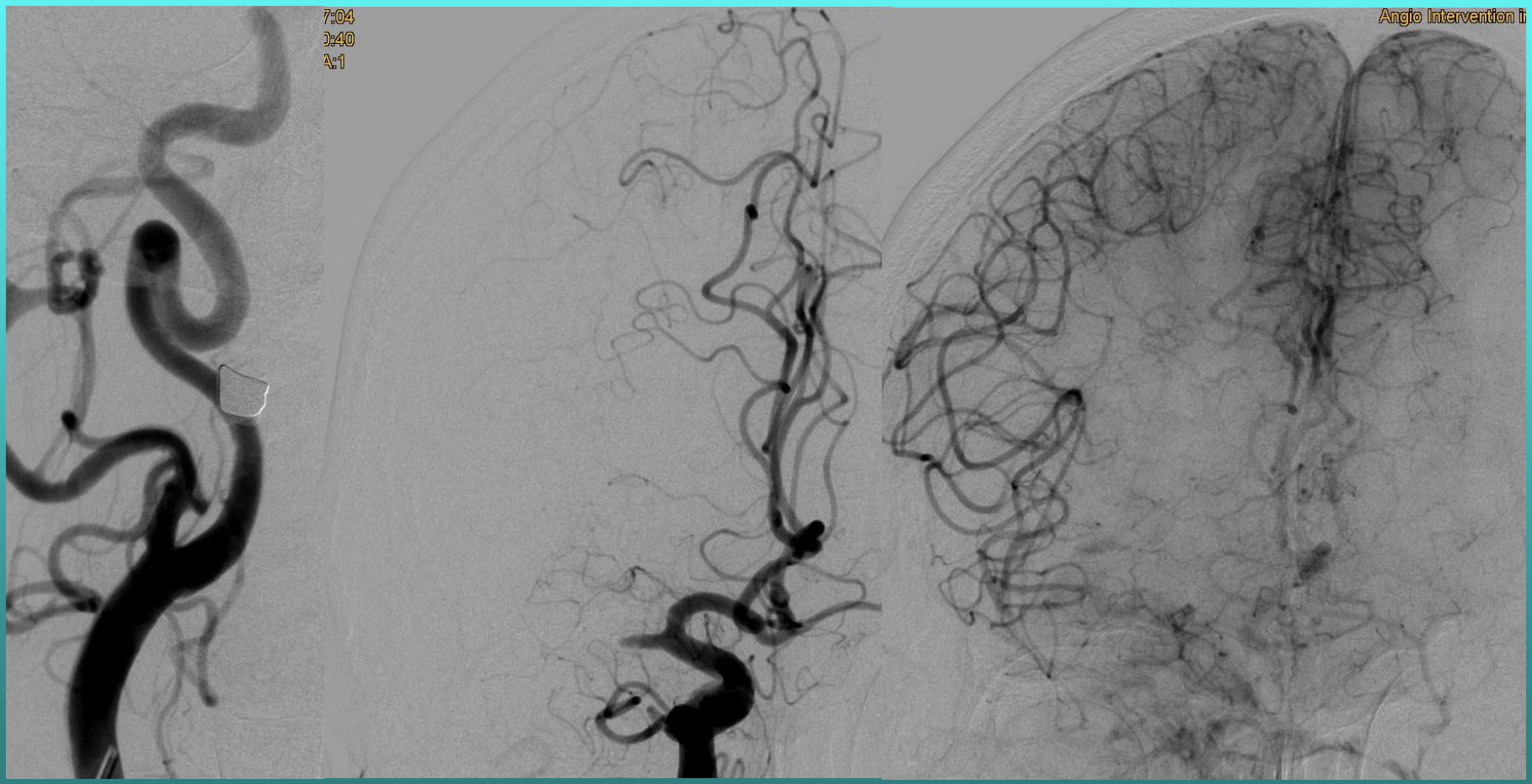
1 intraprocedural thrombus formation

treated with an IV Integrilin bolus

Results with Taxus Element

Klinikum Stuttgart

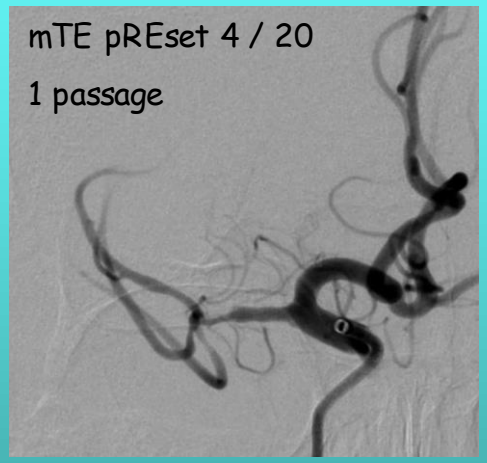
Acute stroke

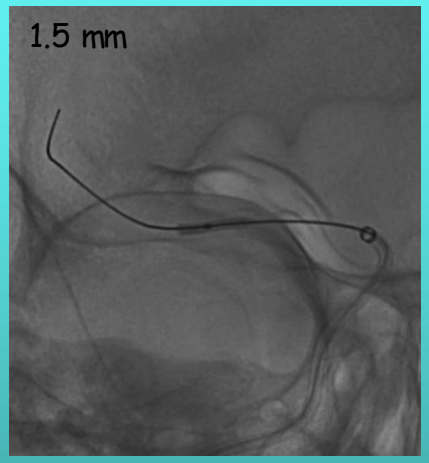


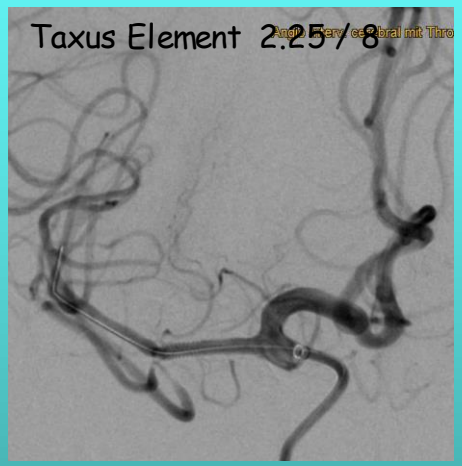
Results with Taxus Element

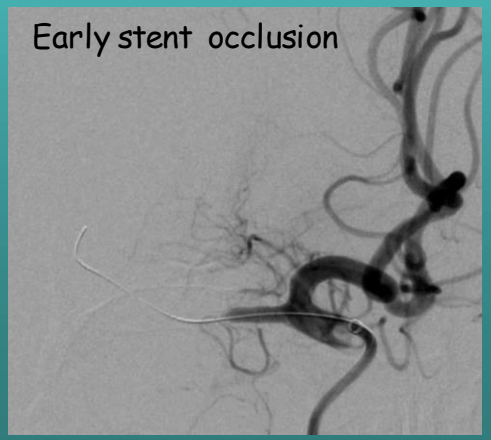
Klinikum Stuttgart

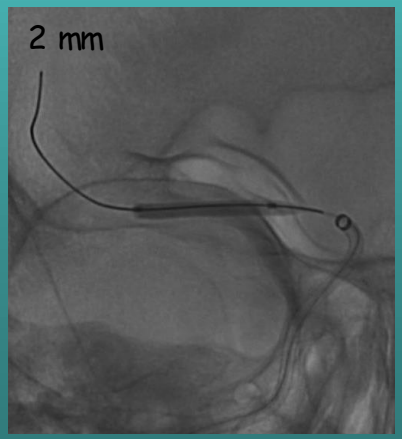
Acute stroke







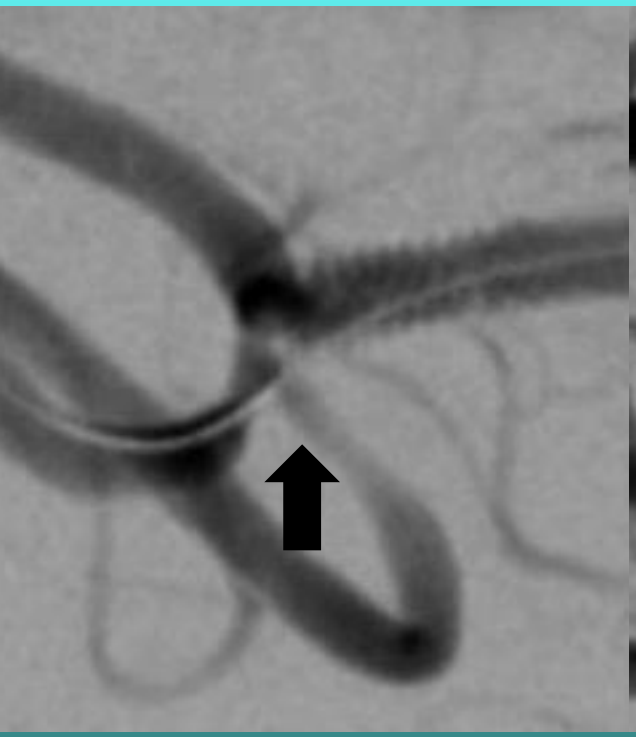


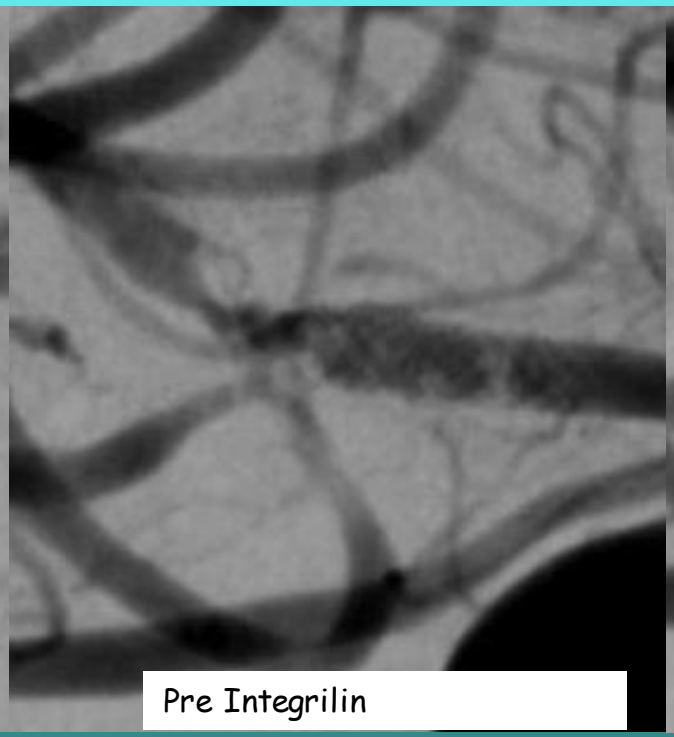


Results with Taxus Element

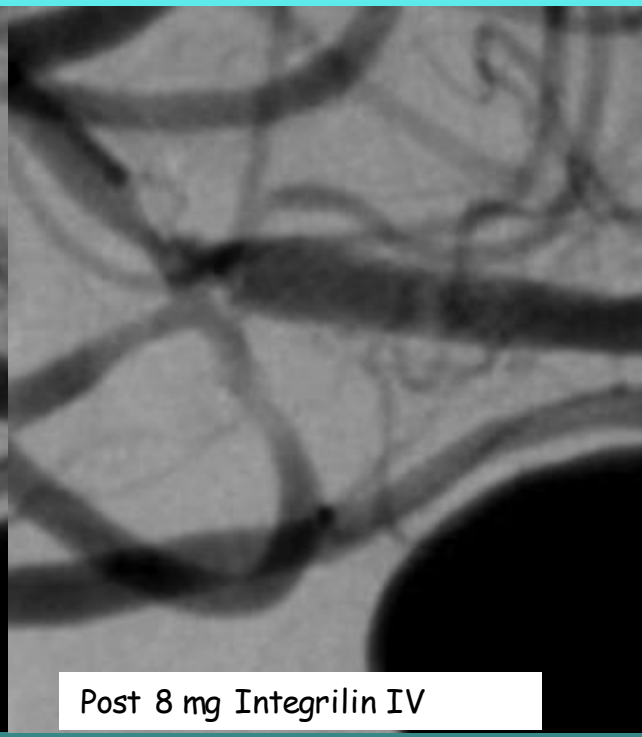
Klinikum Stuttgart

Acute stroke





Pre Integrilin

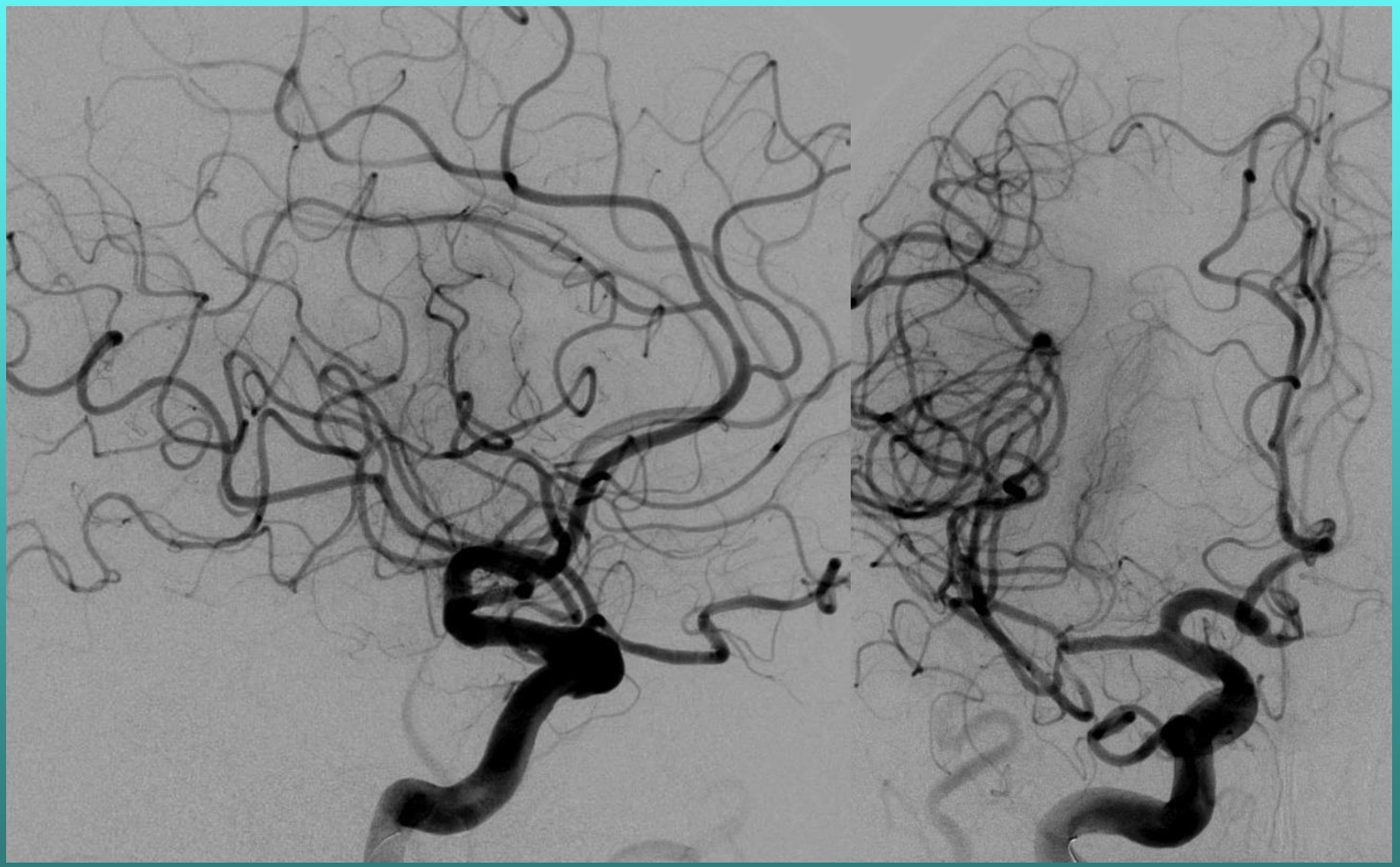


Post 8 mg Integrilin IV

Results with Taxus Element

Klinikum Stuttgart

Acute stroke



Our current concept

Klinikum Stuttgart

Primary treatment

Most stenosis: PTA with a conventional balloon *(pITA)*

Increased recurrence risk: PTA with a DEB *(SeQuent Neo Please)*

Dissection, recoiling: PTA + selfexpanding stent *(pITA, SeQuent Neo Please, Enterprise2)*

Short stenosis, straight vessels...: DES *(Coroflex ISAR)*

Avoid snow plow effect: no PTA, just SE stent *(Solitaire)*

Our current concept

Klinikum Stuttgart

In stent re-stenosis

DEB or DES
(SeQuent Neo Please or Coroflex ISAR)

PTA
(pITA)

Adjacent *de novo* stenosis

like primary treatment

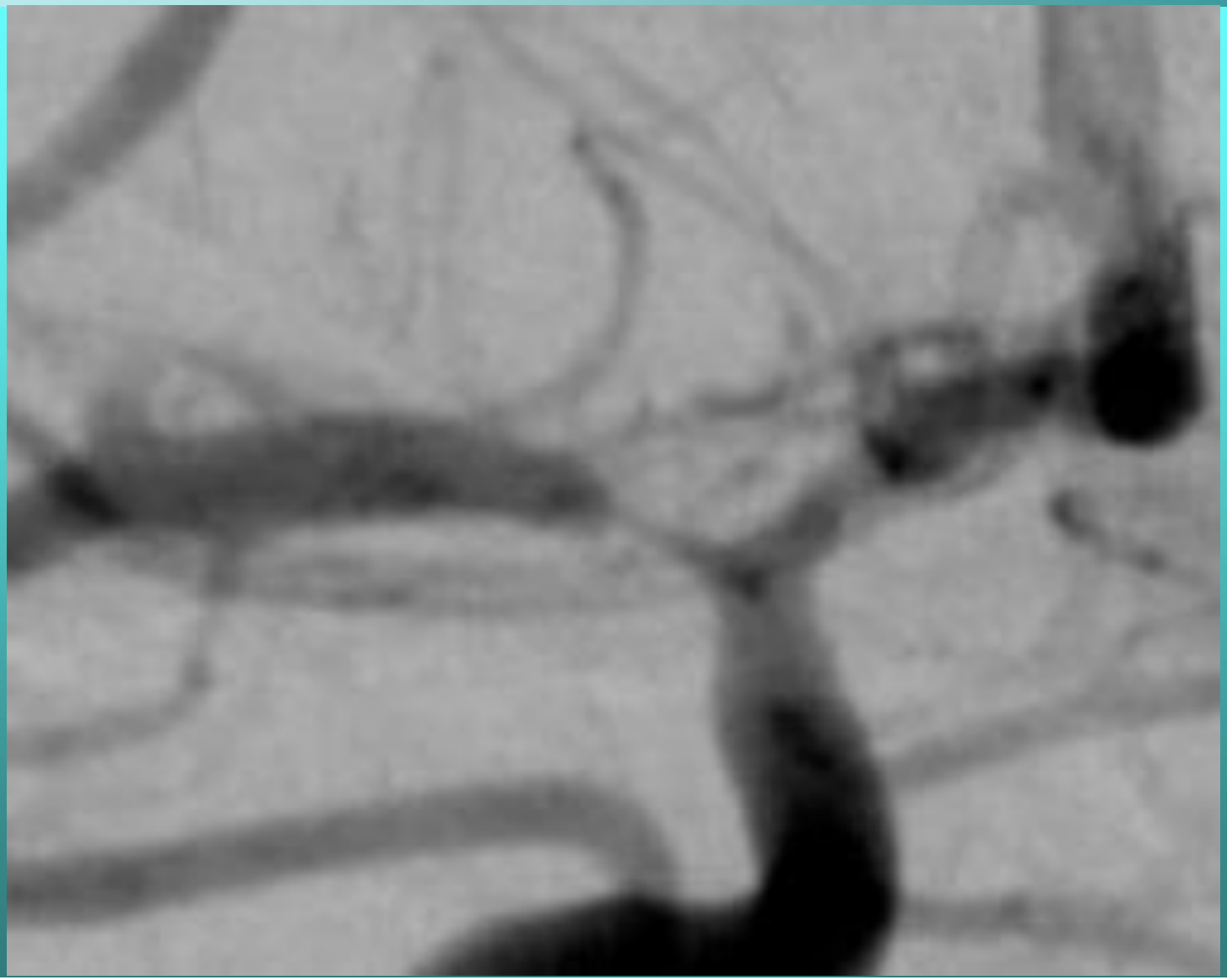
PTA (pITA)

Klinikum Stuttgart

MS & Vasculitis

PTA (pITA)

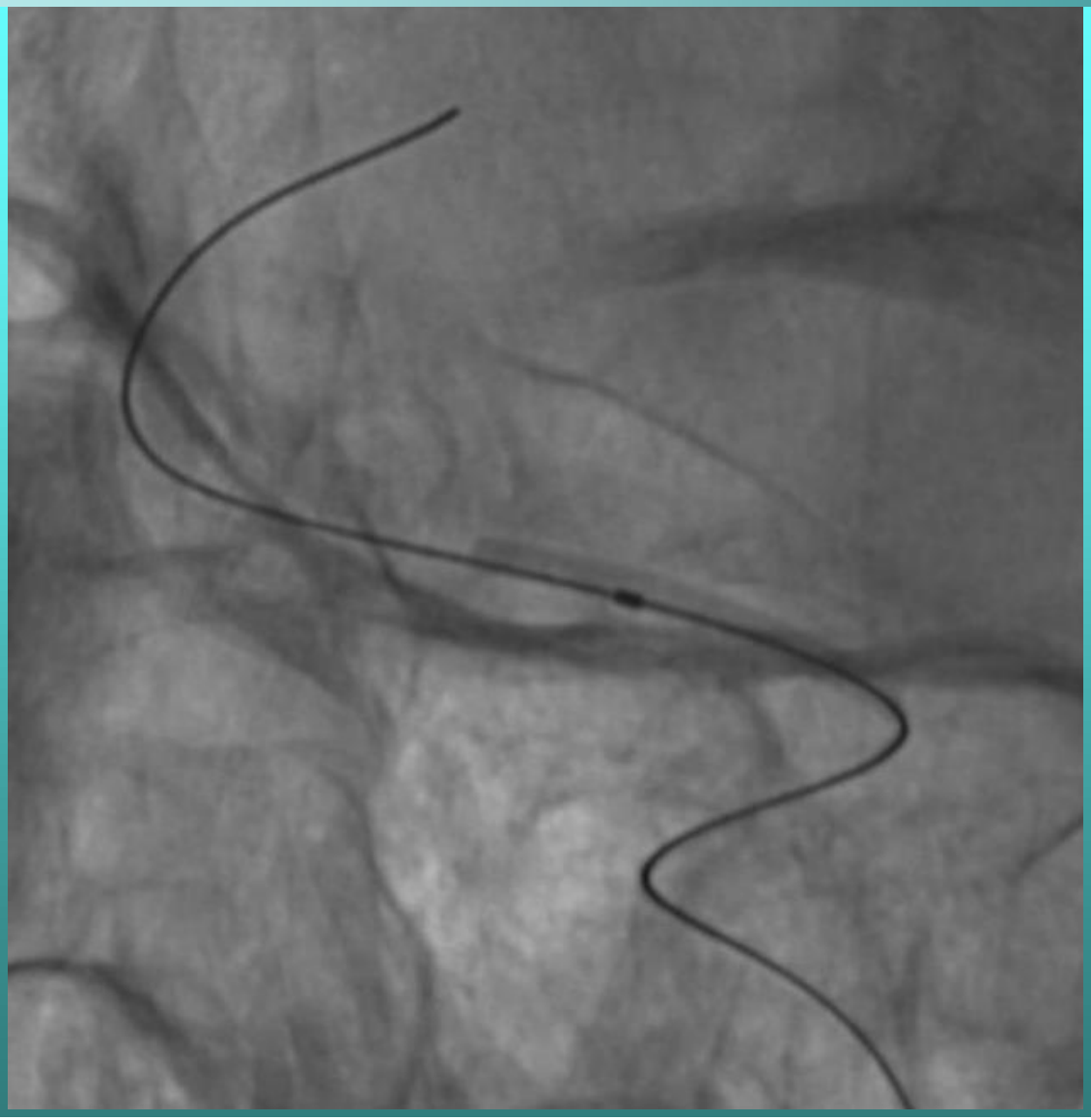
Klinikum Stuttgart



MS & Vasculitis

PTA (pITA)

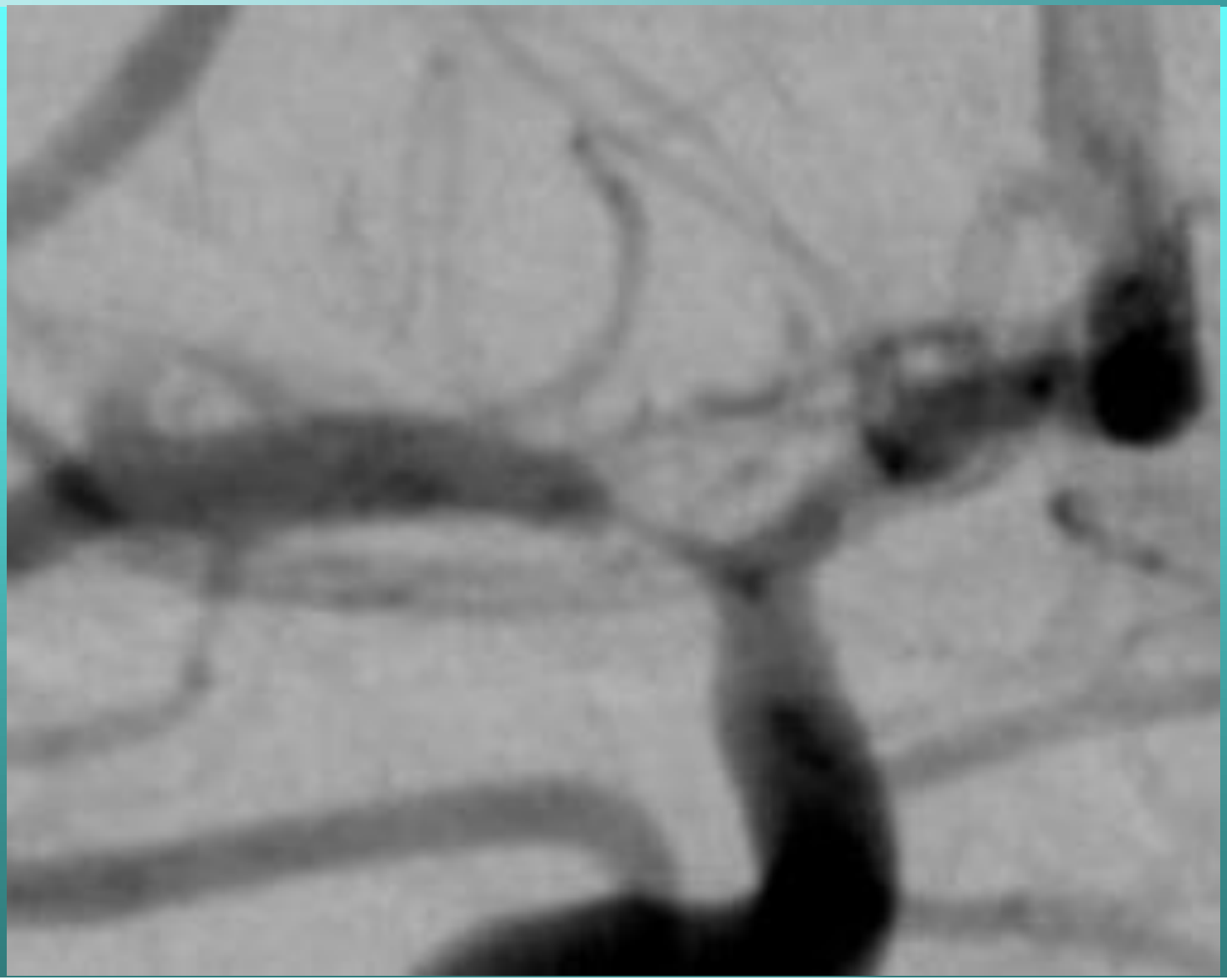
Klinikum Stuttgart



Synchro2 0.014´´, pITA 1.5 mm, 8 atm

PTA (pITA)

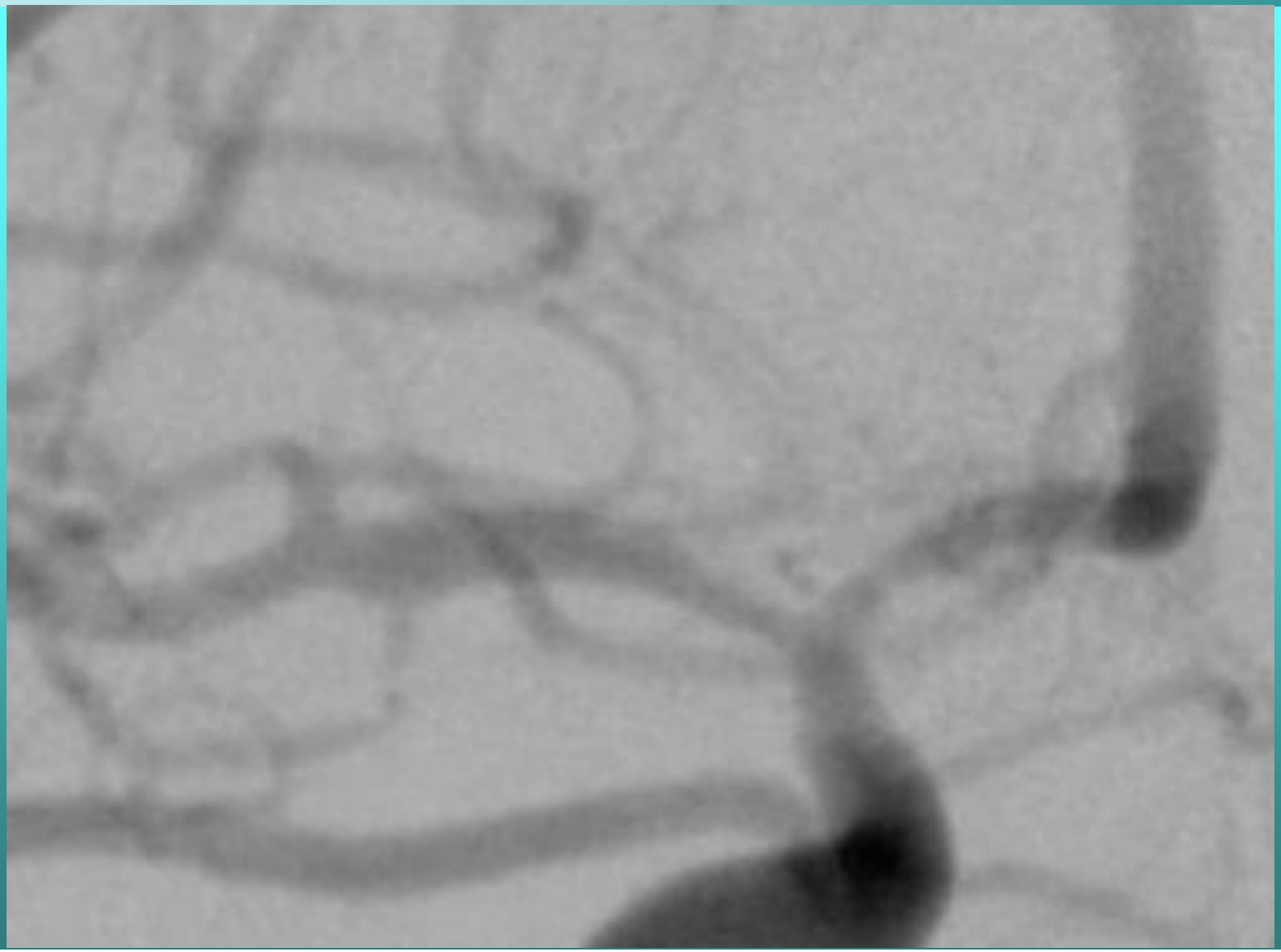
Klinikum Stuttgart



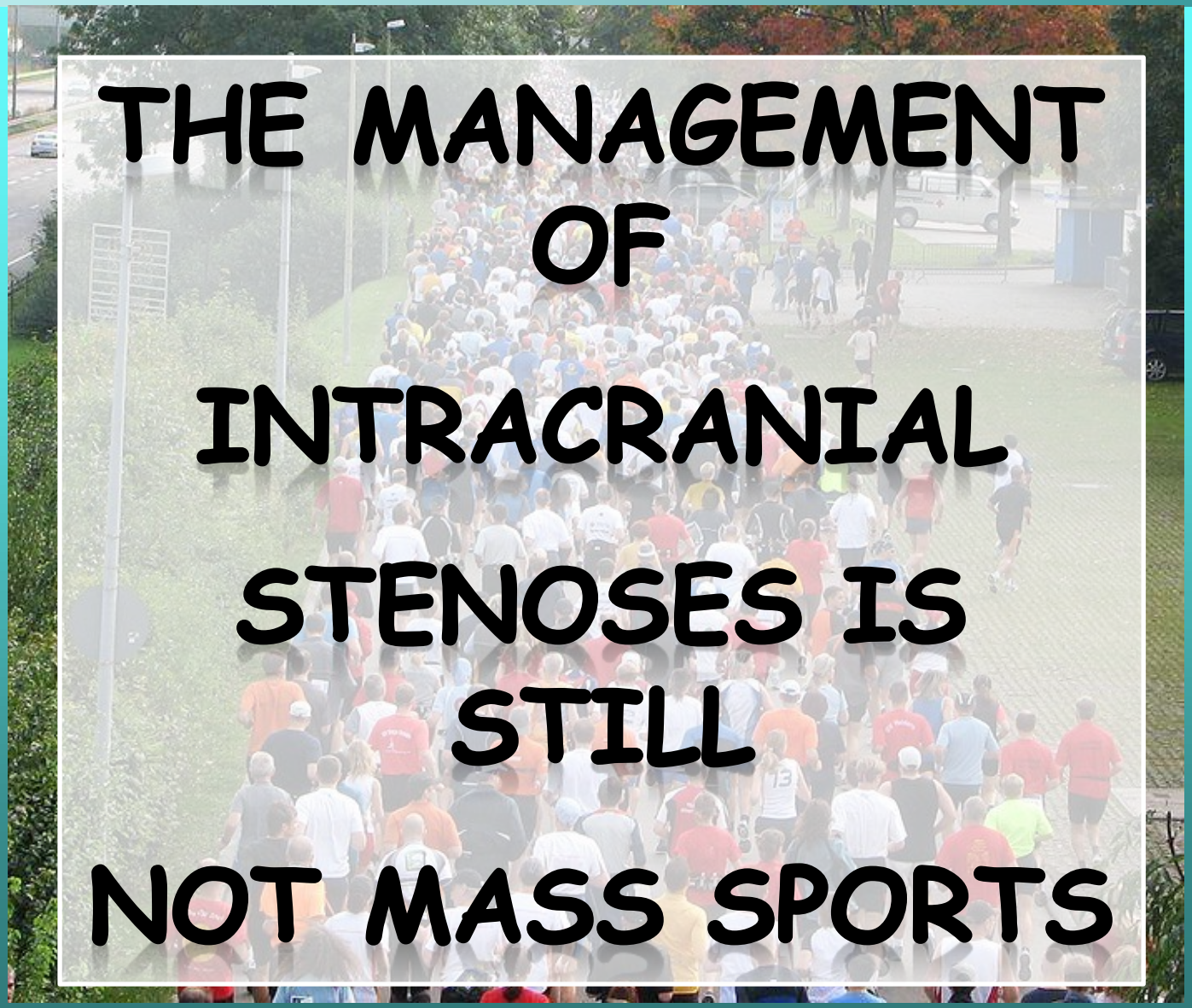
pre

PTA (pITA)

Klinikum Stuttgart



Lumen at least double



THE MANAGEMENT OF INTRACRANIAL STENOSES IS STILL NOT MASS SPORTS