ESASIS – The Hong Kong Wingspan Study

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Outline

1. Protocol for intracranial stenting in Prince of Wales Hospital

2. ESASIS study (Early Stent-assisted Angioplasty in Symptomatic Intracranial Stenosis)

3. Treating the dynamic lesions - Understanding the pathophysiology of intracranial stenosis

Disclosure

None

Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis

(***Circulation*** 2006;113:555-563)

WASID Trial

(***N Eng J Med*** 2005;352(13):1305-1316)

n=569 Mean follow-up 1.8 years

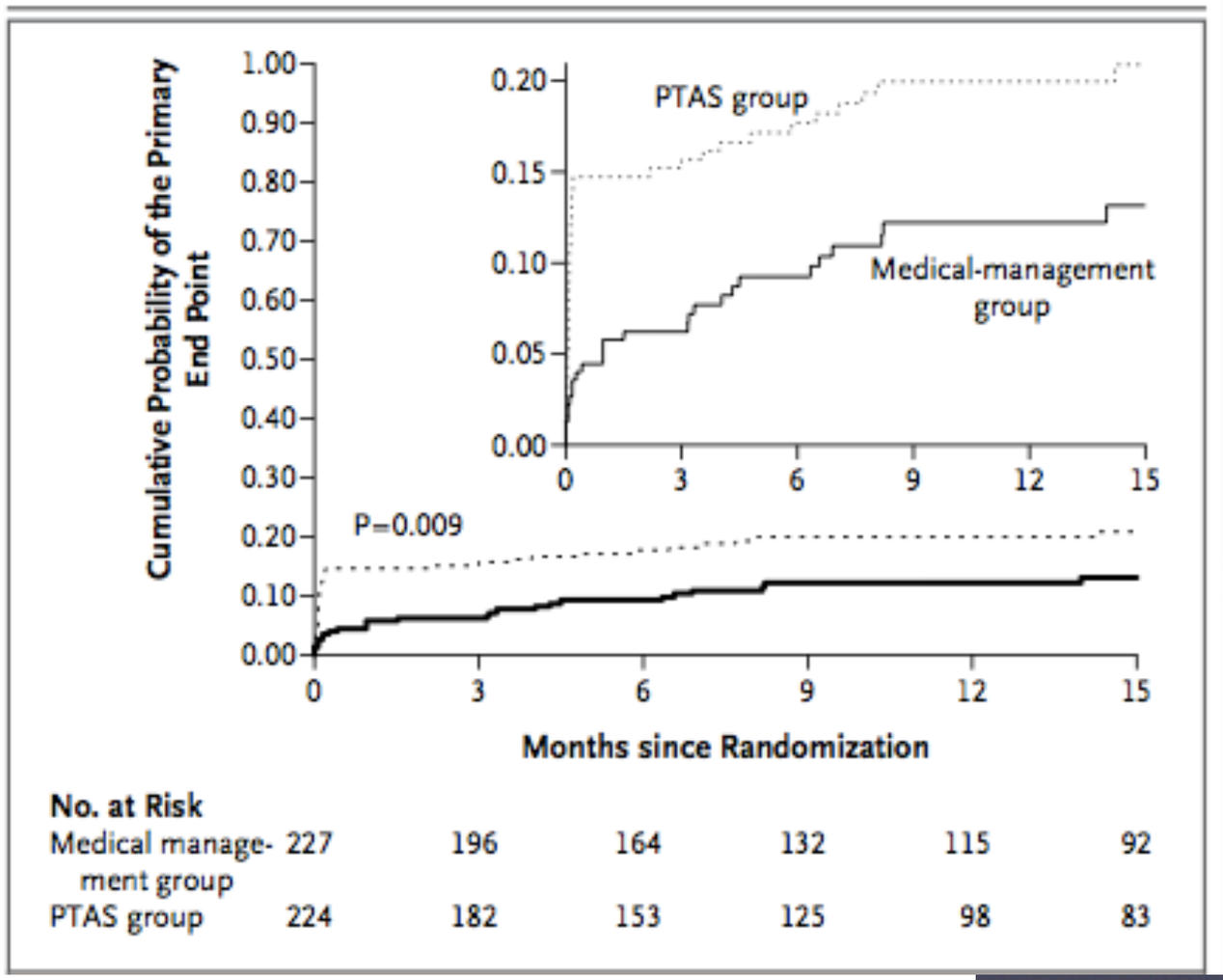
Qualifying Event	Stenosis 50% to 69%	Stenosis 70% to 99%
TIA		
1 year	0.03 (0.01–0.06)	0.14 (0.06–0.22)
2 years	0.08 (0.02–0.13)	0.14 (0.06–0.22)
Stroke		
1 year	0.08 (0.04–0.12)	0.23 (0.15–0.30)
2 years	0.11 (0.07–0.16)	0.25 (0.17–0.33)

Data are presented as mean probability (95% CI).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis



CONCLUSIONS

In patients with intracranial arterial stenosis, aggressive medical management was superior to PTAS with the use of the Wingspan stent system, both because the risk of early stroke after PTAS was high and because the risk of stroke with aggressive medical therapy alone was lower than expected. (Funded by the National Institute of Neurological Disorders and Stroke and others; SAMMPRIS ClinicalTrials.gov number, NCT00576693.)

Chimowitz, et al.

U.S. Food and Drug Administration
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Wingspan is now approved only for patients who are between 22 and 80 years old AND who meet ALL of the following criteria:

- who have had two or more strokes despite aggressive medical management;
- whose most recent stroke occurred more than seven days prior to planned treatment with Wingspan;
- who have 70-99 percent stenosis due to atherosclerosis of the intracranial artery related to the recurrent strokes; and
- who have made good recovery from previous stroke and have a modified Rankin score of 3 or less prior to Wingspan treatment. The Rankin scale is used to measure the degree of disability in stroke patients. Lower scores indicate less disability.

The Wingspan Stent System should not be used for:

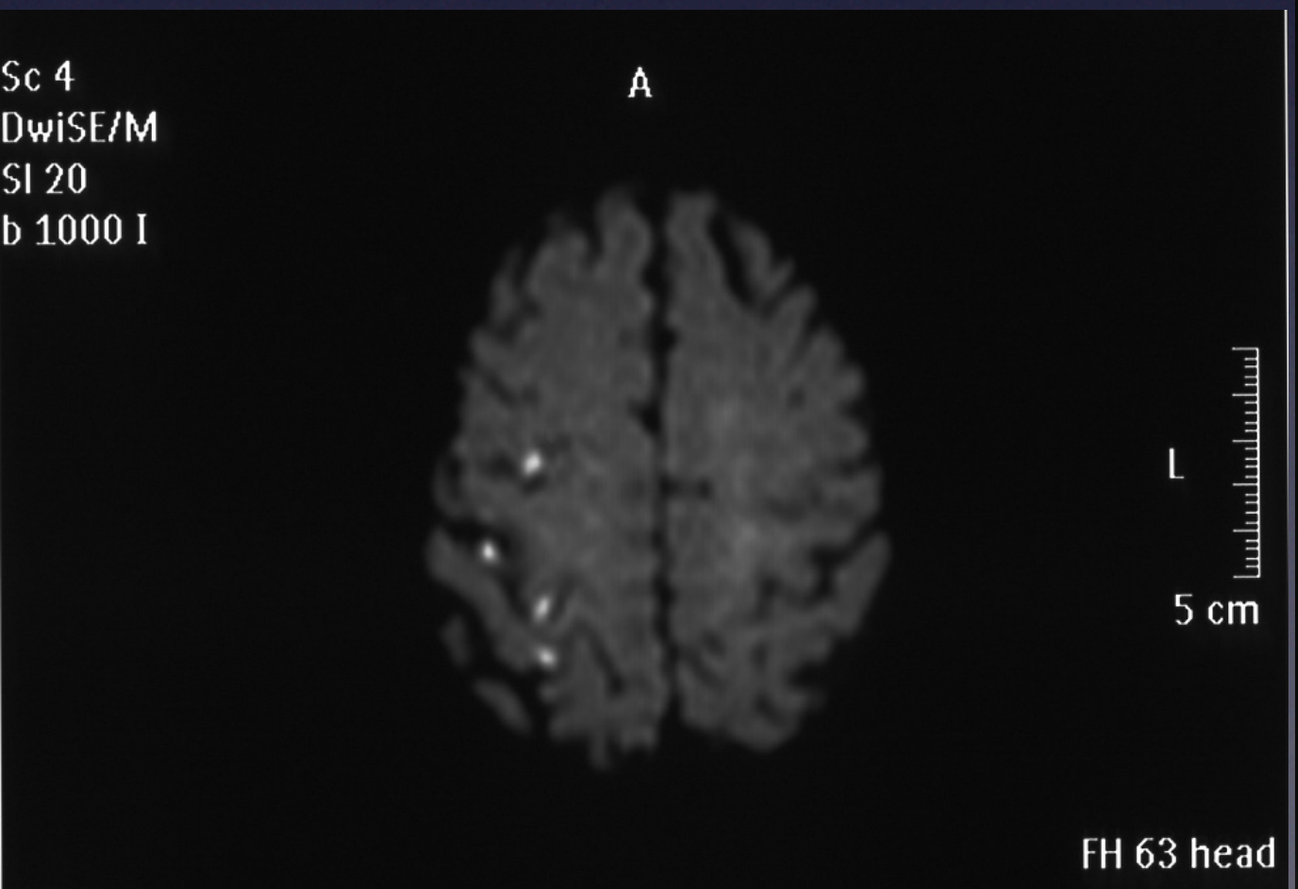
- the treatment of stroke with an onset of symptoms within seven days or less of treatment; or
- for the treatment of transient ischemic attacks (TIAs).

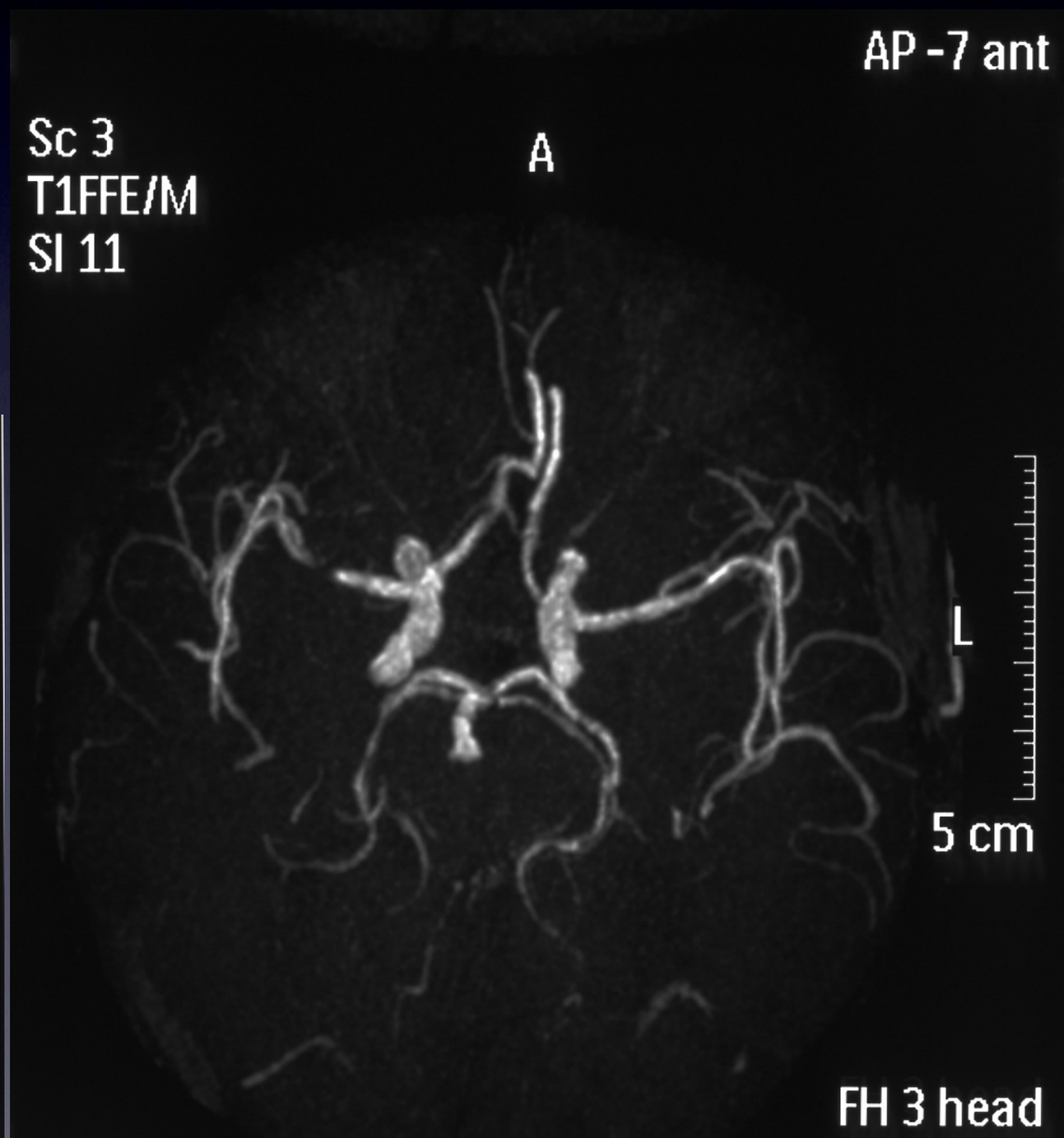
31 Jan 2013

Patient selection

M/59
Hypertension, type II DM, hyperlipidemia
Mild left hemiparesis
NIHSS 3

Failed aspirin





Interdisciplinary Model

Pre-medication: dual anti-platelets (aspirin and clopidogrel)

Local anesthesia

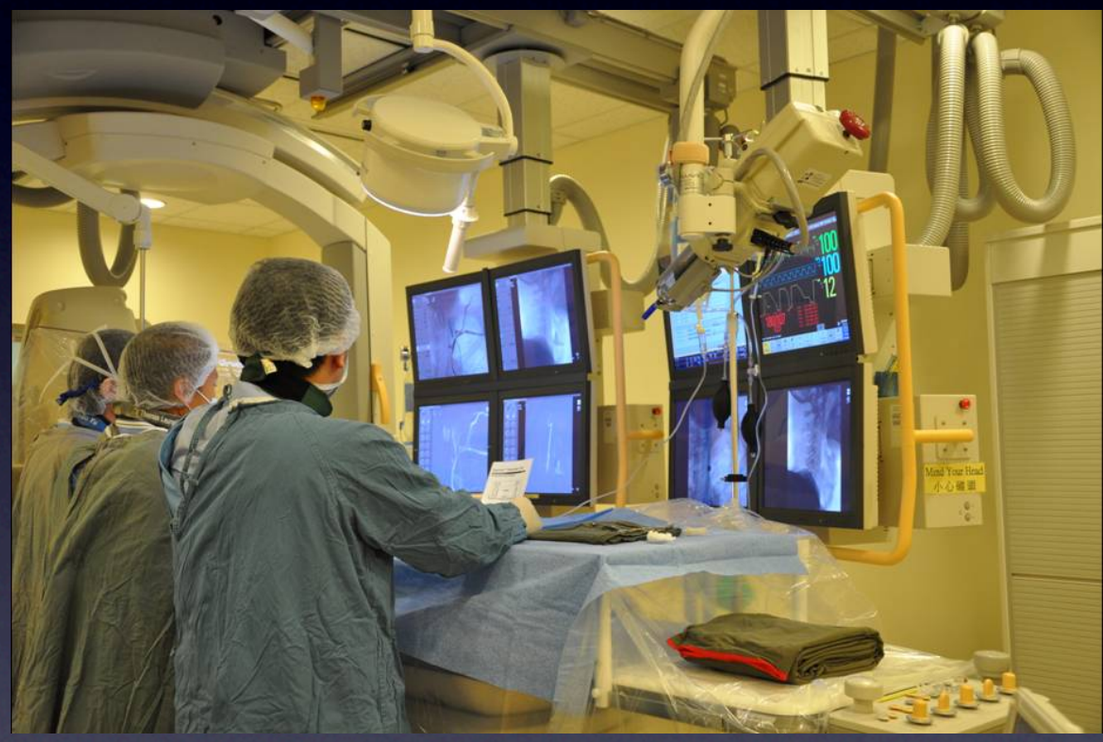
Pre-operative 3D-DSA

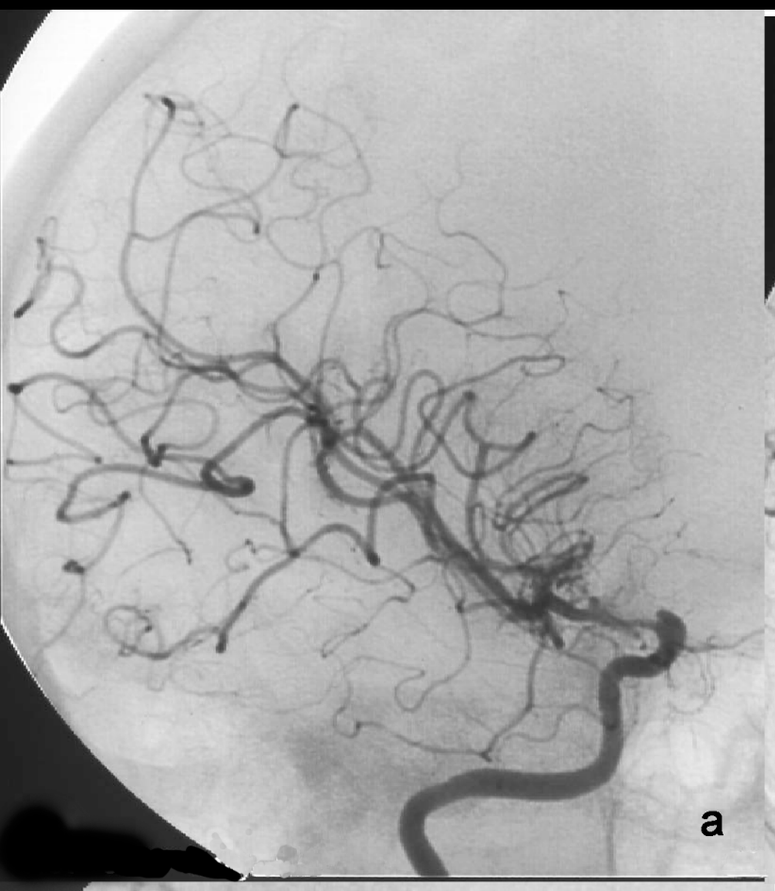
Activated clotting time 180-250 seconds (Heparin: 2500 units)

A brief duration of balloon inflation time

Dual anti-platelets for 6 weeks after the procedure

Protocol-driven pre- and post-operative care in stroke unit

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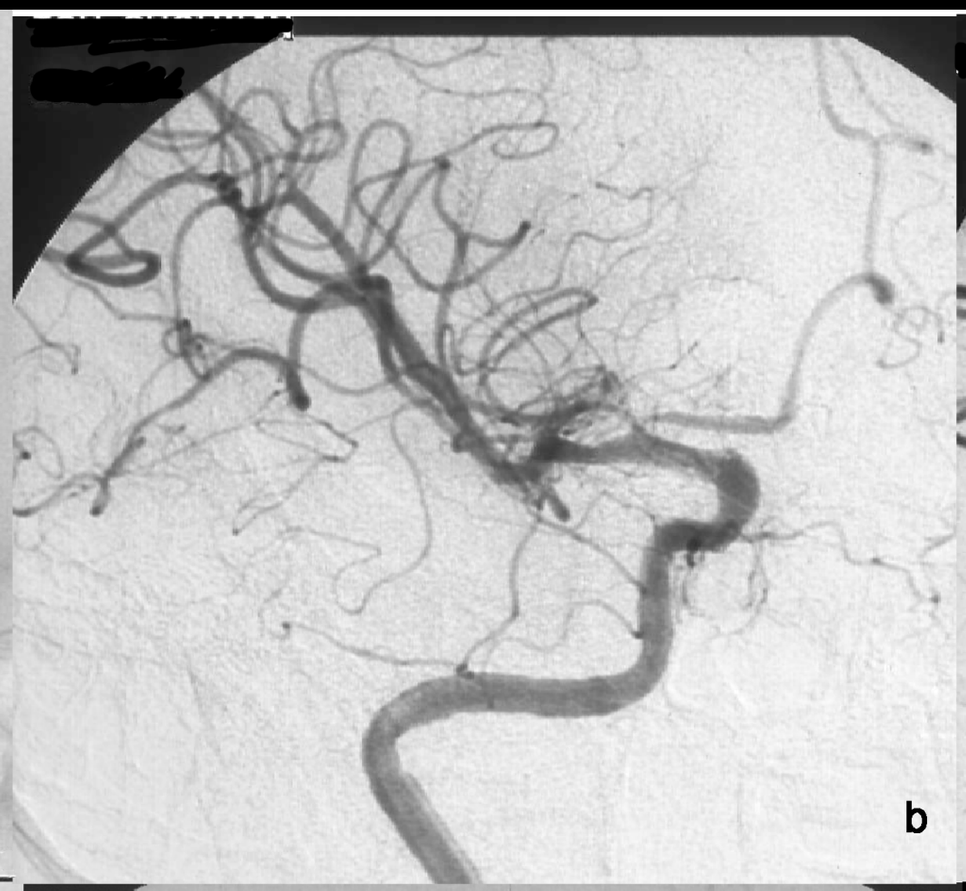
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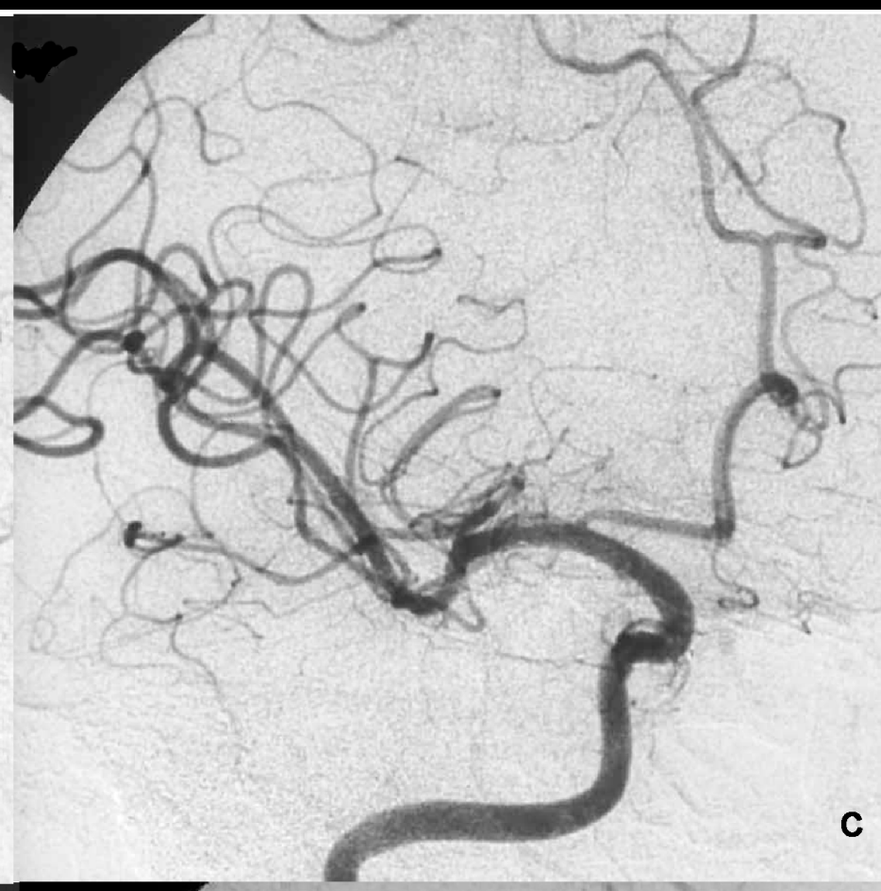
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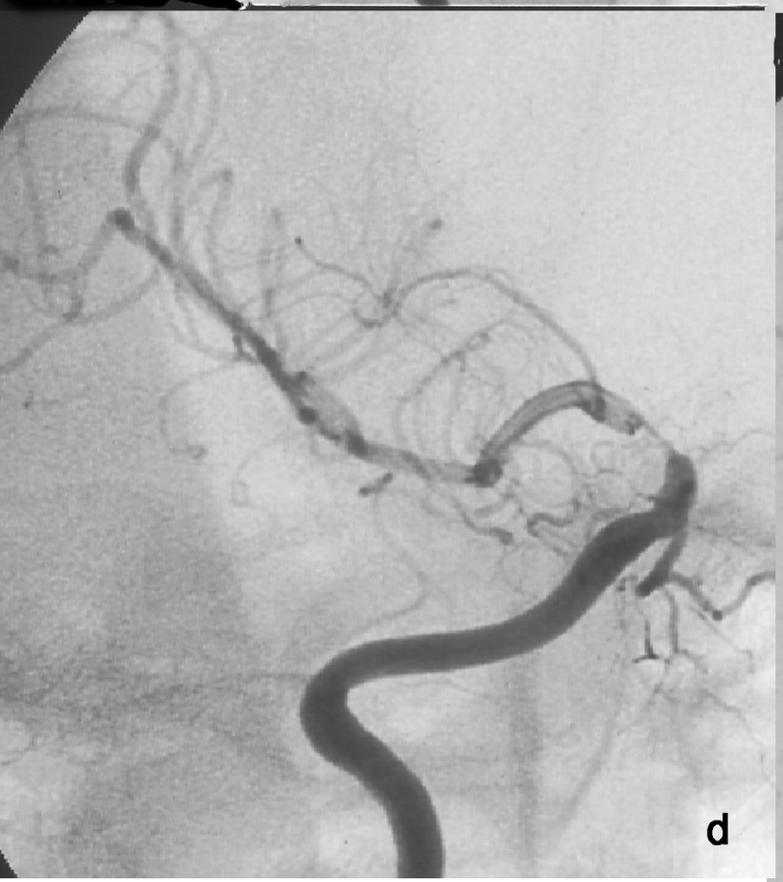
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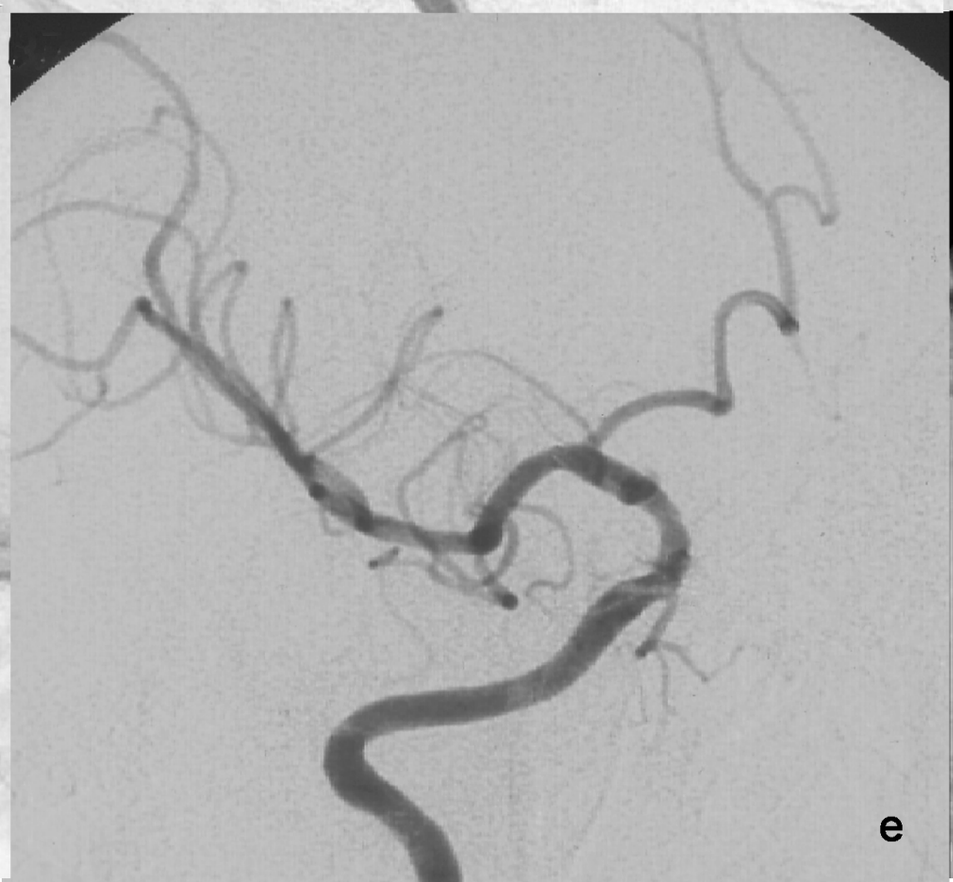
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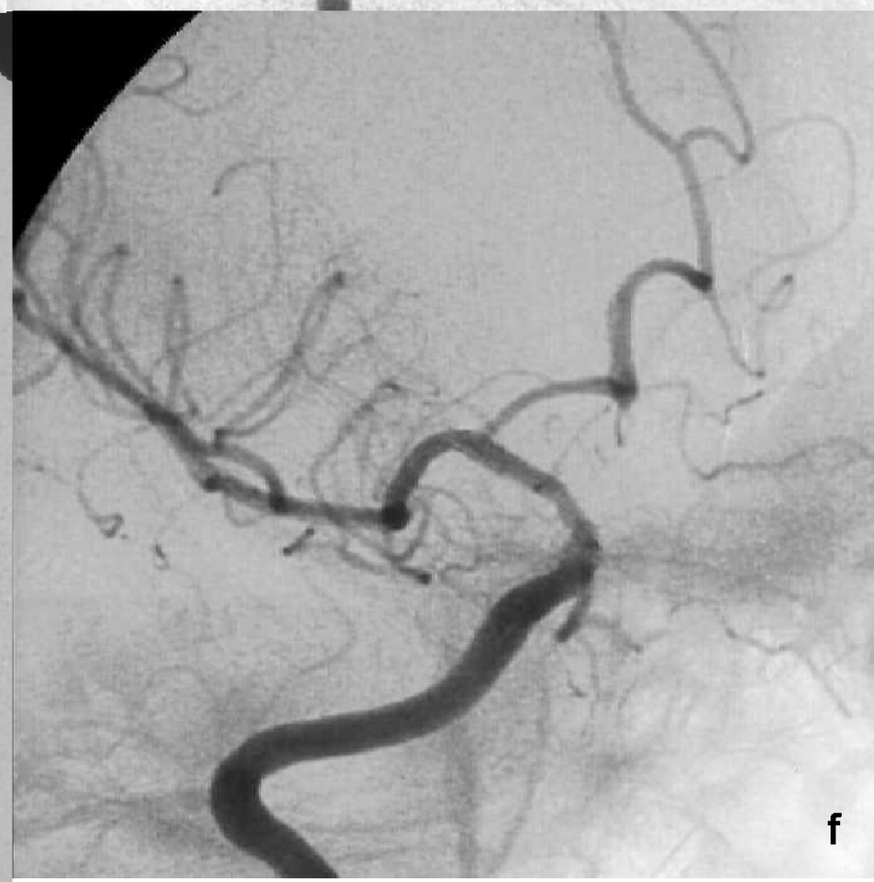
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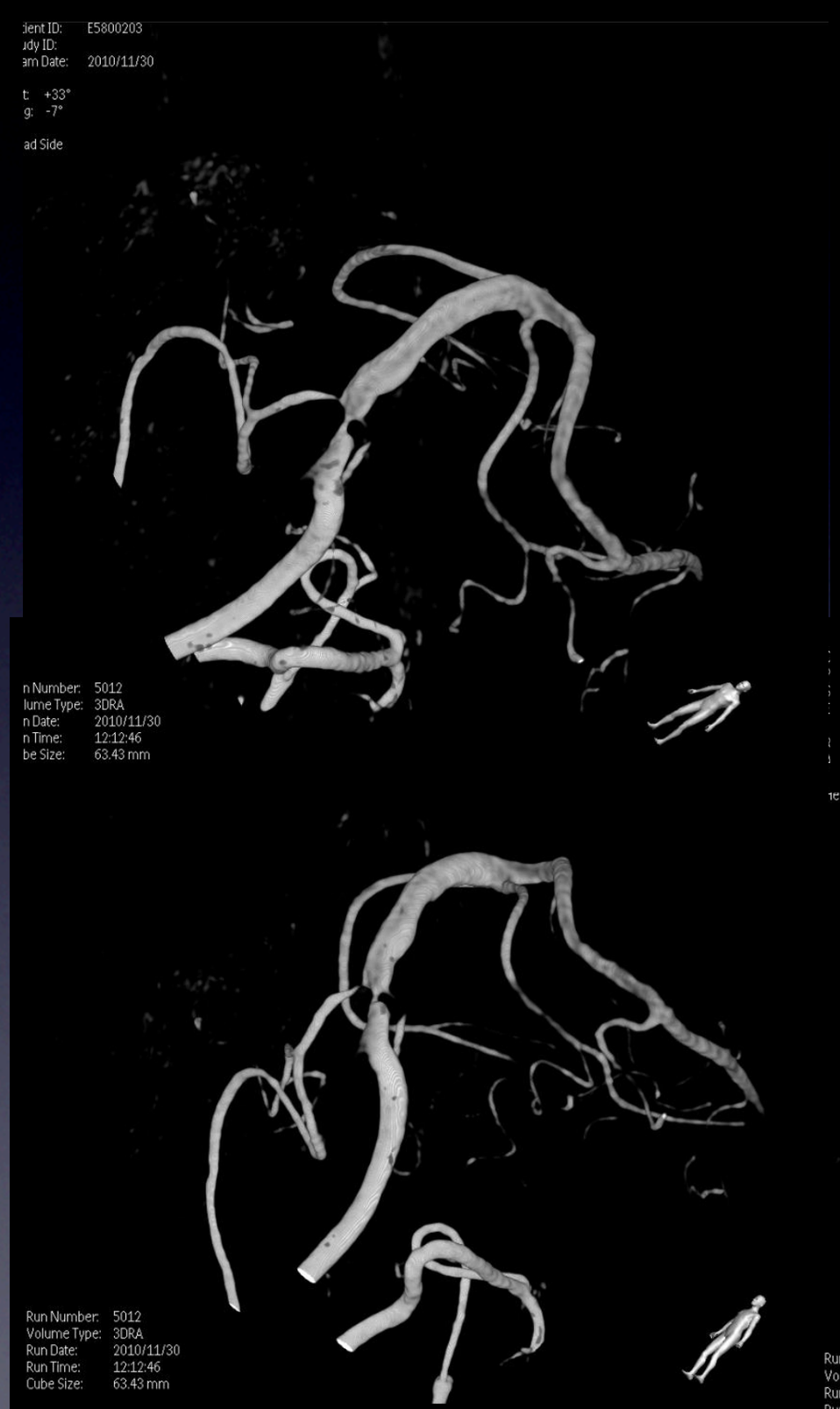
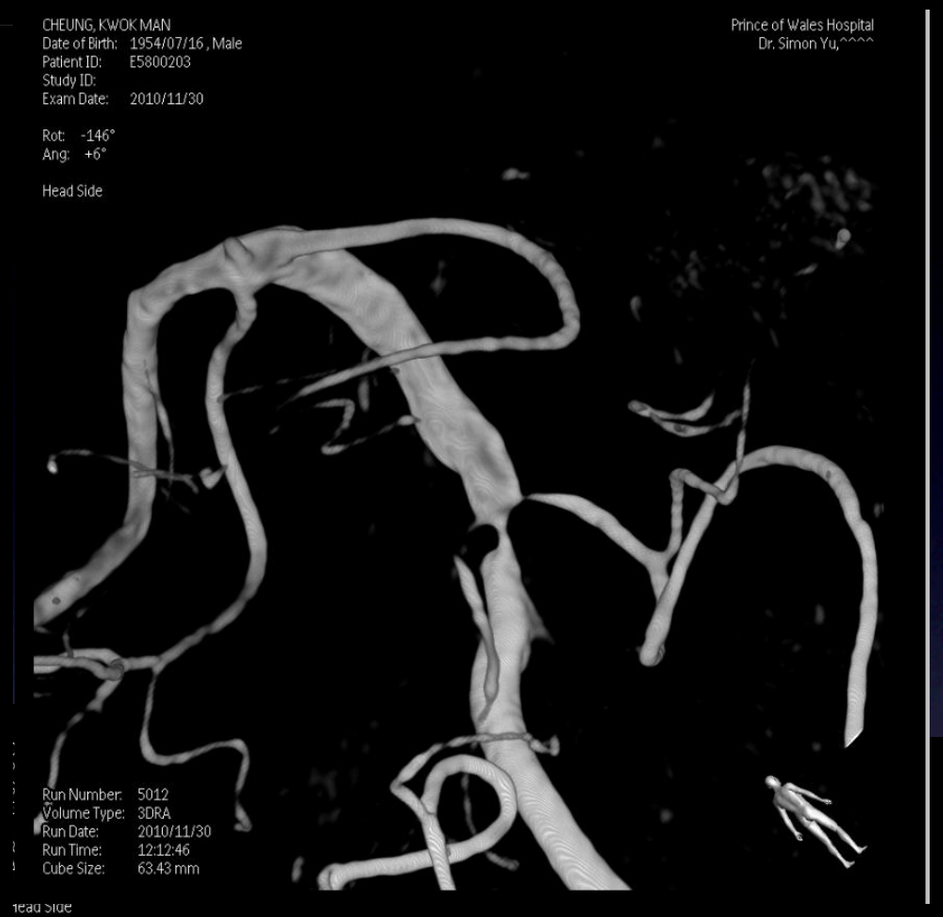
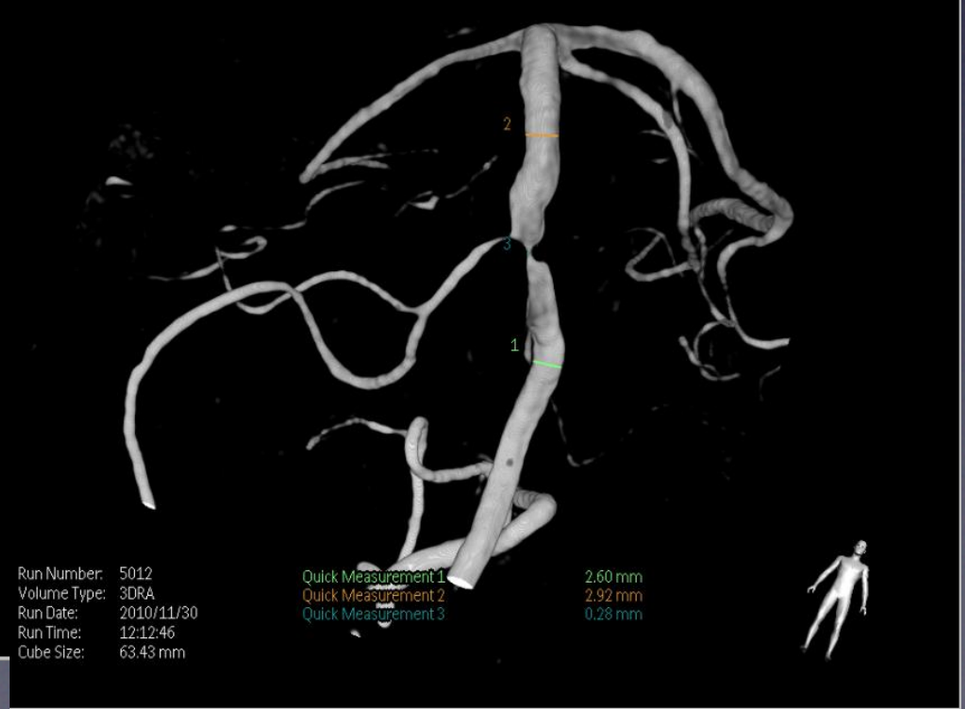
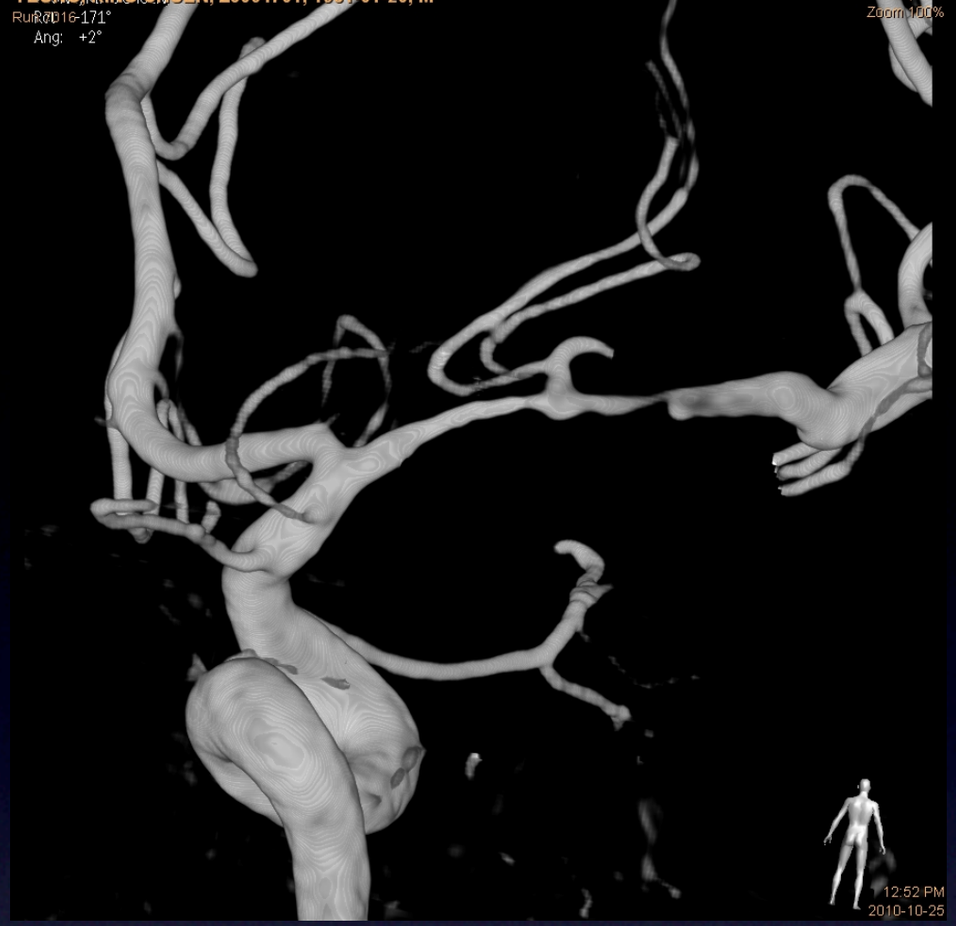
3D Rotational Angiogram prior to stenting









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Iopamiral, 2.1-2.4ml/sec
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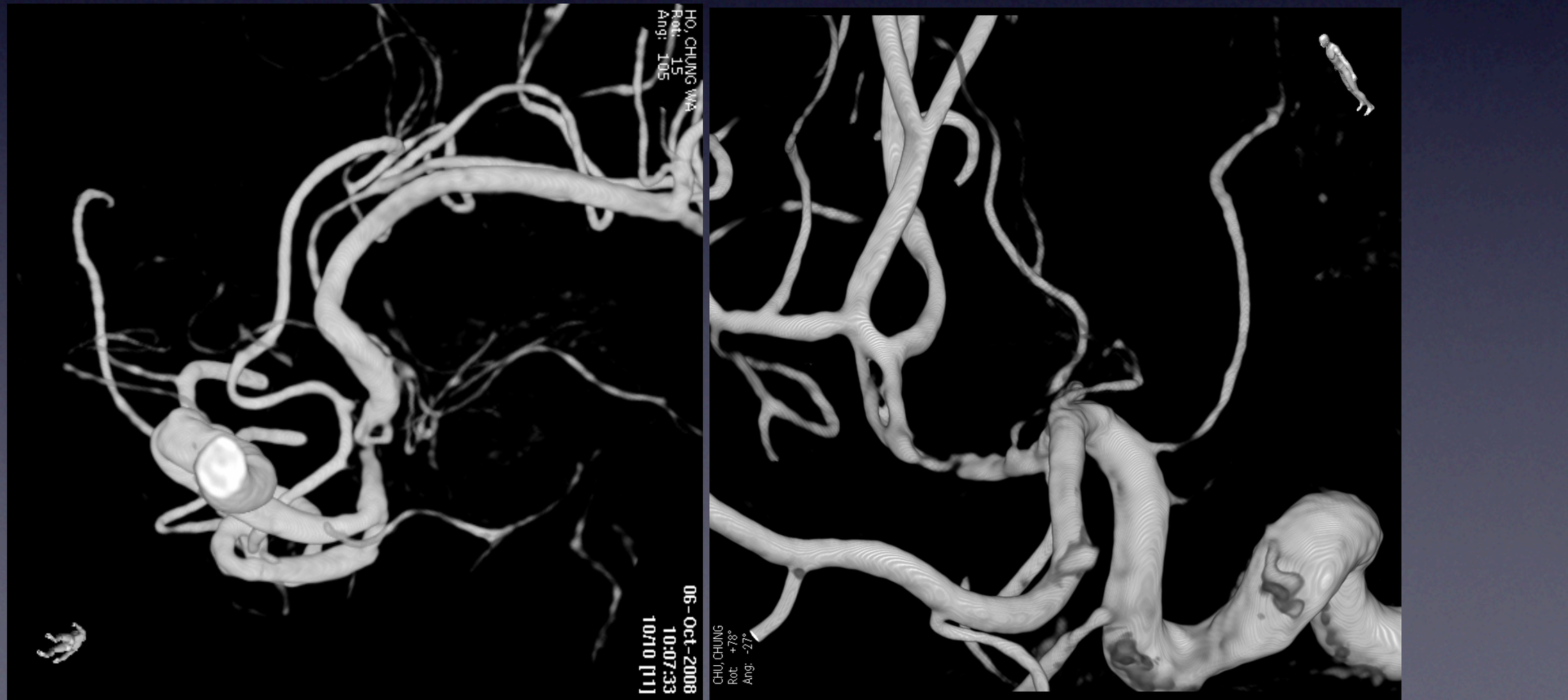
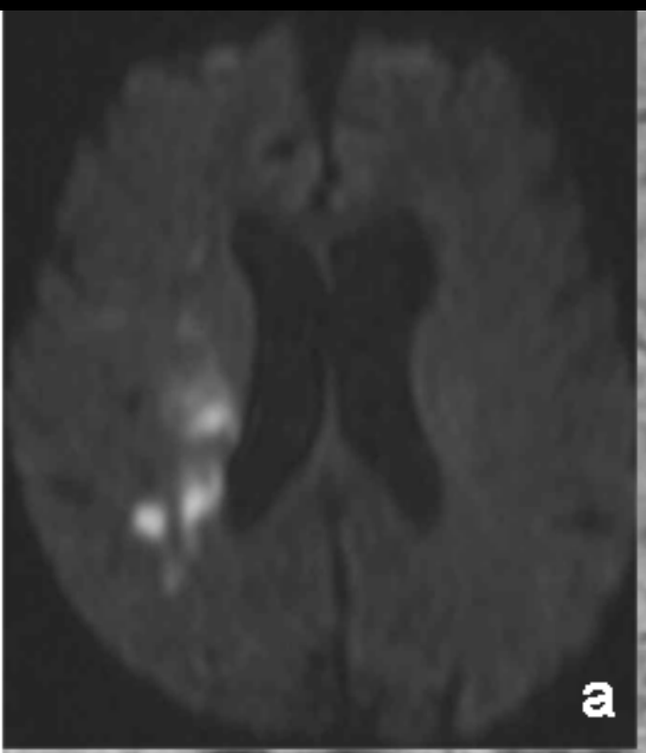
Contrast window

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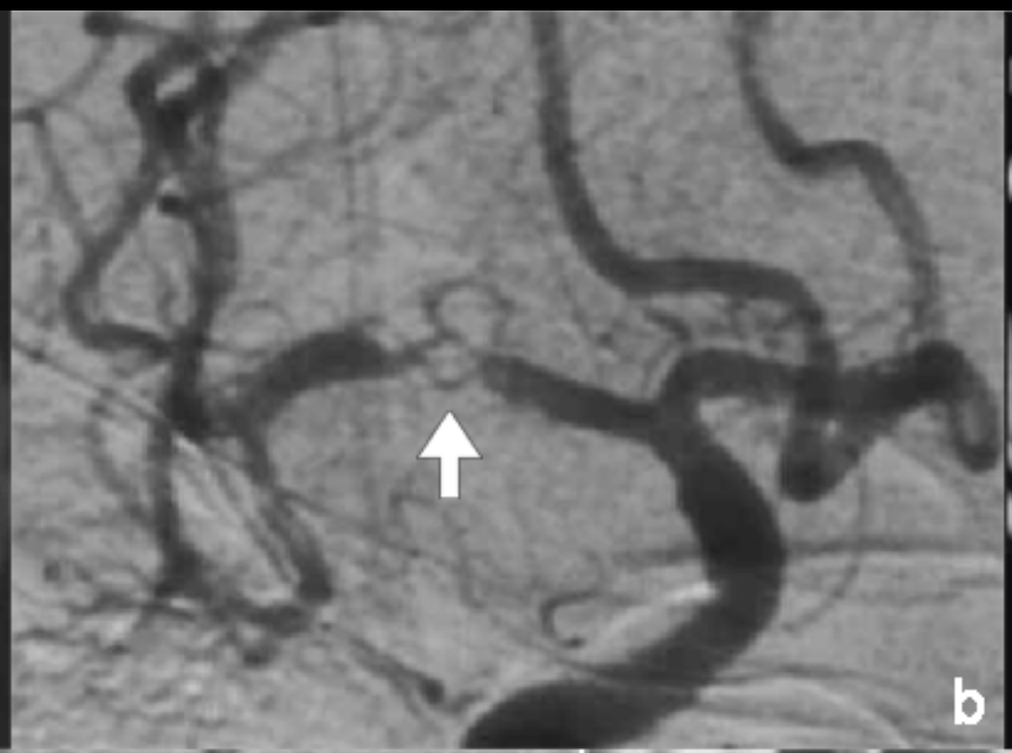
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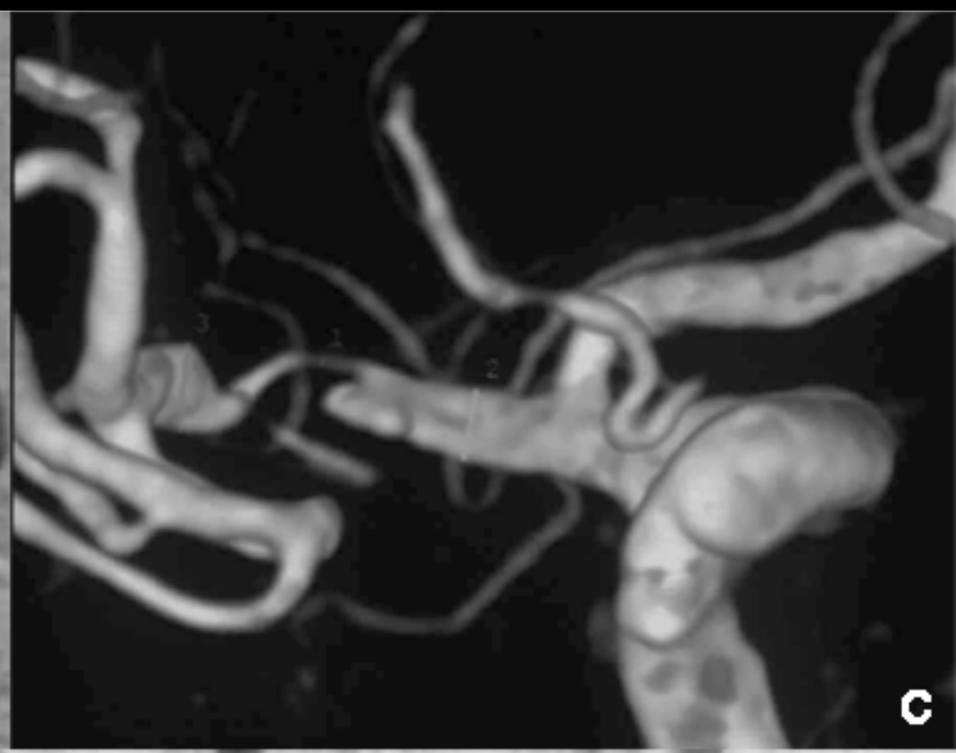
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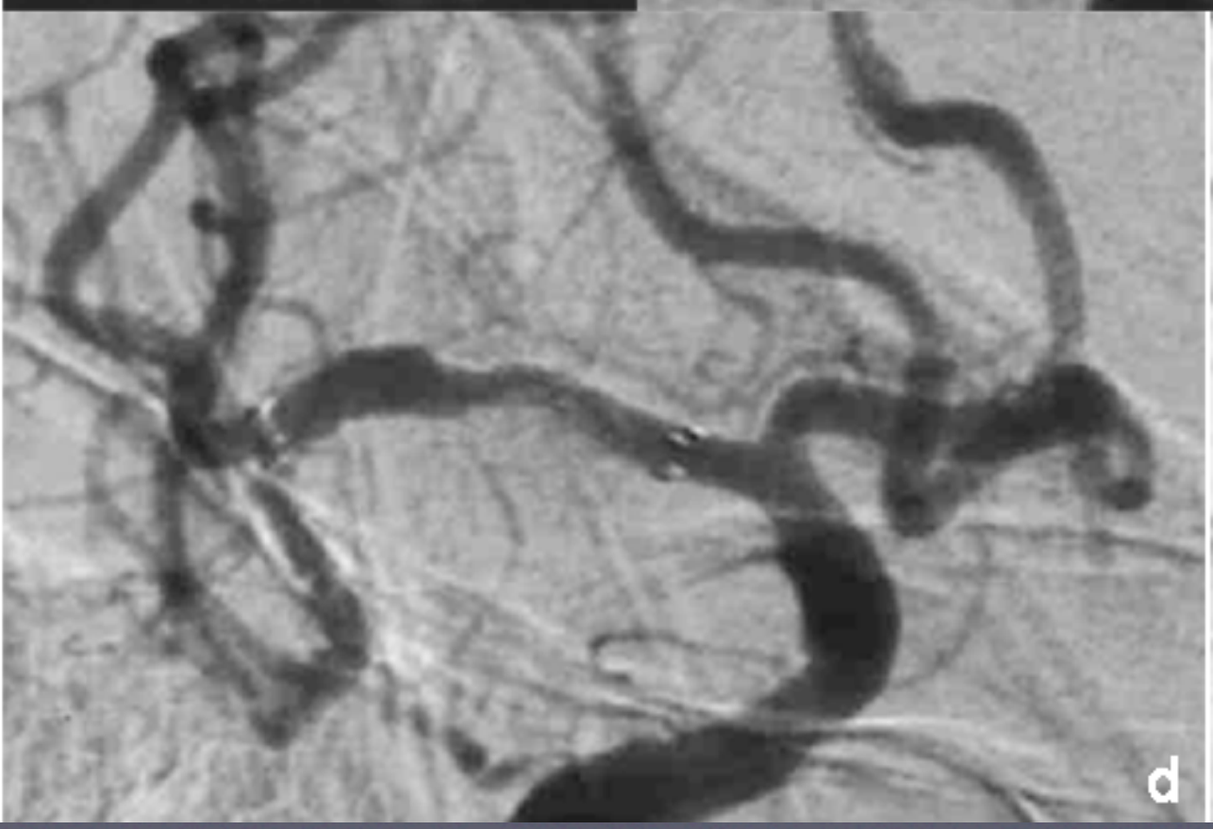
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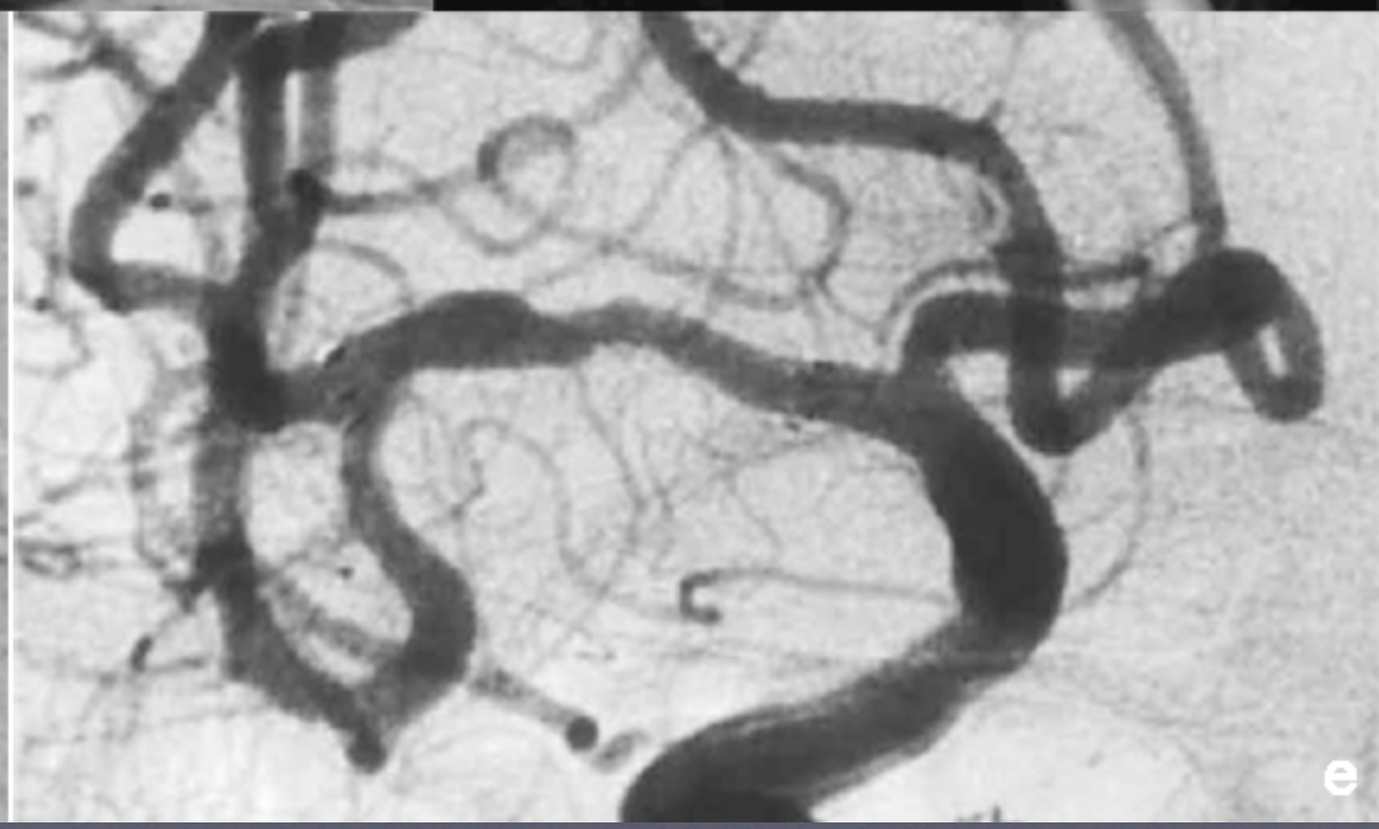
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Would Self-Expanding Stent Occlude Middle Cerebral Artery Perforators?

Thomas W. Leung, MRCP; Simon C.H. Yu, FRCR; Wynnie W.M. Lam, FRCR;
Anne Y.Y. Chan, MRCP; Alexander Y.L. Lau, MRCP; Lawrence K.S. Wong, MD

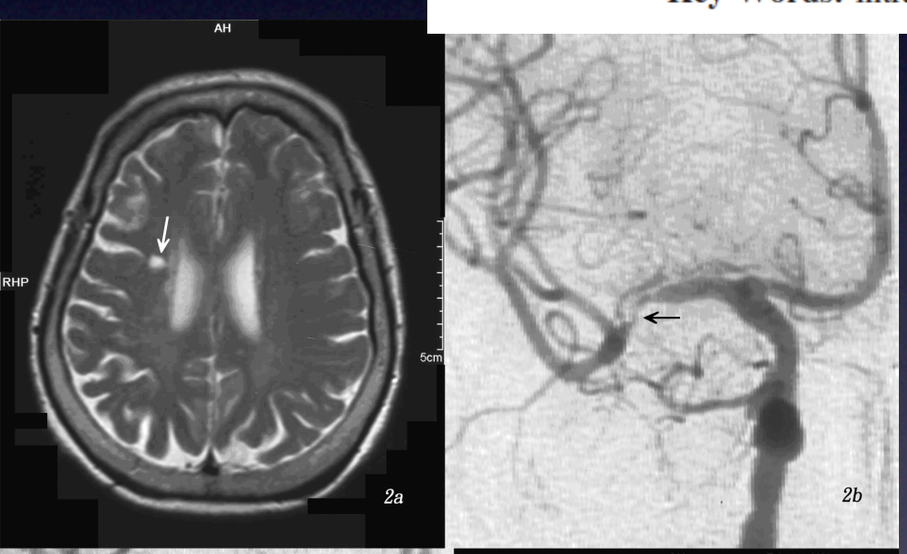
Background and Purpose—A major concern of intracranial stenting is perforator infarction. It is unclear whether the sustained radial force of a self-expanding stent or subsequent stent restenosis would cause late occlusion of perforators.

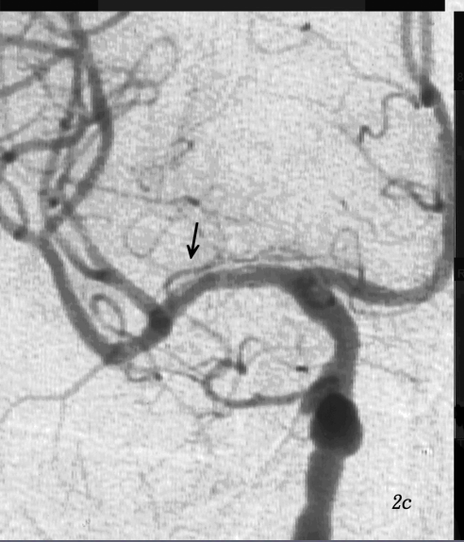
Methods—We compared the baseline and poststent (≥4 months) MRI scans of patients who underwent self-expanding stenting for recurrent ischemic symptoms attributed to a MCA stenosis ≥60%. New infarcts in the ipsilateral striatocapsular region were recorded.

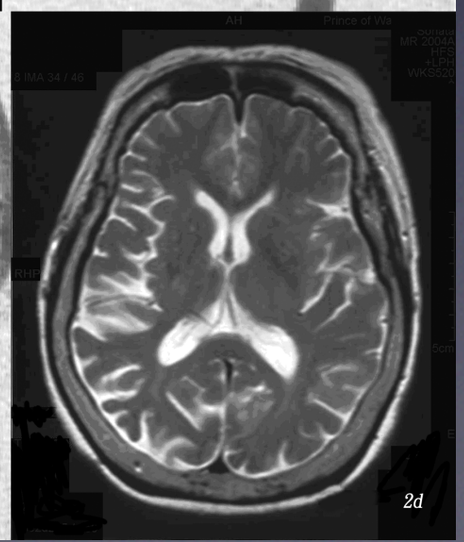
Results—MCA stenting was technically successful in 23 of 24 recruited patients. No new perforator territory infarct was found in follow-up MRI scans of all recruited patients. Postoperatively, all patients reported no further TIA or stroke over a median follow-up of 15 months.

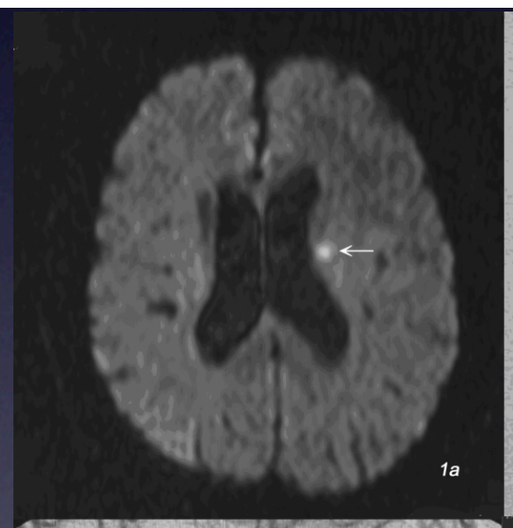
Conclusions—The use of a self-expanding stent in patients with high-grade MCA stenosis may not pose a major risk to the perforators. (***Stroke*. 2009;40:1910-1912.**)

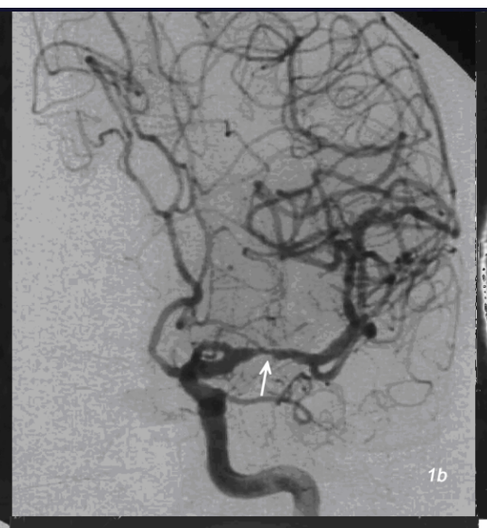
Key Words: intracranial stenosis ■ angioplasty ■ stenting ■ perforator territory infarction

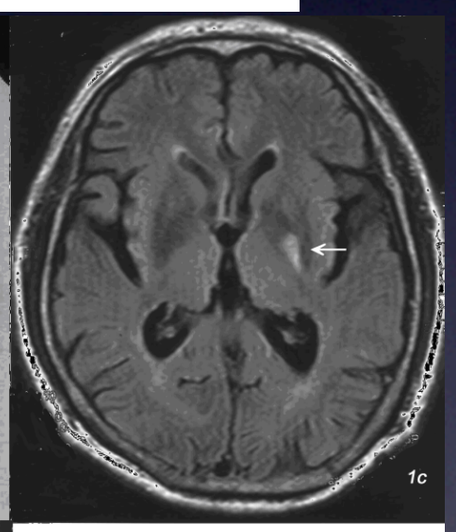


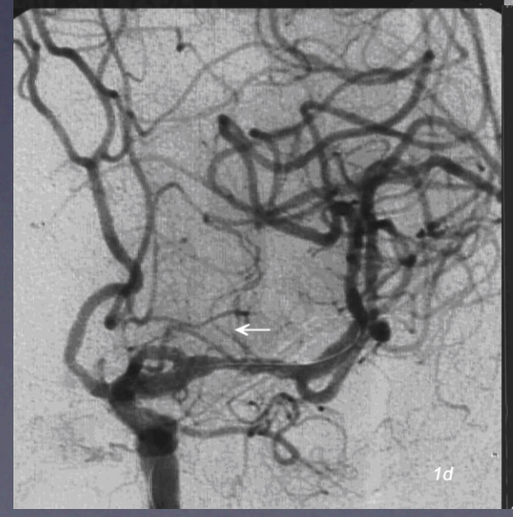


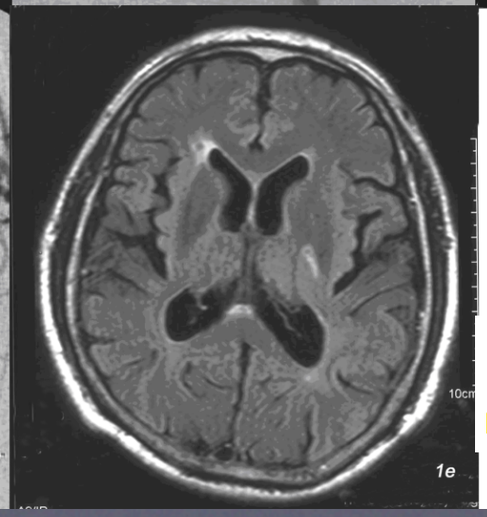












Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Stroke Association
A Division of American Heart Association

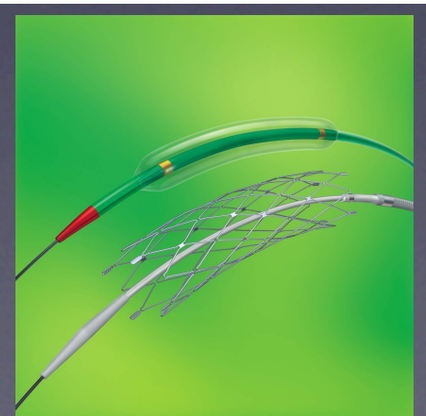
Procedural problems

Table 1 Technical problems encountered during procedure and causes of procedure failure

Patient sequence	Stenosis location	Stenosis degree	Technical problem encountered during the procedure	Cause of procedure failure
4	ICA and MCA	50%	Difficult stent tracking and delivery, fracture core of stent delivery system	
5	ICA	60%	Nose cone bending caused stent sheath kinking and stretching during stent deployment	
7	ICA	60%	Stretching of stent sheath during stent deployment	
8	BA	75%		Arterial rupture after angioplasty
15	ICA and MCA	50%	TIA during manipulation of balloon catheter across stenosis	TIA
27	ICA	90%	Nose cone trapped between guidewire and stent tip after stent deployment	
42	ICA	75%	Difficult stent tracking and delivery, fracture core of stent delivery system, TIA	TIA
44	MCA	83%	TIA	
47	ICA and MCA	96%	Failure passage of balloon across stenosis	Failure passage of balloon
48	MCA	90%	Kinking of balloon catheter after guidewire removal	
56	MCA	70%	Transient blindness and severe headache during stent system advancement	
59	MCA	87%	Transient blindness during stent system advancement	TIA
66	ICA	75%		Perforation of M2 perforators by guidewire during angioplasty

BA, basilar artery; ICA, internal carotid artery; MCA, middle cerebral artery; TIA, transient ischemic attack.

Neurosurgery 2012; 70: 104-113
J Neurointerventional Surg 2013;00:1-7



Patients analyzed in quarters

Table 3 Leaning curve analysis using data splitting method

Variables	1st quarter	2nd quarter	3rd quarter	4th quarter	Trend difference across quarters
Patient sequence (patient no)	1–24 (24)	25–48 (24)	49–72 (24)	73–95 (23)	
Age (mean±SD)	67.46±10.484	62.75±11.433	62.13±10.999	66.57±9.336	No difference across quartersp>0.085
95% CI	63.03 to 71.89	57.92 to 67.58	57.48 to 66.77	62.53 to 70.6	
Degree of stenosis (mean±SD)	69.96±12.539	77.82±8.368	76.39±9.942	77.91±8.286	Difference between 1st and 2nd quarter, p=0.033.
95% CI	64.53 to 75.38	74.29 to 81.35	72.19 to 80.59	74.24 to 81.58	No difference across other quarters
Location					
MCA	10	16	15	10	Difference between 1st and 2nd quarter in frequency of location at VBA, p=0.023. No difference across other quarters
ICA	6	7	5	8	
VBA	8	1	4	5	
Event to stenting <30 days (rate)	10 (41.7%)	15 (62.5%)	14 (58.3%)	18 (78.3%)	Difference between 1st and 4th quarter, p=0.011. Difference between 4th quarter and the rest, p=0.05
Procedural problem (rate)	4 (16.7%)	5 (20.8%)	2 (8.3%)	0	Difference between 4th quarter and the rest, p=0.046
Technical failure (rate)	2 (8.3%)	2 (8.3%)	2 (8.3%)	0	No difference across quarters,p>0.33
Guidewire- or angioplasty-related hemorrhagic complication <30 days (rate)	1 (4.2%)	1 (4.2%)	1 (4.2%)	0	No difference across quarters,p=1

ICA, internal carotid artery; MCA, middle cerebral artery; VBA, vertebrobasilar artery.

A learning curve effect

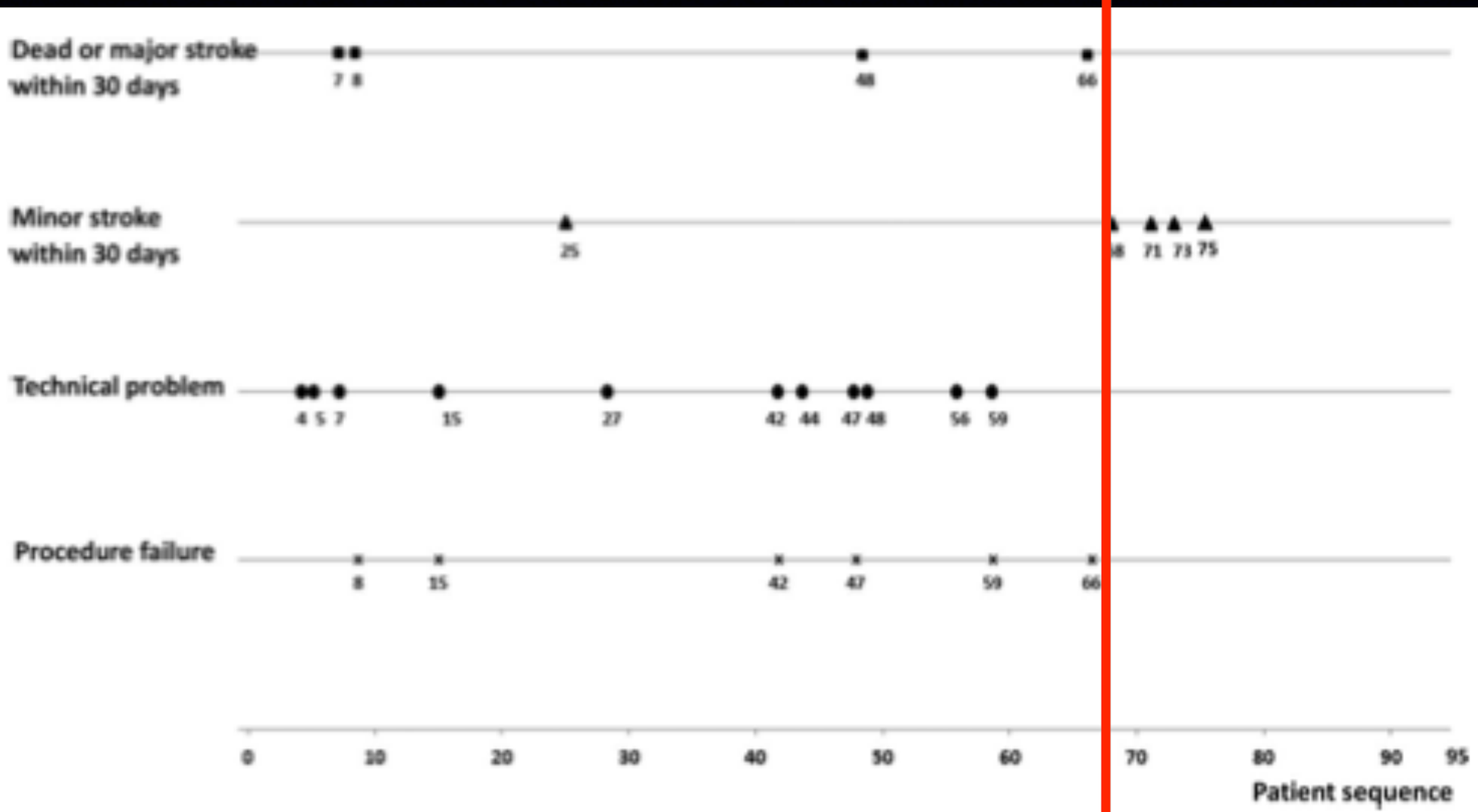


Figure 1 Occurrence of study endpoints in chronological sequence.

Neurosurgery 2012; 70: 104-113
J Neurointerventional Surg 2013;00:1-7

Centre For Clinical Trials

Quality and Efficiency in Clinical Research & Drug Development

CENTRE FOR CLINICAL TRIALS, CLINICAL TRIALS REGISTRY

1. Unique Trial Number (assigned by CCT) :	CUHK_CCT00116
2. Trial Registration Date (yyyy/mm/dd) :	2006-10-13
i. Registration Status:	Prospective

** The date of registration will be established by the primary registering entity.*

3. Secondary IDs (optional) :	ESASIS

** May be assigned by sponsors or other parties (there may be none).*

4. Source(s) of Funding :	Division of Neurology, Department of Medicine and therapeutics; Prince of Wales Hospital, The Chinese University of Hong Kong; and Vascular and Intervention Radiology Foundation

Name of the organization(s) that provided funding for the study

5. Primary Sponsor :	Division of Neurology, Dept of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong

The main entity responsible for performing the research

6. Secondary Sponsor :	Department of Imaging and Interventional Radiology, The Chinese University of Hong Kong

The secondary entities, if any, responsible for performing the research, N/A if not applicable

7. Responsible Contact Person (public contact person for patients interested in participating) :	
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8. Research Contact Person (person to contact for scientific inquiries) :	
i. Name	Dr. Thomas WH Leung
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iii. Telephone	852-26323877
iv. Email	drtleung@cuhk.edu.hk
v. Affiliation	Principal Investigator
9. Official Scientific Title of the Study :	Early stent-assisted angioplasty in symptomatic intracranial stenosis (ESASIS)

** This title must include the name of intervention, condition being studied and the outcome (e.g., The international Study of Digoxin and Death from Congestive Heart Failure)*

10. Public Title :	ESASIS

Algorithm of ESASIS

Acute ischemic stroke within 6 weeks

TCD
MRI/MRA
CTA

Screening (n=219)

Excluded (n=143)

Consent then DSA/3DRA

(n=179)

Excluded (n=84)

Evaluation of DSA followed by immediate randomization

(n=95)

Stent arm

(n=47)

Procedure in the same setting

12-month DSA

Medical arm

(n=48)

Treatment targets:
LDL <70 mg/dL
HbA1c <6.5%
blood pressure <140/80mmHg.

Yong Loo Lin School of Medicine
Department of Pharmacology

NUS National University of Singapore

TO : Executive Committee of the Early Stent-assisted Angioplasty in Symptomatic Intracranial Stenosis (ESASIS) Trial

FROM : Data Safety Monitoring Board (DSMB) ESASIS Trial

DATE : 3rd September 2013

The ESASIS DSMB met at the Prince of Wales Hospital on 2nd September 2013 and reviewed the following :

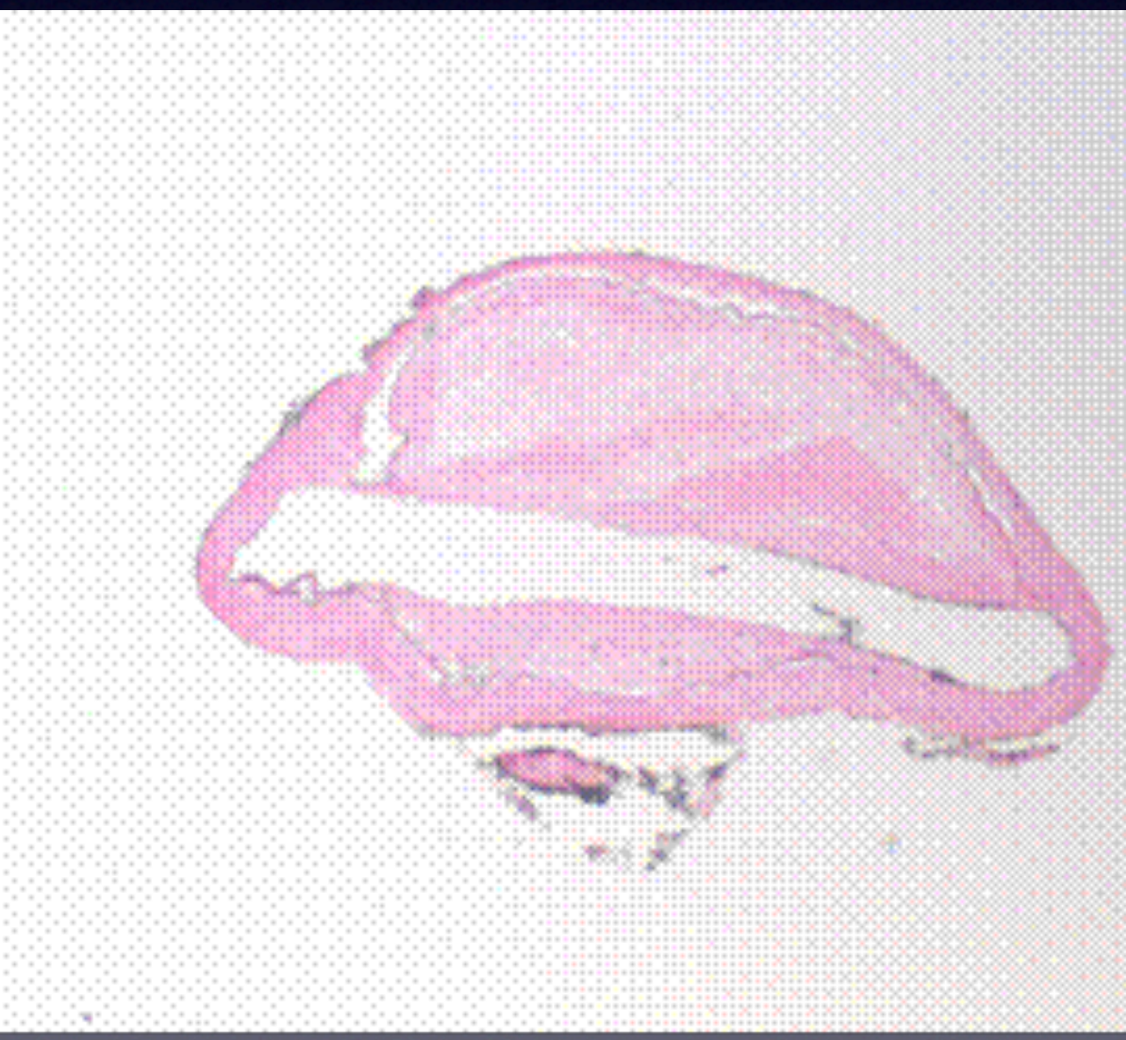
a) 30 day safety data (combined stroke and death) for 95 patients randomized as of 27th August 2013. The rate of combined stroke / death is 8.3% for the medical arm and 2.1% in the stent arm.
b) 12 month safety data (SAEs) for 95 patients (5 of whom have yet to complete 12 months follow-up). There was a total of 52 SAEs in 28 patients. There was no excess of SAEs in the stent arm.

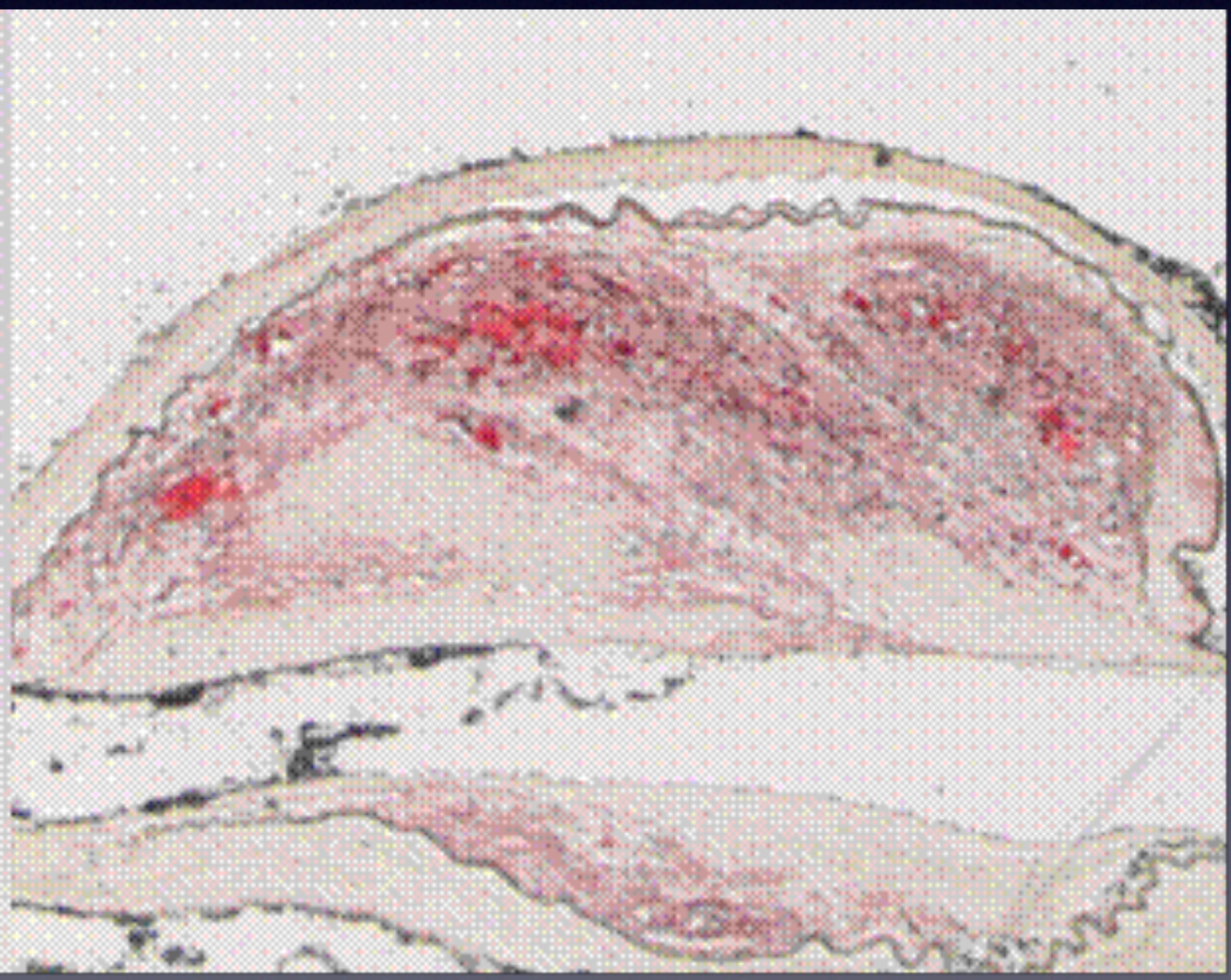
We therefore recommend that the ESASIS trial continues recruitment with close monitoring of safety.

To identify the subset of patients most vulnerable for relapse

To improve the safety and efficacy of endovascular treatment

Pathology of Intracranial Atherosclerosis





How high-grade intracranial atherosclerosis would evolve under optimal medical therapy?

Patients with recent stroke attributed to a high-grade (>70%) intracranial stenosis

Dual anti-platelet agents (aspirin 80mg daily or clopidogrel 75mg daily) for 1 week

Pre-specified treatment targets:

1) LDL <70 mg/dL
2) HbA1c <6.5%
3) BP systolic/diastolic <140/80mmHg.

Clinical follow-up: day-30, 3 months, 6 months and 12 months.

BP diary + fasting blood samples collected at baseline, 3 months and 6 months.

3D-rotational angiography at baseline and 12 months.

Paired images reviewed by a radiologist blinded to the sequence.

Outcome stratified into: static (same +/-5%); progressive (increase >5%); regressive (reduce >5%)

39 patients (M/F : 27/12) have passed 12-month follow-up

Mean age 67.4 ±9.5yrs

MCA (n=24), ICA (n=10), VA (n=3) and BA (n=2)

Results

	Baseline (median, IQR)	Year-1 (median, IQR)
Stenosis degree	75.0 (71.0-88.0)	63.0 (54.8-77.8)
Hemoglobin A1C, %	6.1 (5.7, 6.8)	5.9 (5.6, 6.4)
TCH, mg/dL	209.0 (170.3-236.1)	135.5 (127.7-143.2)
HDL, mg/dL	42.6 (34.8, 50.3)	53.0 (42.6, 58.1)
TG, mg/dL	129.4 (106.3-168.3)	97.5 (70.9-124.0)
LDL, mg/dL	131.6 (100.6-158.7)	65.8 (58.1-81.3)
SBP, mmHg	145 (125-165)	125 (112-138)
MAP, mmHg	100 (90-112)	90 (83-100)

IQR: inter-quartile range; TCH: total cholesterol; HDL: high-density lipoprotein; TG: triglyceride; LDL: low-density lipoprotein; SBP: systolic blood pressure; MAP: mean artery pressure.

Static n=7

Progressive n=4

Regressive n=27

Regression and healing of ulcers

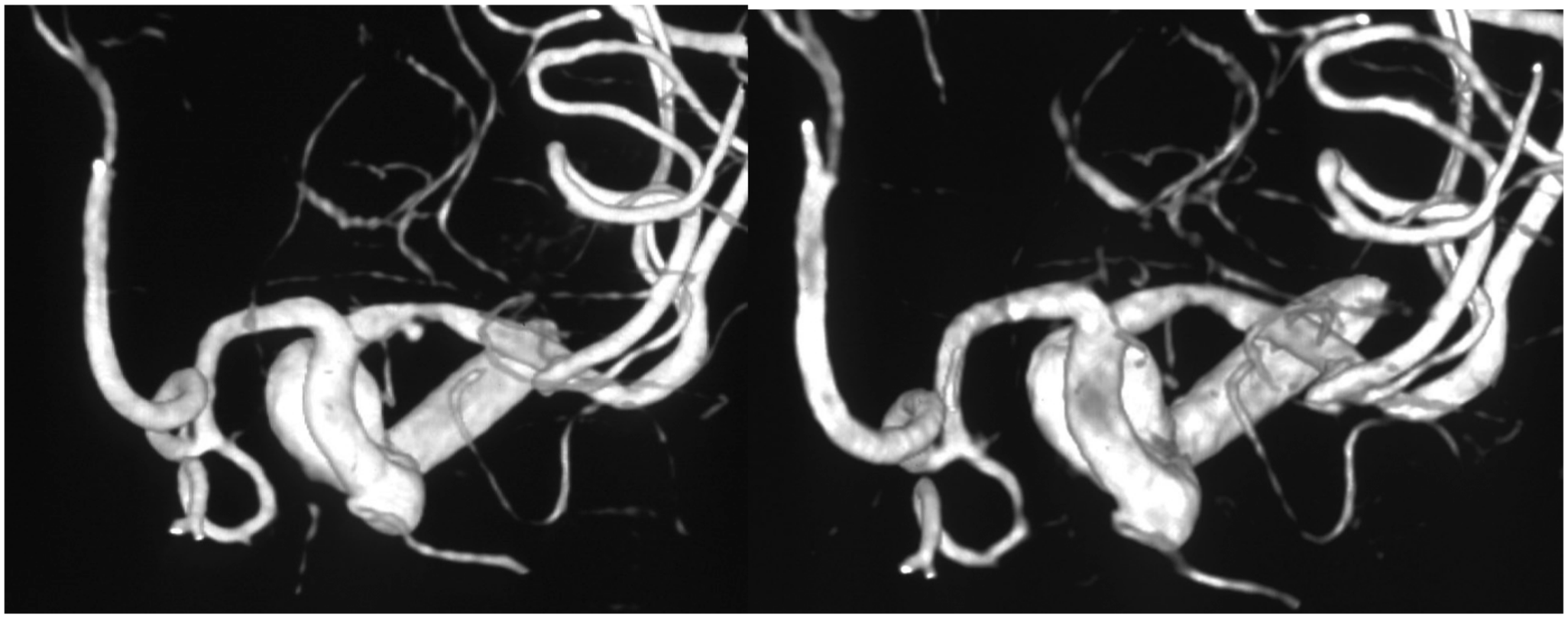
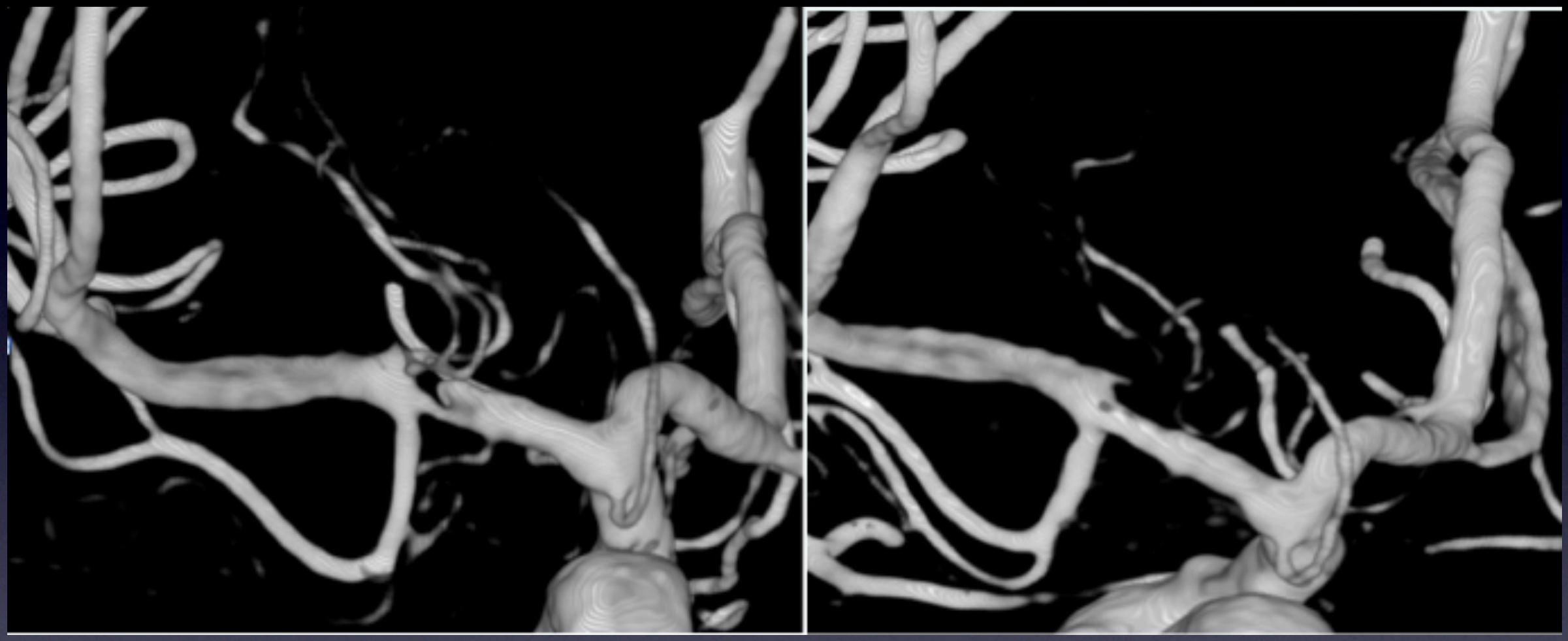


Figure 1: 3-dimensional rotational angiograms showing regression of a high-grade middle cerebral artery plaque in a 70-year-old man who received intensive medical therapy after an ischemic stroke attributed to this ulcerative stenosis.



However, among these 39 patients, 8 patients (21%) developed stroke (n=5) or TIA (n=3) in the same vascular territory during the 12-month follow-up:

4 incidents occurred within 30 days from the index stroke

(one patient died of ovarian cancer before 12-month angiogram)

The remaining 7 patients all had significant regression of the symptomatic lesion in 12 months

Baseline 81.3% → 49.0%

2 Potential Implications:
A reduction in stenosis is not sufficient to prevent stroke
Platelet cap rather than true atherosclerosis at baseline?

CHAN, CHI CHEONG
D0939928
*17-Sep-54, M, 53Y

23-May-08
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5 IMA 67 / 58

AH

Prince of Wales Hospital
Sonata
MR 2004A
HFS
+LPH
WKS520
ê

RFA

5cm

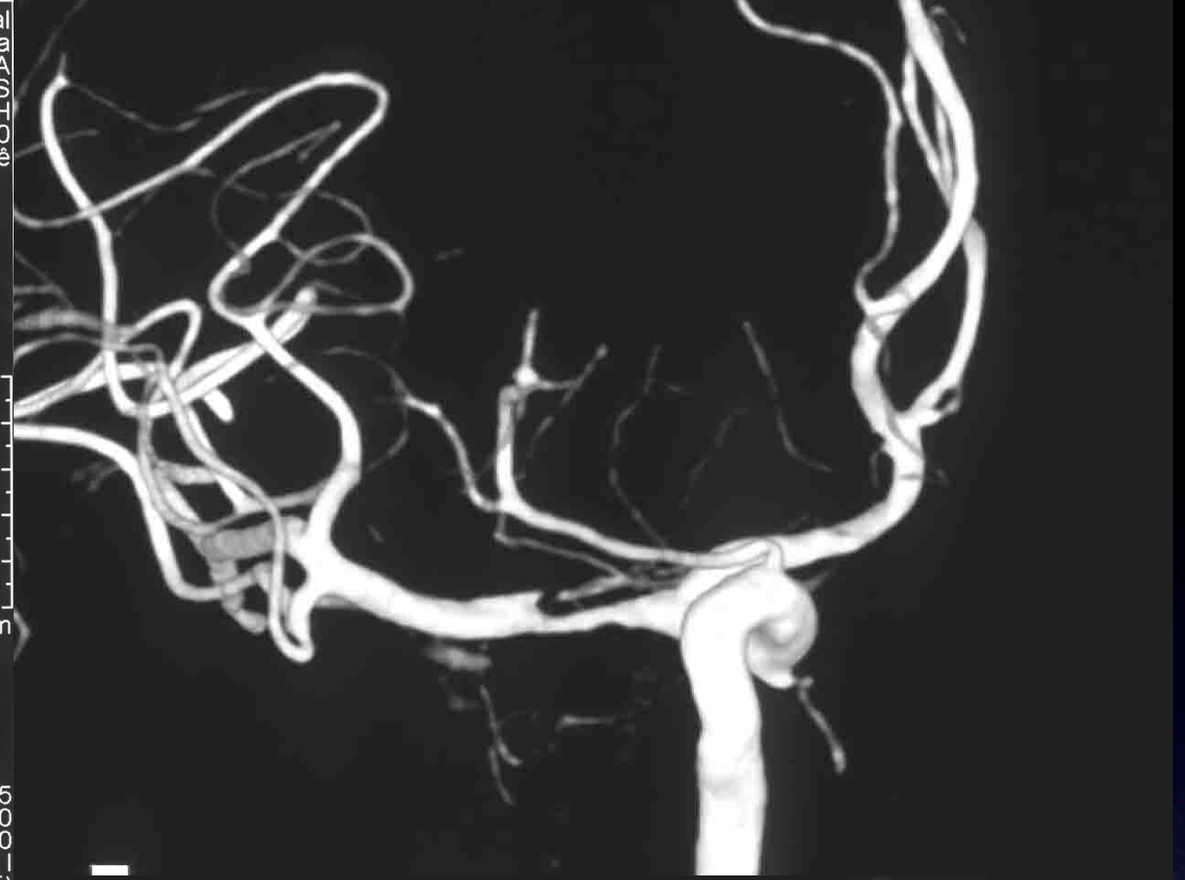
MF 1.08

TR 3400.0
TE 122.0
TA 00.15
BW 1345.0
M/ND

SP H6.5
SL 5.0
FoV 230*230
180p*256 I
Tra>Cor(-10.9)>Sag(2.5)

A4/FS
HE
*ep_b1000t / 90

W 320
C 142



*17-Sep-54, M, 53Y

03-Jul-08
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4 IMA 65 / 58

MR 2004A
HFS
+LPH
WKS520
ê

RHP

10cm

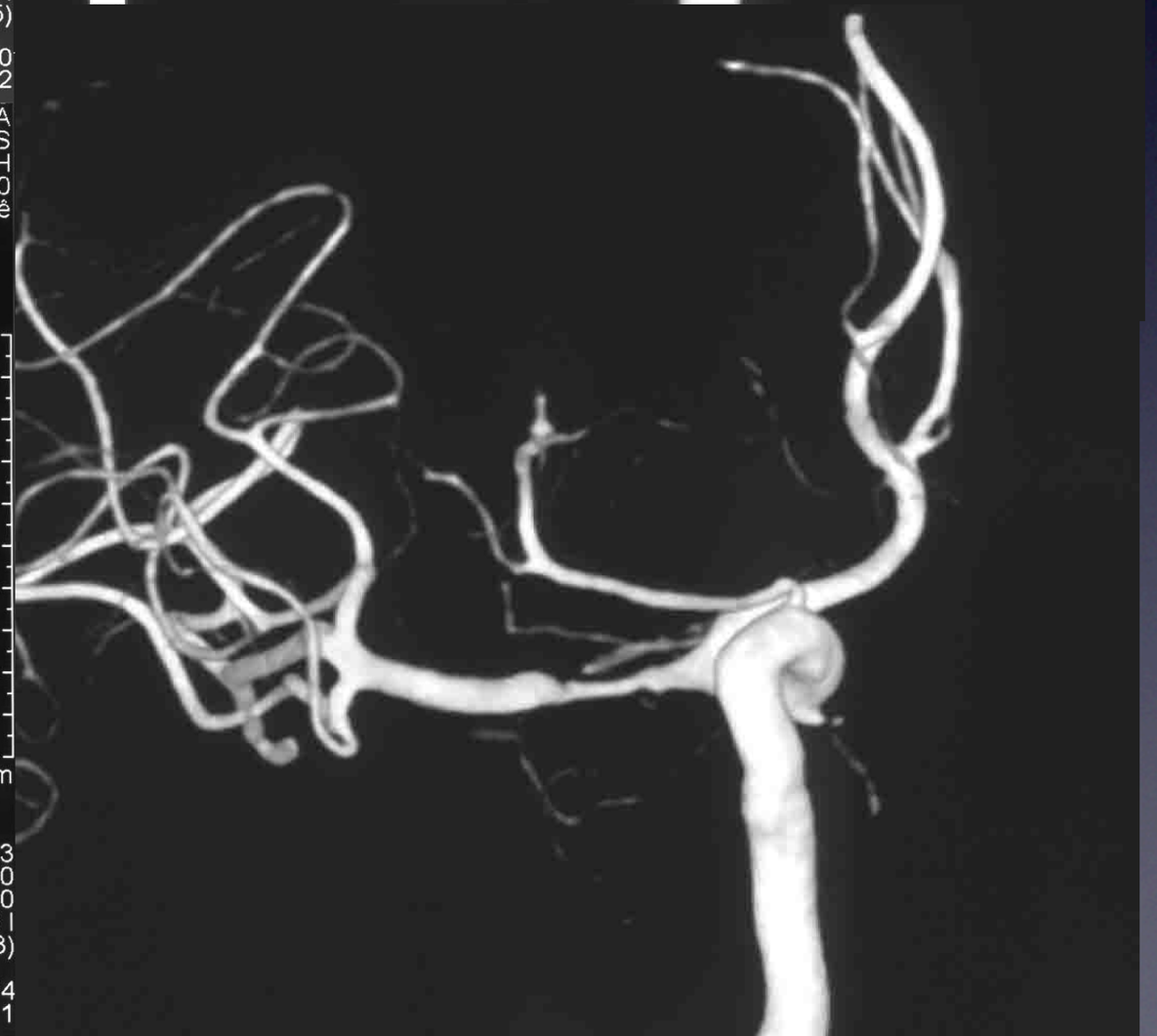
MF 0.98

TR 3400.0
TE 122.0
TA 00.15
BW 1345.0
M/ND

SP H6.3
SL 5.0
FoV 230*230
180p*256 I
Tra>Cor(-17.1)>Sag(-1.3)

A4/FS
HE
*ep_b1000t / 90

W 274
C 111

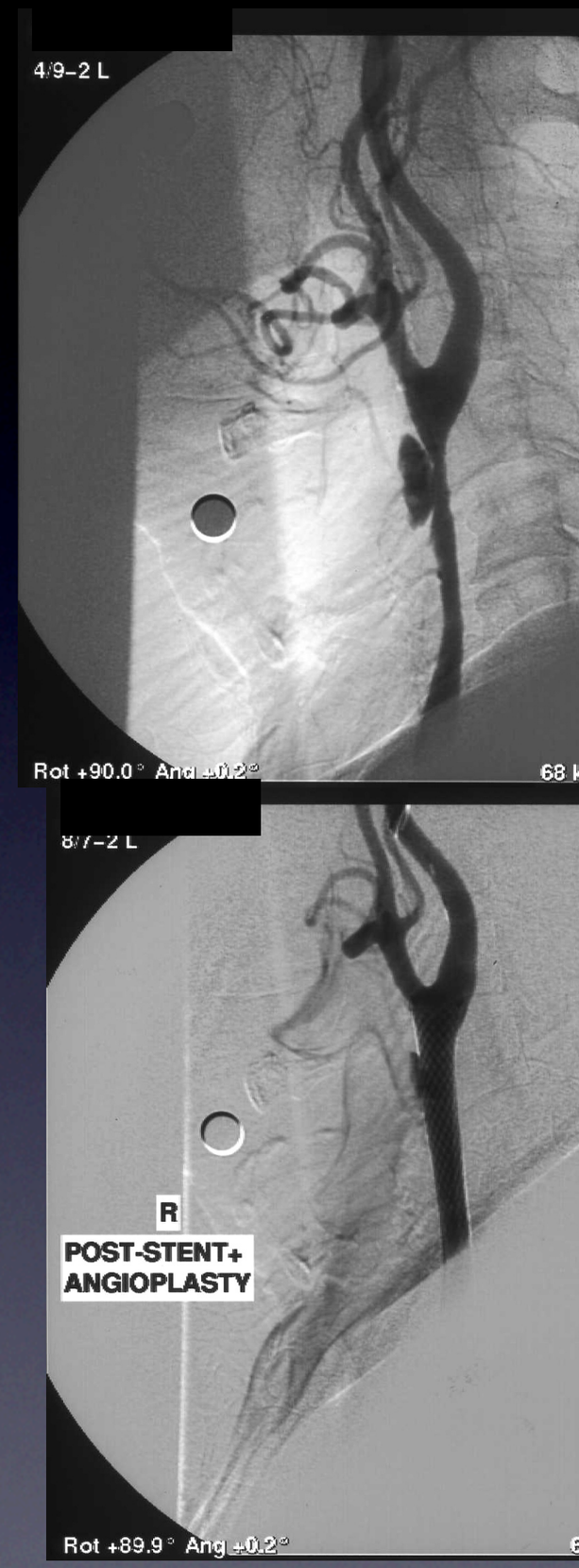


If an adjunctive treatment (be it endovascular tx or not) has to claim the upper hand, ideally it should:

Safely improve vessel patency and antegrade flow (in patients with hemodynamic strokes)
(This is good but perhaps insufficient)

Prevent early thromboembolism (reinforce anti-platelets effect ?drug eluting stent)

Stabilize the plaque, possess anti-inflammatory effect, and facilitate healing of the ulcers



While we know so little…

Adherence to strict risk factor control according to major international guidelines or SAMMPRIS aggressive treatment strategy. Individualized therapy may be needed in refractory cases.

The degree of stenosis is likely not the only factor governing relapse. We should improve the safety and efficacy of any endovascular therapy to be proposed.

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Stroke Team members in Prince of Wales Hospital, Hong Kong








Neurosurgeons Radiologists AED Nurses





Neurology Team