Unruptured Intracranial Aneurysms: Current Treatment

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Disclosures

- None relative to this talk
- Consultant- CereVasc
- DSMB Contour trial
- DSMB Embolize trial Medtronic

Intracranial scans done with increased frequency

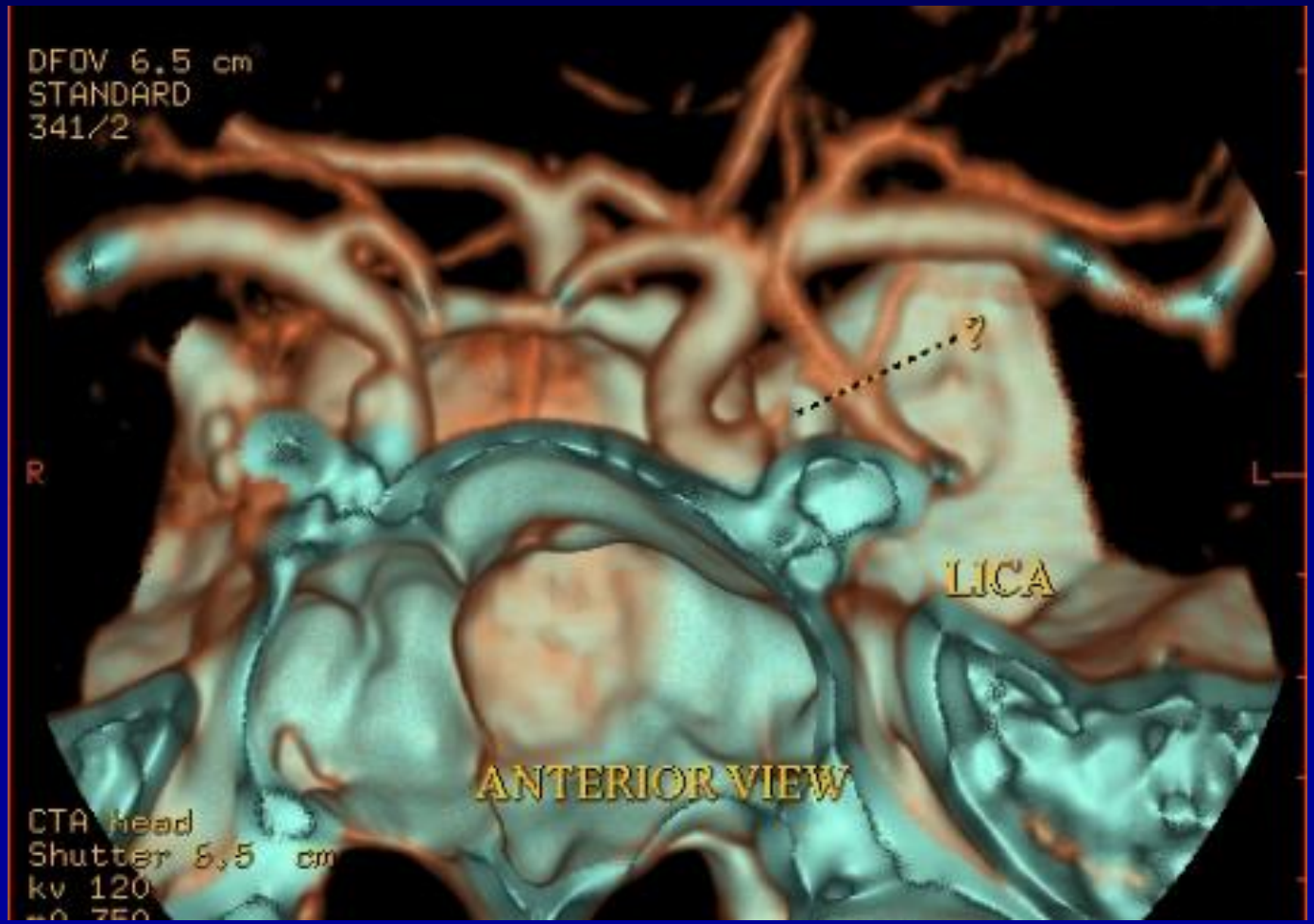
- Mild head injury
- Neurologic TIA
- Cancer
- Screening

Once an aneurysm is detected or ‘read’ on a scan – the immediate question for the physician and the patient is what to do?

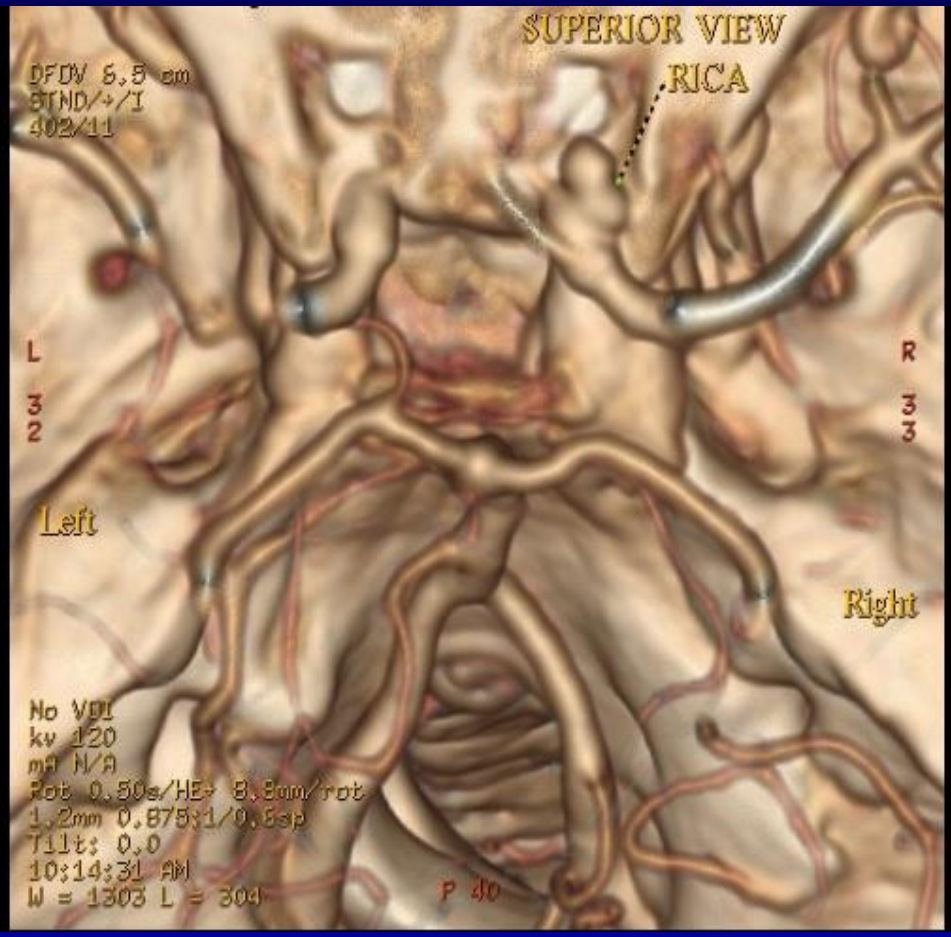
Once an aneurysm is detected:

- Prove that it is really an aneurysm
- Decide what constitutes an aneurysm
  - "outpouching"
  - "fullness"

Small Internal carotid artery aneurysm



76Y.O. with headaches



Imaging of unruptured aneurysms

- MRI/MRA
- CT/CTA
- Cerebral angiography

How common are unruptured aneurysms?

INTRACRANIAL ANEURYSMS

- Prevalence at autopsy: 2-5%
- 2-5 million Americans have unruptured cerebral aneurysm

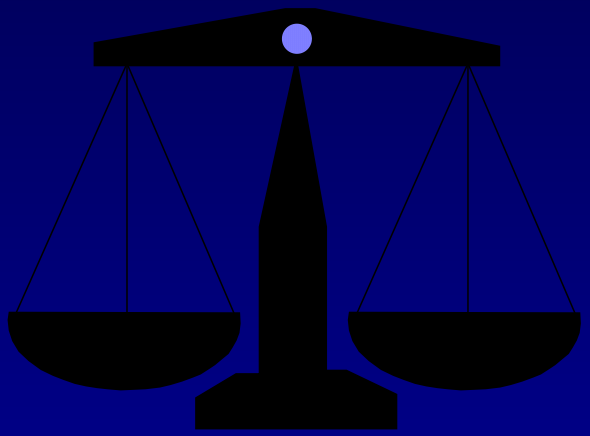
I find an aneurysm in a patient: What do I advise?

Unruptured aneurysm detected

-Previous concept that rupture was related only to size is outdated

- Currently, a much more nuanced analysis is needed incorporating patient specific factors and aneurysm specific factors

Decision Making in Unruptured Aneurysm Treatment?



- **<u>Rupture Risk</u>**
- ISUIA Data
- UCAS
- Metanalysis
- PHASES score

- **<u>Treatment risk</u>**
- **Endovascular**
- **Surgical**

Decision-making for unruptured aneurysms: natural history vs treatment risks

- Natural History-patient and lesion specific factors
  - Size, Location of lesion, Age of patient (life horizon), Risk factors (smoking, ethnicity), Female
- Risk of treatment-patient and lesion specific factors
  - Age, Size, Comorbidities
  - Decreasing risk with improved technology and techniques

Decision-making for unruptured aneurysms: NATURAL HISTORY

Nuanced Understanding: some location aneurysms pose greater risk than other lesions.

- ISUIA
- UCAS
- Meta-analyses
- PHASES score

International Study of Unruptured Intracranial Aneurysms (I.S.U.I.A)

N Engl J Med 1998;339:1725-33

The Lancet 2003;362:103-110

ISUIA Retrospective Components

GROUP 1 (n = 727)

No history of SAH
from another aneurysm

Rates of Rupture

< 10 mm	0.05% per year
> 10 mm	~1% per year
≥ 25 mm	6 % in first year

Predictors of Rupture

Increasing size

Location (basilar tip, posterior cerebral or vertebrobasilar distribution, posterior communicating region)

GROUP 2 (n = 722)

History of SAH
from a different aneurysm
repaired successfully

Rates of Rupture

< 10 mm	0.5% per year
> 10 mm	~1% per year
≥ 25 mm	insufficient data (n=3)

Predictors of Rupture

Location (basilar tip)

Older age

I.S.U.I.A. - II

- Lancet, 2004
- With further follow up, rates of hemorrhage were higher for lesions under 10 mm in both group 1 and group 2
- Criteria for who to treat expanded

ISUIA 2003 Retrospective Component

GROUP 1 (n = 1077)
No history of SAH
from another aneurysm

GROUP 2 (n = 615)
History of SAH
from a different aneurysm
repaired successfully

5-year Cumulative Rupture Rate

	<7 mm		7-12 mm	13-24 mm	≥25 mm
	Group 1	Group 2			
AC/MC/IC	0	1.5%	2.6%	14.5%	40%
Post-P comm	2.5%	3.4%	14.5%	18.4%	50%

- Predictors of rupture:
  - Size: 7-12 mm, RR 3.3;
  - Location (Tip of basilar, RR 2.3; P-comm, RR 2.1)

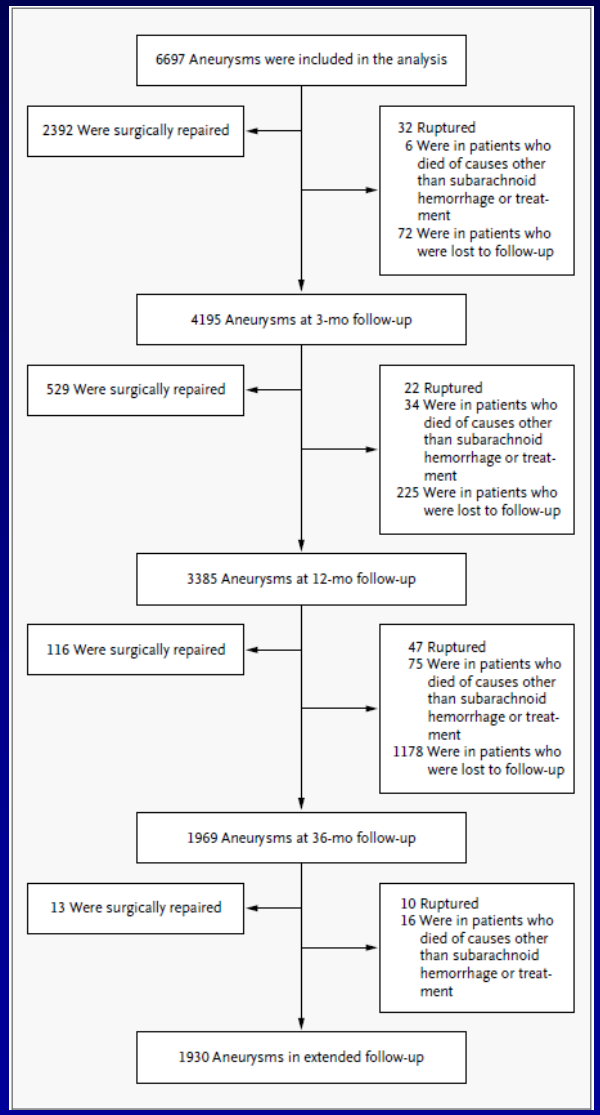
Unruptured Cerebral Aneurysms in a Japanese Cohort (UCAS)- NEJM, 2012

The Unruptured Cerebral Aneurysm Study of Japan*

Hypothesis: Unruptured cerebral aneurysms of 5mm or more rupture at an annual rate of more than 0.5%

Methods:

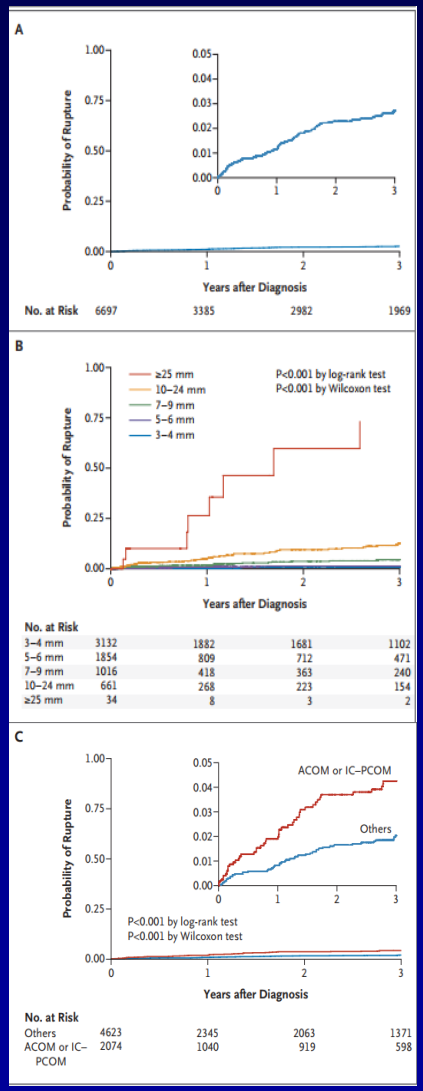
- 6413 patients >20 years of age with unruptured cerebral aneurysms >3mm identified; 5720 patients with 6697 aneurysms met eligibility criteria (fusiform and dissecting aneurysms were excluded)
- Follow-up data collected at 3, 12, and 36 months and at 5 and 8 years with clinical status assessed by mRS
- Data collection ended when the patient died or aneurysm ruptured (or the patient could no longer be followed)



*The UCAS Japan Investigators. NEJM 336(26):2474-2482, 2012.

The Unruptured Cerebral Aneurysm Study of Japan*

Probability of rupture:



Overall: 0.95% annual rate of rupture

Size

Location

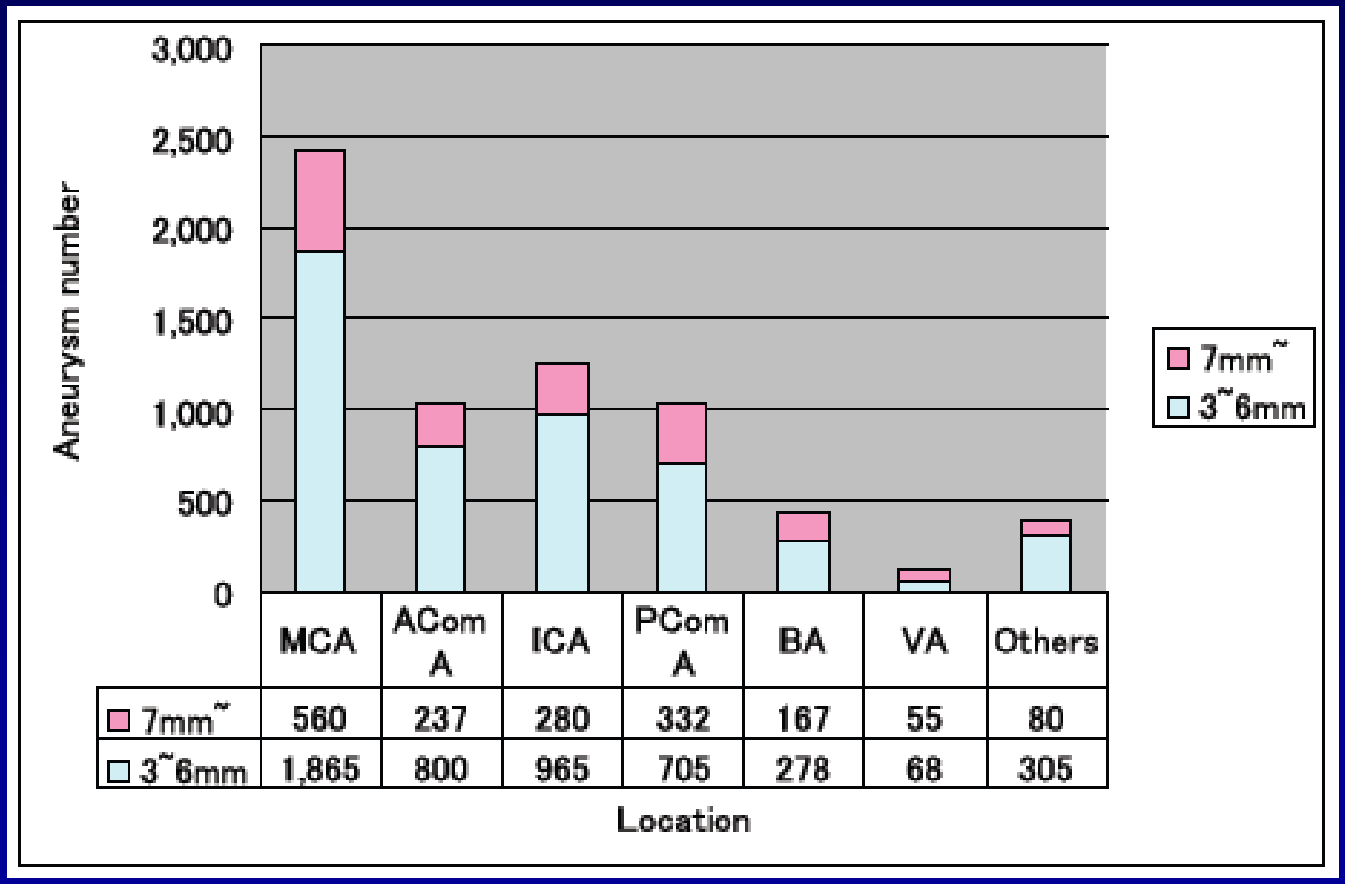
Table 3. Annual Rate of Rupture According to Size and Location of Aneurysm.

Location of Aneurysm	Rate of Rupture per Aneurysm per Year (95% CI)				
	3–4 mm	5–6 mm	7–9 mm	10–24 mm	≥25 mm
			percent		
Middle cerebral artery	0.23 (0.09–0.54)	0.31 (0.10–0.96)	1.56 (0.74–3.26)	4.11 (2.22–7.66)	16.87 (2.38–119.77)
Anterior communicating artery	0.90 (0.45–1.80)	0.75 (0.28–2.02)	1.97 (0.82–4.76)	5.24 (197–13.95)	39.77 (9.95–159.00)
Internal carotid artery	0.14 (0.04–0.57)	0	1.19 (0.30–4.77)	1.07 (0.27–4.28)	10.61 (1.49–75.3)
Internal carotid–posterior communicating artery	0.41 (0.15–1.10)	1.00 (0.37–2.66)	3.19 (1.66–6.12)	6.12 (1.66–6.13)	126.97 (40.95–393.68)
Basilar tip and basilar-superior cerebellar artery	0.23 (0.03–1.61)	0.46 (0.06–3.27)	0.97 (0.24–3.89)	6.94 (3.74–12.90)	117.82 (16.60–836.43)
Vertebral artery–posterior inferior cerebellar artery and vertebrobasilar junction	0	0	0	3.49 (0.87–13.94)	0
Other	0.78 (0.25–2.43)	1.37 (0.34–5.50)	0	2.81 (0.40–19.99)	0
Total	0.36 (0.23–0.54)	0.50 (0.29–0.84)	1.69 (1.13–5.93)	4.37 (3.22–5.93)	33.40 (16.60–66.79)

*The UCAS Japan Investigators. NEJM 336(26):2474-2482, 2012.

The Unruptured Cerebral Aneurysm Study of Japan*

Aneurysms:



	MCA	ACom A	ICA	PCom A	BA	VA	Others
7mm~	560	237	280	332	167	55	80
3~6mm	1,865	800	965	705	278	68	305

*The UCAS Japan Investigators. NEJM 336(26):2474-2482, 2012.

The Unruptured Cerebral Aneurysm Study of Japan*

Patients/Results:

- Size, specific location, and presence of a daughter sac were independent risk factors affecting the risk of rupture
- All aneurysms >7mm were at a significantly increased risk of rupture
- Acomm and Pcomm but not posterior circulation aneurysms were at a significantly increased risk of rupture
- Women and patients with hypertension had an increased risk of rupture
- Prior SAH, smoking history, family history, and the presence of multiple aneurysms were not associated with risk of rupture

Table 2. Risk Factors Associated with Rupture of Cerebral Aneurysms.*

Risk Factor	Hazard Ratio (95% CI)	P Value
Female sex	1.54 (0.99–2.42)	0.05
Age ≥70 yr	1.21 (0.81–1.78)	0.34
Hypertension	1.41 (0.96–2.07)	0.08
Hyperlipidemia	0.54 (0.28–1.03)	0.06
Daughter sac	1.63 (1.08–2.48)	0.02
Largest dimension of aneurysm		
3–4 mm	Reference	
5–6 mm	1.13 (0.58–2.22)	0.71
7–9 mm	3.35 (1.87–6.00)	<0.001
10–24 mm	9.09 (5.25–15.74)	<0.001
≥25 mm	76.26 (32.76–177.54)	<0.001
Location of aneurysm		
Middle cerebral artery	Reference	
Anterior communicating artery	2.02 (1.13–3.58)	0.02
Internal carotid artery	0.43 (0.18–1.01)	0.05
Internal carotid–posterior communicating artery	1.90 (1.12–3.21)	0.02
Basilar tip and basilar–superior cerebellar artery	1.49 (0.78–2.83)	0.23
Vertebral artery–posterior inferior cerebellar artery and vertebrobasilar junction	0.68 (0.16–2.87)	0.60
Other	1.48 (0.61–3.60)	0.39

*The UCAS Japan Investigators. NEJM 336(26):2474-2482, 2012.

UCAS-We are starting to see data of rupture in unruptured aneurysms stratified by size, site, irregular shape

Regarding size

- A glaring fact left unanswered- When patients present with aneurysmal SAH, 75% have lesions less than 10 mm
- Therefore- when unruptured lesions are small, they are less likely to bleed yet when aneurysms bleed, they are likely to be small!

TABLE 3. Literature Review, Proportion of Ruptured Aneurysms < 5 mm

Author	Publication year	Location	Patients	Enrollment start	Enrollment finish	<5 mm (%)
Lee[44]	2015	Korea	200	2012	2014	47
Froelich[27]	2016	Australia	131	2010	2015	49
Dolati[28]	2015	Canada	123	2008	2012	37
Zhao[29]	2014	China	766	2006	2013	51
Kashiwazaki[16]	2013	Japan	851	2003	2011	28
Tahir[17]	2009	Pakistan	55	2004	2007	24
Nahed[19]	2005	USA	152	2001	2004	33
Taylor[20]	2004	USA	127	1998	1999	33
Forget[21]	2001	USA	245	1996	2000	35
Shiue[22]	2011	Australia	432	1995	1998	22
ISAT[25]	2002	Intl	2143	1994	1997	52
Horiuchi[23]	2006	Japan	2577	1988	2002	39
Osawa[24]	2001	Japan	2055	1988	1998	38
Ohashi[18]	2004	Japan	280	1984	2001	26
Inagawa[45]	2010	Japan	285	1980	1998	24
Kassell[12]	1983	Intl	676	1980	1987	13
Rosenorn[13]	1993	Denmark	908	1978	1983	18
Sundt[14]	1982	USA	644	1969	1981	23
Mccormick[15]	1970	USA	54	1970	1970	4

*Bender et al. Neurosurgery 0(0):1-8, 2017.

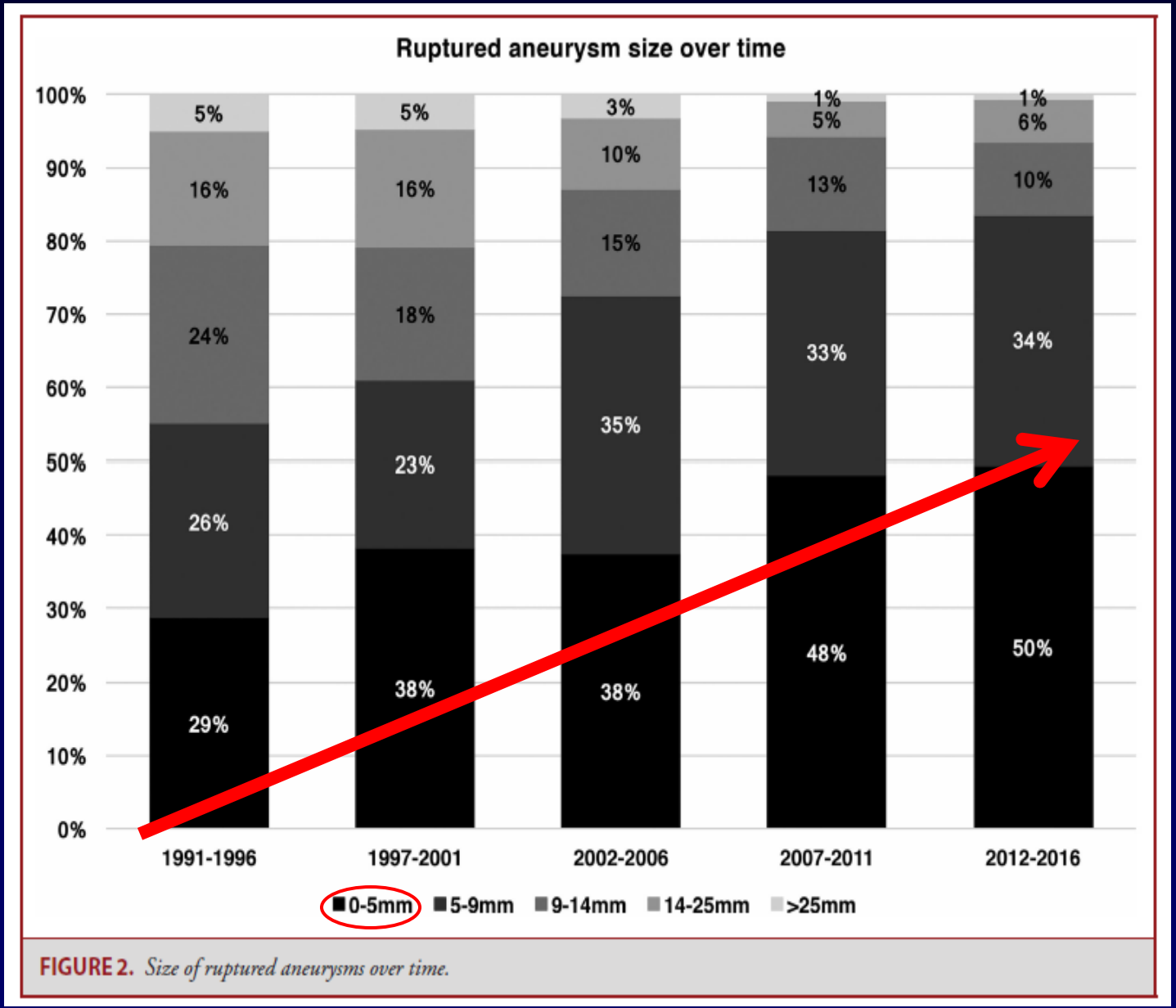
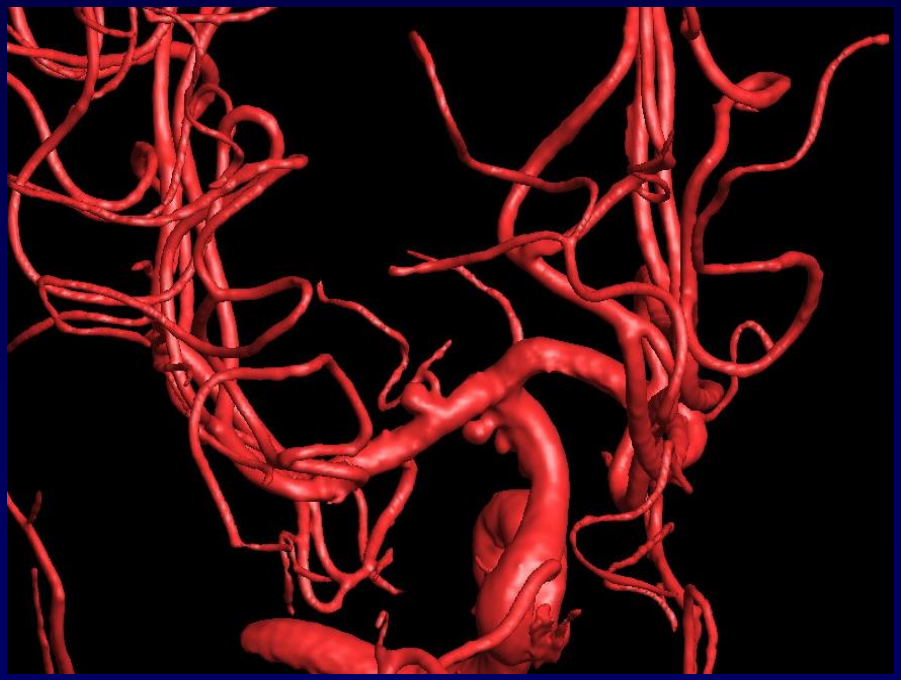
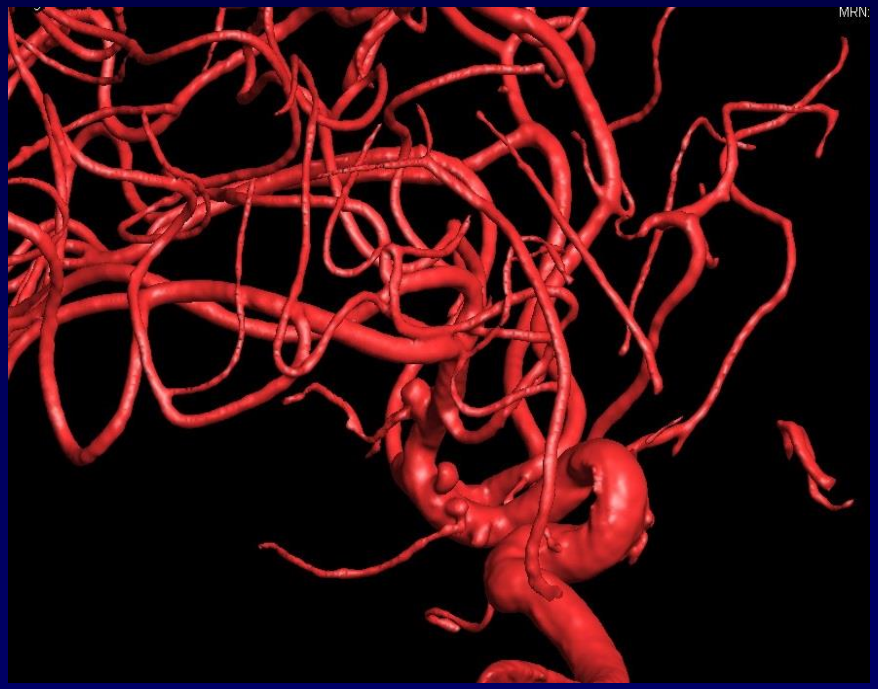


FIGURE 2. *Size of ruptured aneurysms over time.*

*Bender et al. Neurosurgery 0(0):1-8, 2017.

Multiple, small aneurysms in 50 year old woman with strong family history of aneurysmal SAH





Multiple aneurysms

- Does a patient with 3 unruptured aneurysms have triple the risk of hemorrhage?
  - The risk is probably increased, but by how much is not known
  - If one has hemorrhaged, the patient is often motivated to treat other lesions regardless of size

REMEMBER!

- 75% of all ruptured aneurysms that present for treatment are smaller than 10mm
- *DARN IT!, THE OFFICE VISIT FOR THE 5 MM UNRUPTURED ANEURYSM HAS JUST BECOME AN HOUR!*

PHASES score

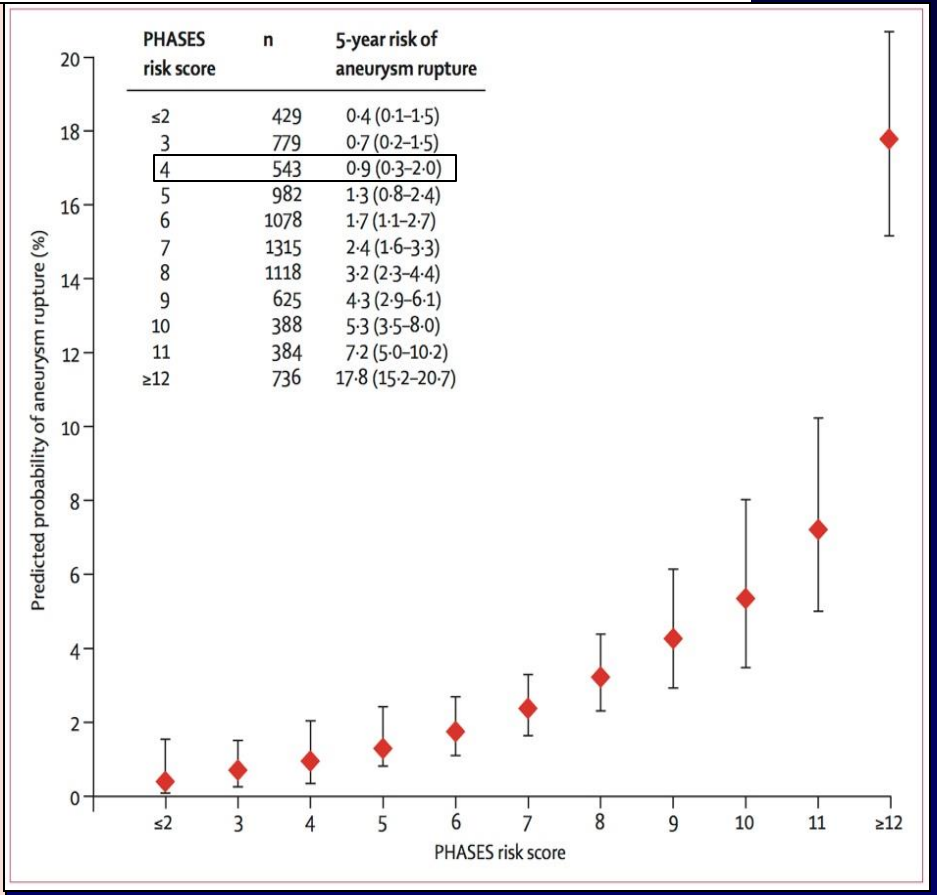
Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies

Lancet Neurol 2014; 13: 59–66

Published Online
November 27, 2013
http://dx.doi.org/10.1016/
S1474-4422(13)70263-1

Jacoba P Greving, Marieke J H Wermer, Robert D Brown Jr, Akio Morita, Seppo Juvela, Masahiro Yonekura, Toshihiro Ishibashi, James C Torner, Takeo Nakayama, Gabriël J E Rinkel, Ale Algra

PHASES aneurysm risk score	Points
(P) Population	
North American, European (other than Finnish)	0
Japanese	3
Finnish	5
(H) Hypertension	
No	0
Yes	1
(A) Age	
<70 years	0
≥70 years	1
(S) Size of aneurysm	
<7·0 mm	0
7·0–9·9 mm	3
10·0–19·9 mm	6
≥20 mm	10
(E) Earlier SAH from another aneurysm	
No	0
Yes	1
(S) Site of aneurysm	
ICA	0
MCA	2
ACA/Pcom/posterior	4



THE PSYCHOLOGY OF UNRUPTURED ANEURYSMS

‘ANXIETY’ OVER UNRUPTURED ANEURYSMS

- Patient anxiety –
  - Many hours spent in clinic reducing anxiety- particulary for 1-4 mm “aneurysms”(outpouchings, irregularities, etc)
  - Family history
- Physician anxiety – primary care physician, emergency room physician, others (“we learned in med school aneurysms are dangerous”)

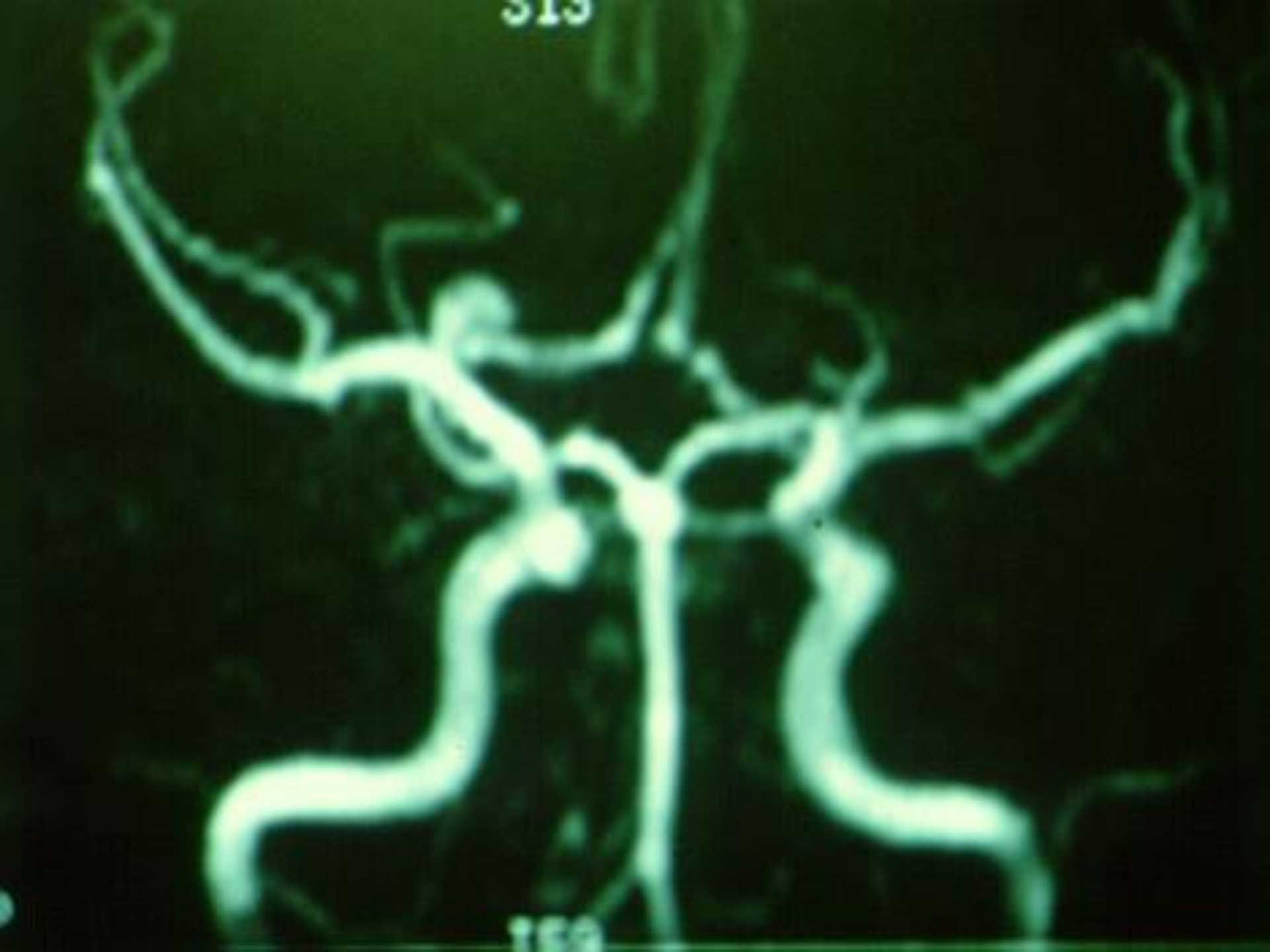
Modifiers of hemorrhage risk (natural history)

- Anatomic factors- Lesion specific factors
  - Size
  - Location
  - Lobularity (irregular shape)
  - Multiplicity of lesions (???)
- Patient specific factors
  - Age -Younger age-longer life horizon
  - Family history
  - Ethnicity
  - Anxiety
  - Smoking

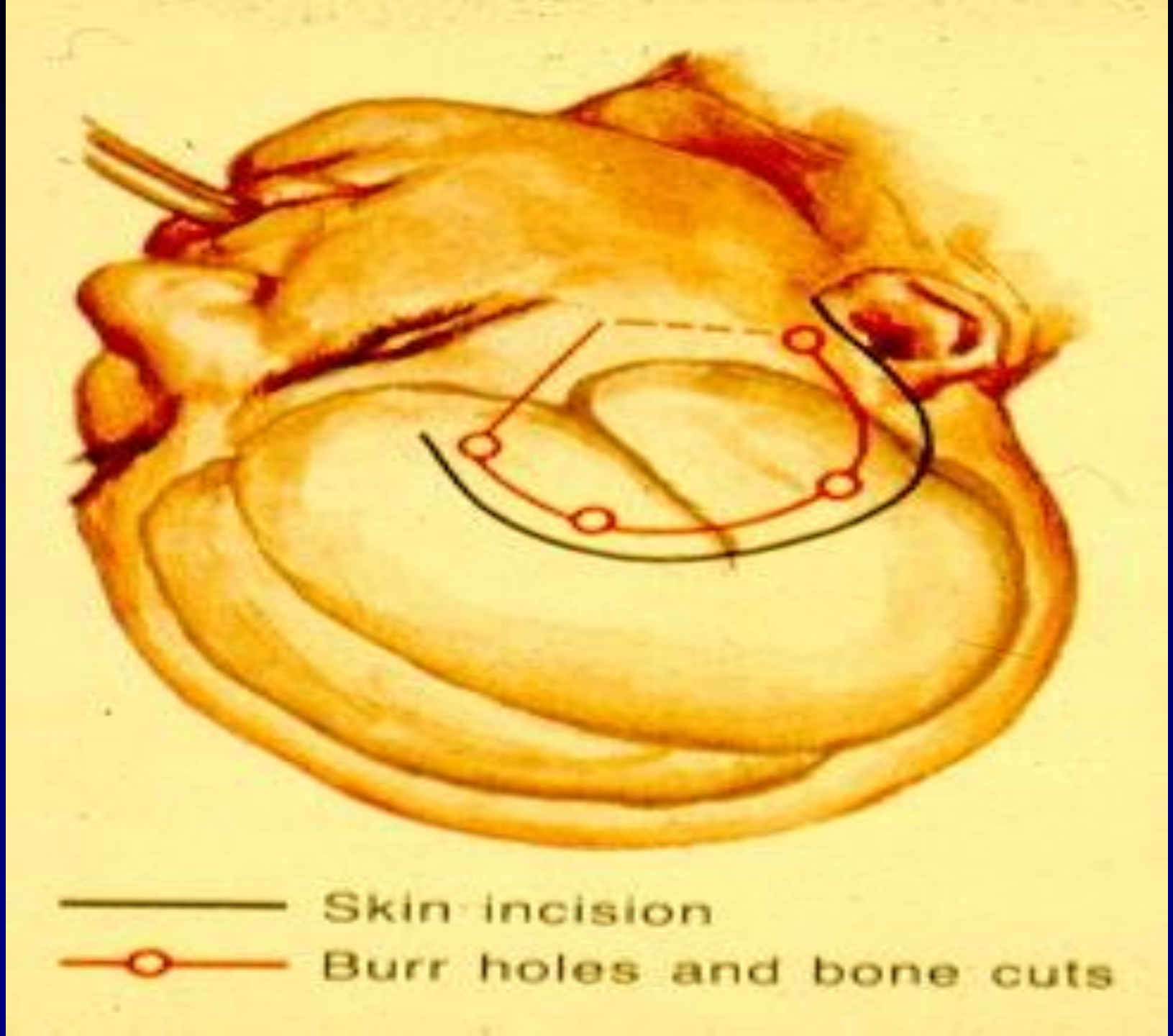
TREATMENT RELATED RISKS FOR UNRUPTURED INTRACRANIAL ANEURYSMS

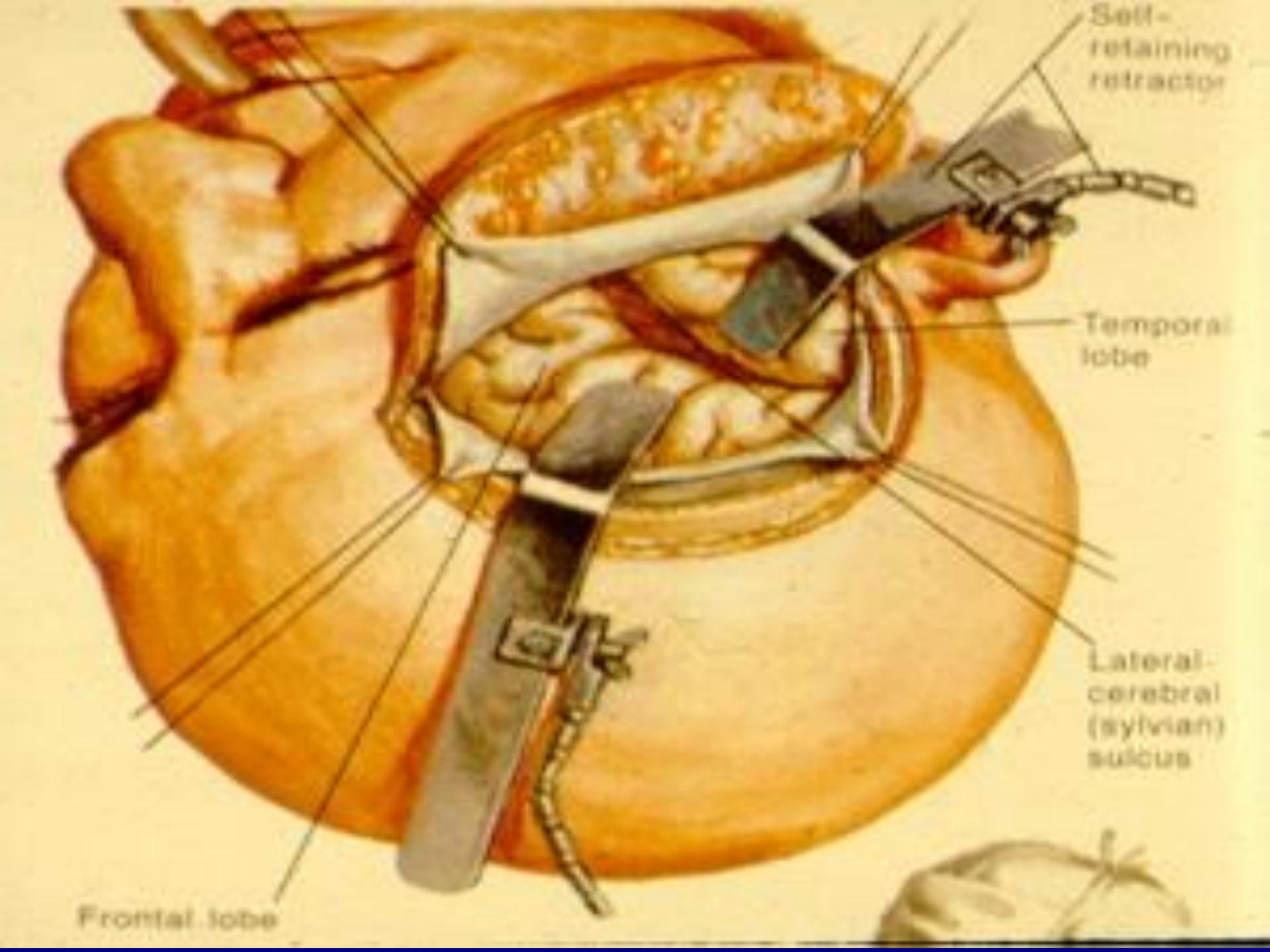
Types of treatment

- Open surgery (craniotomy)
  - Clipping
  - Bypass surgery
- Endovascular
  - Coiling
  - Stent assisted coiling
  - Other endosaccular devices
  - Flow diversion

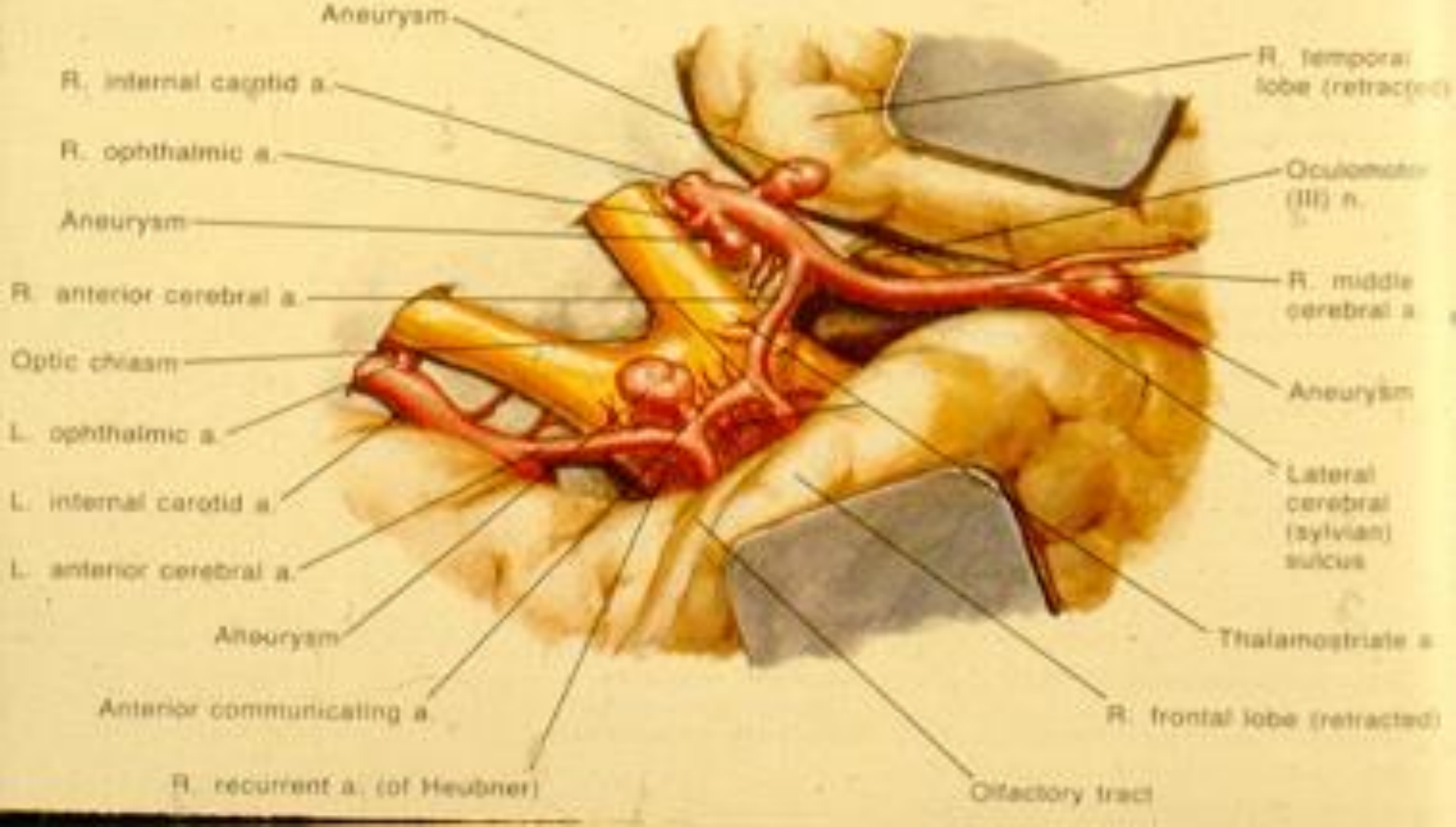


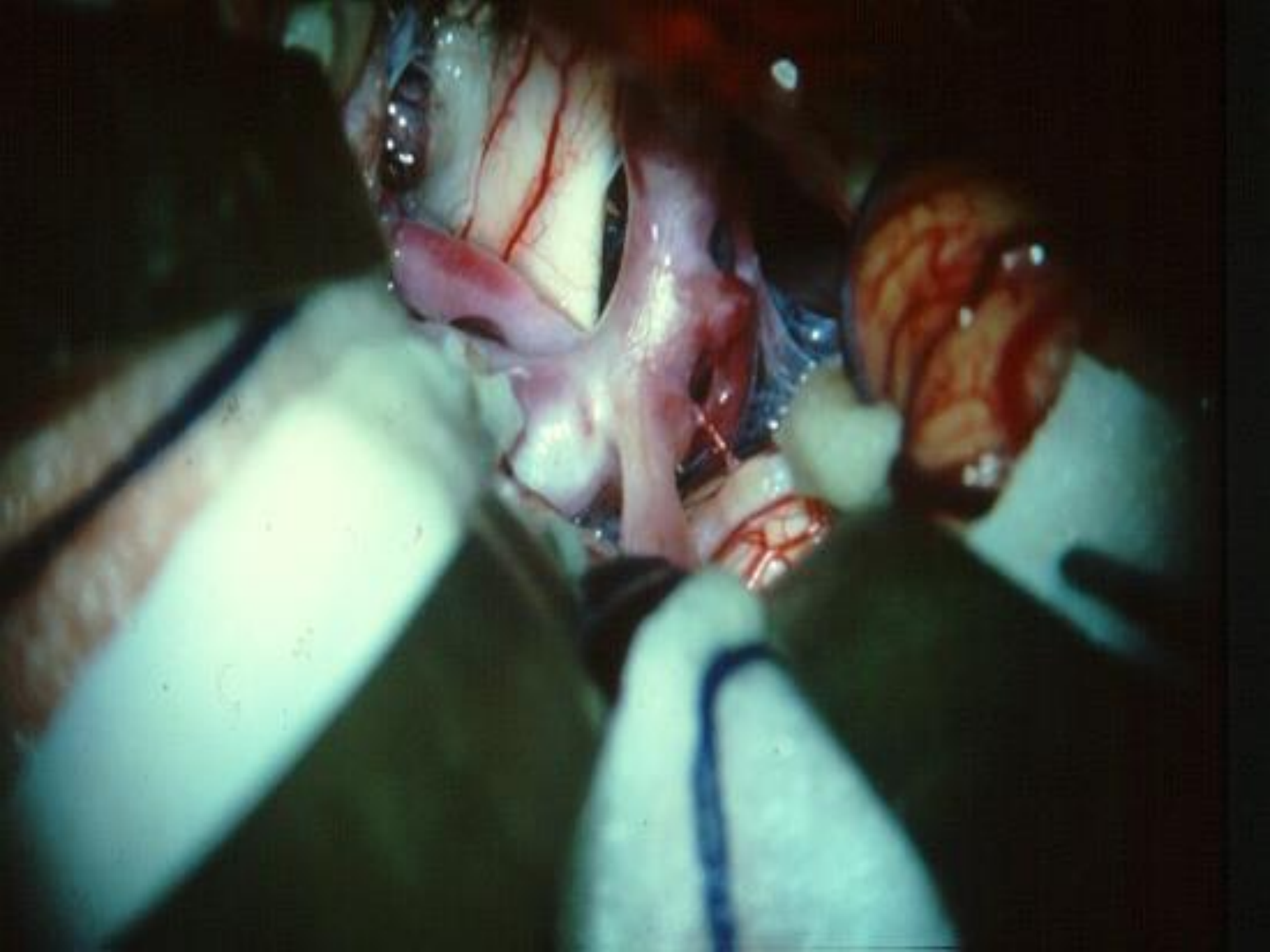

II
MASSACHUSETTS GENERAL HOSPITAL *PR-24*

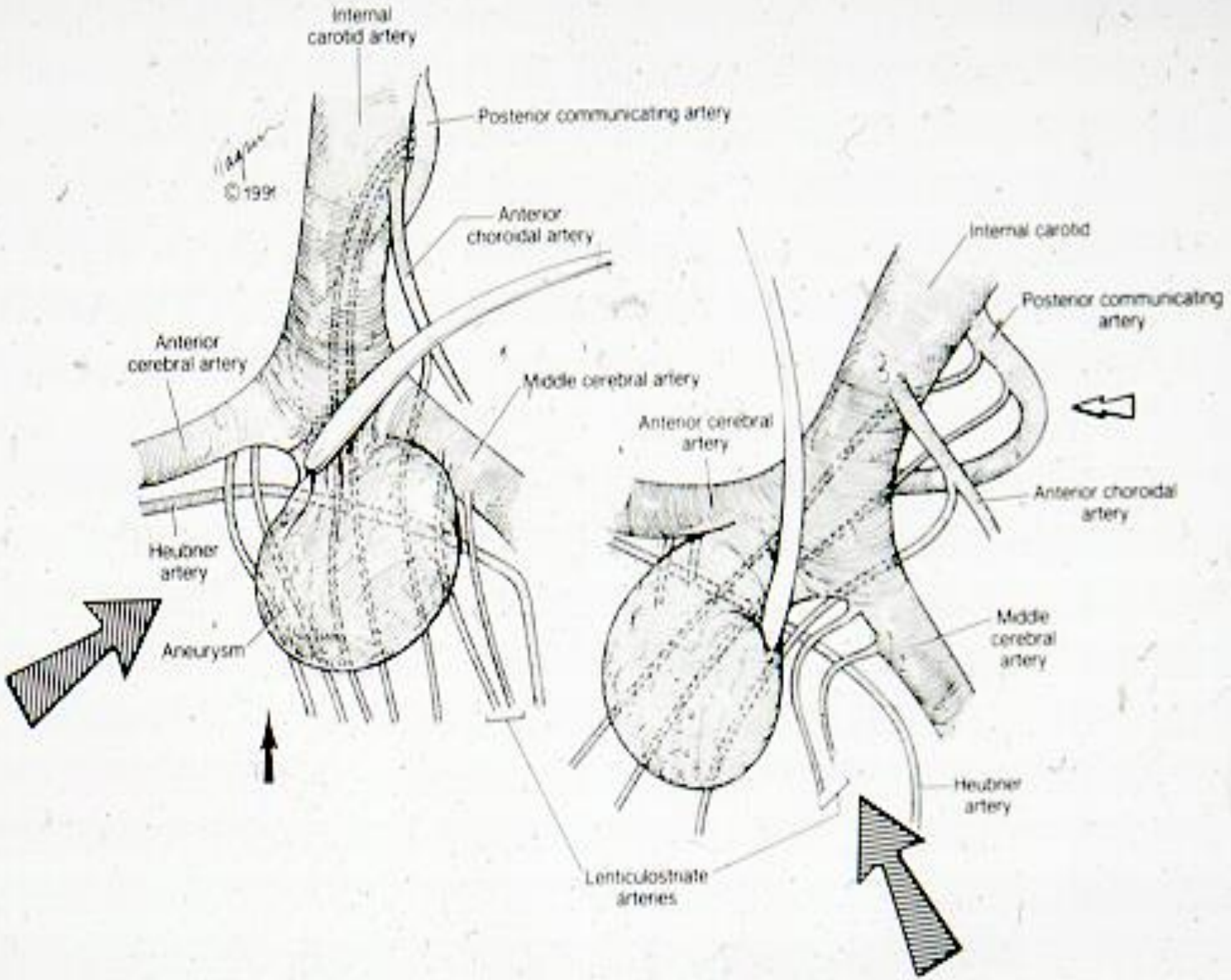

Skin incision
Burr holes and bone cuts

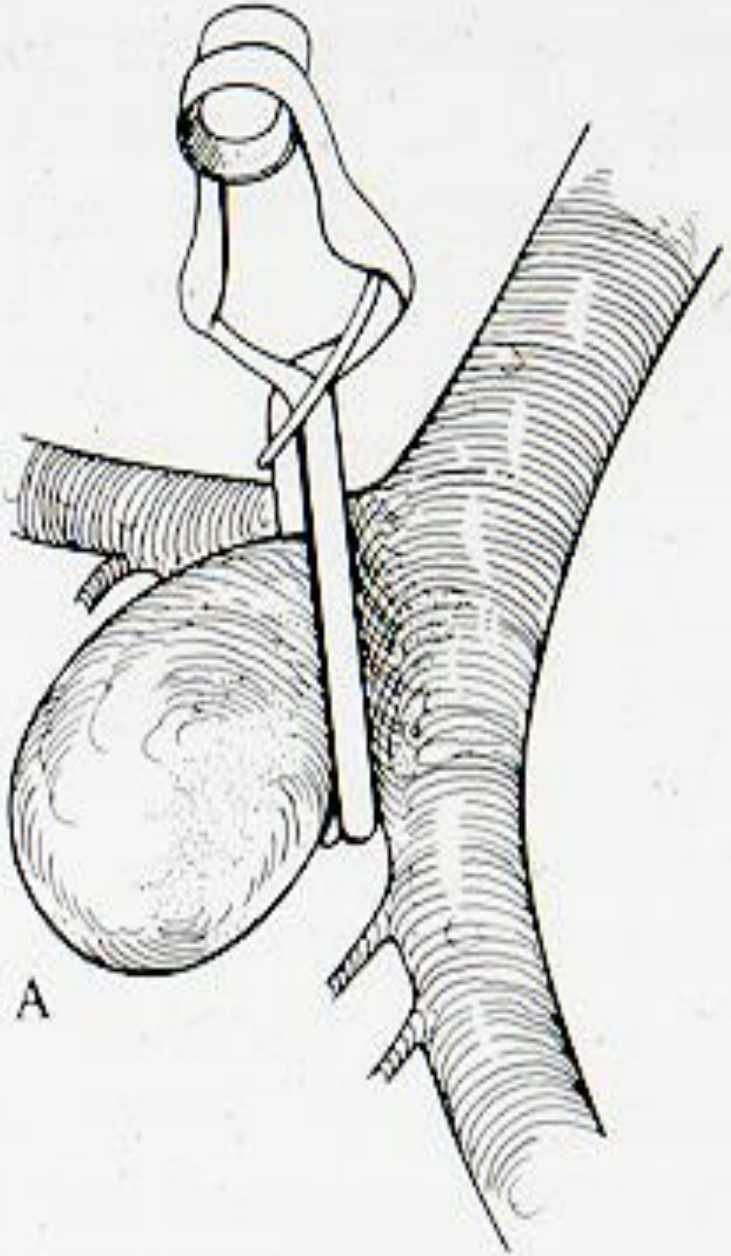

Self-retaining retractor
Temporal lobe
Lateral cerebral (sylvian) sulcus
Frontal lobe


Operating
microscope


Aneurysm
R. internal caotid a.
R. ophthalmic a.
Aneurysm
R. anterior cerebral a.
Optic chiasm
L. ophthalmic a.
L. internal carotid a.
L. anterior cerebral a.
Aneurysm
Anterior communicating a.
R. recurrent a. (of Heubner)
R. tempora
lobe (retrac
Oculomoto
(III) n.
R. middle
cerebral a.
Aneurysm
Lateral
cerebral
(sylvian)
sulcus
Thalamostriate a.
R. frontal lobe (retracted)
Olfactory tract




Internal carotid artery
Posterior communicating artery
© 199
Anterior choroidal artery
Anterior cerebral artery
Middle cerebral artery
Heubner artery
Aneurysm
Internal carotid
Posterior communicating artery
Anterior cerebral artery
Anterior choroidal artery
Middle cerebral artery
Heubner artery
Lenticulostriate arteries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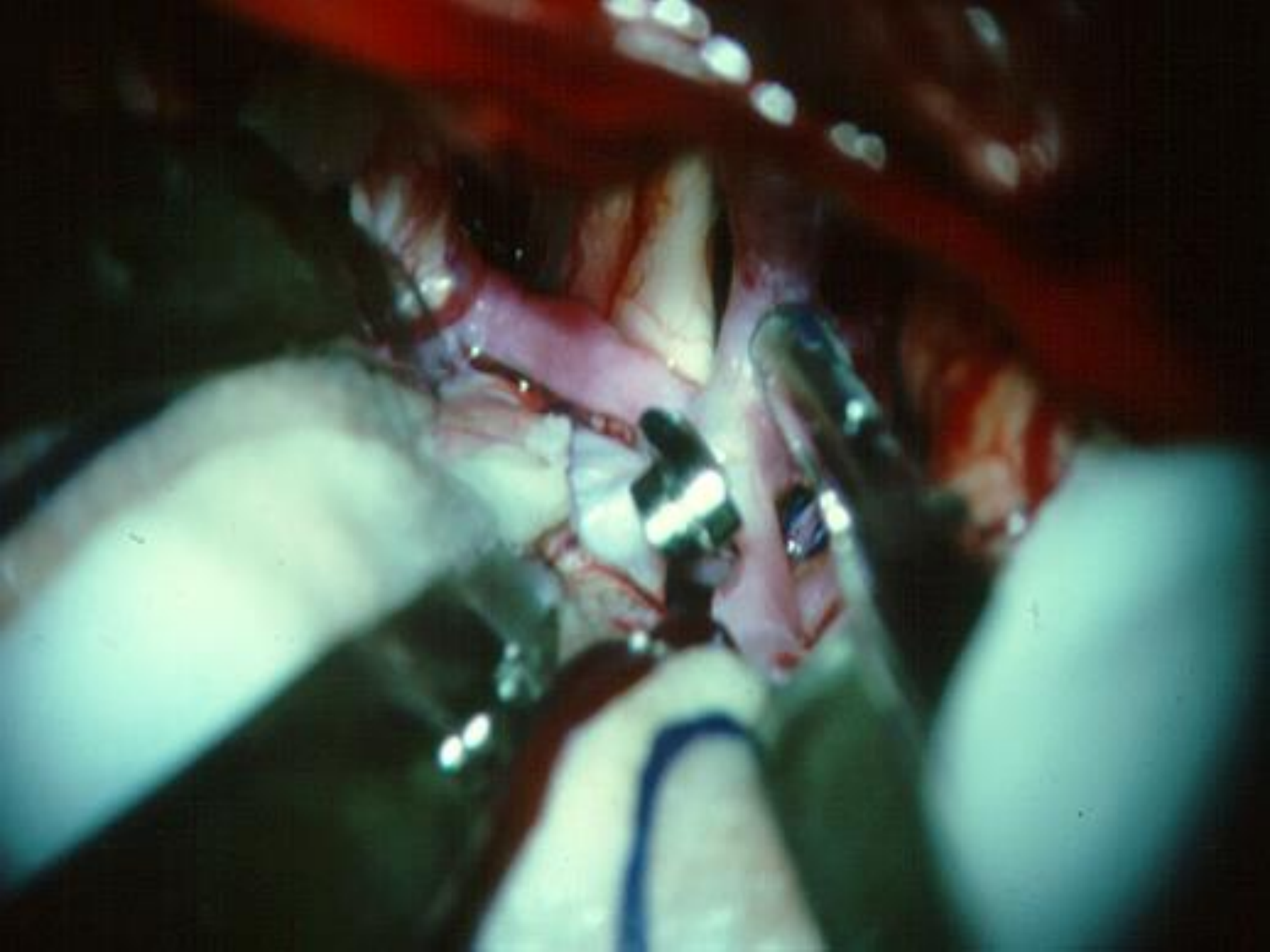
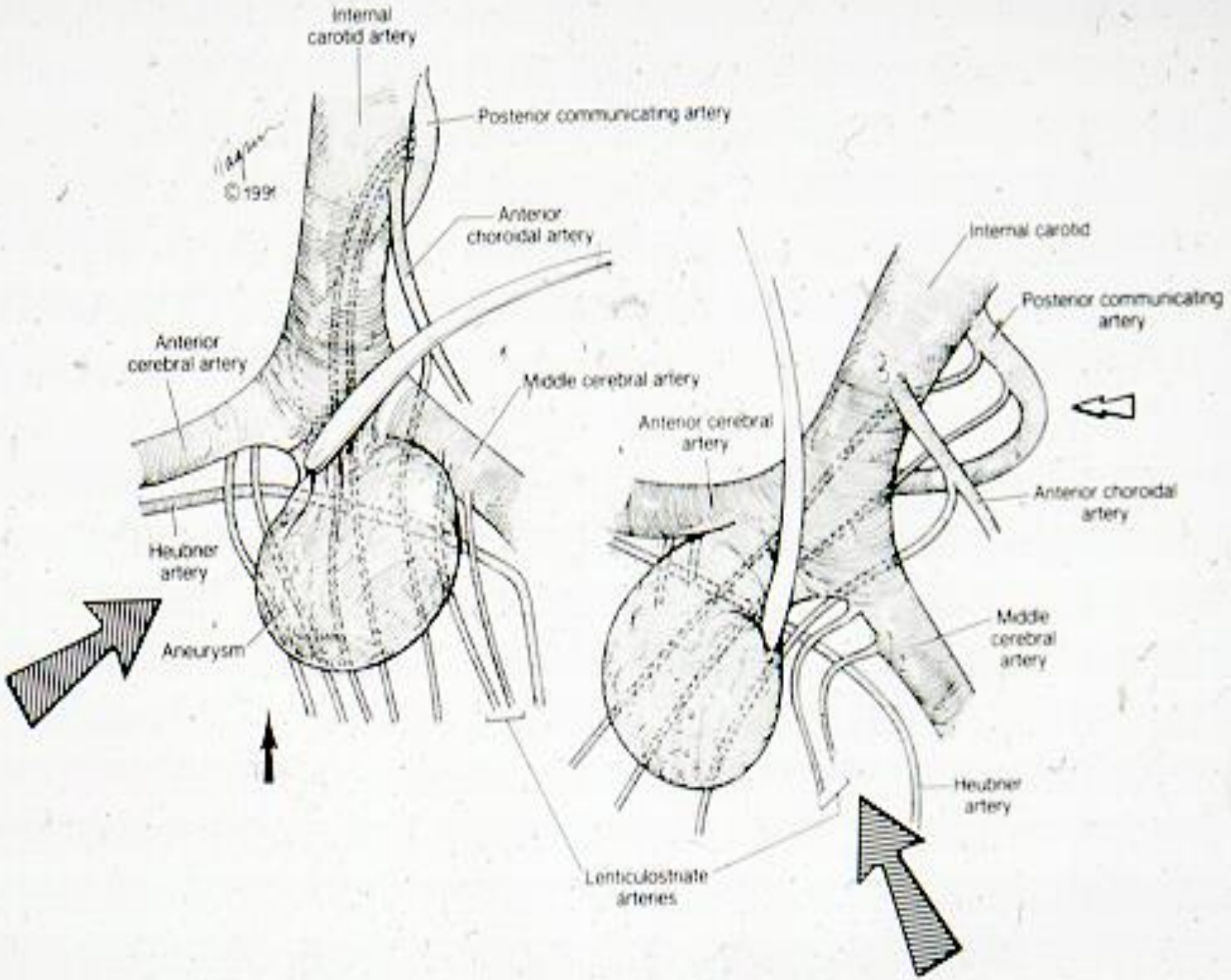
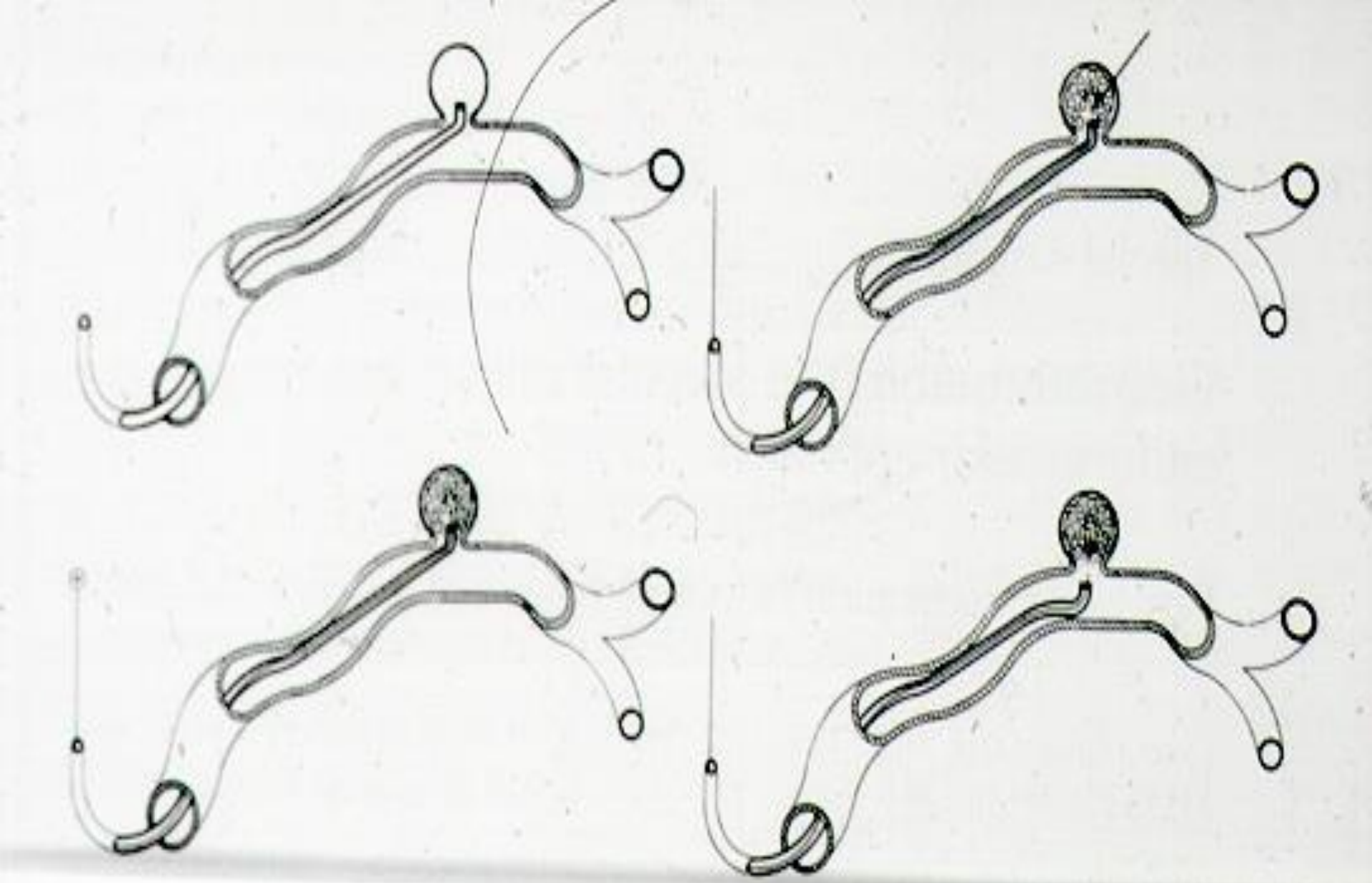
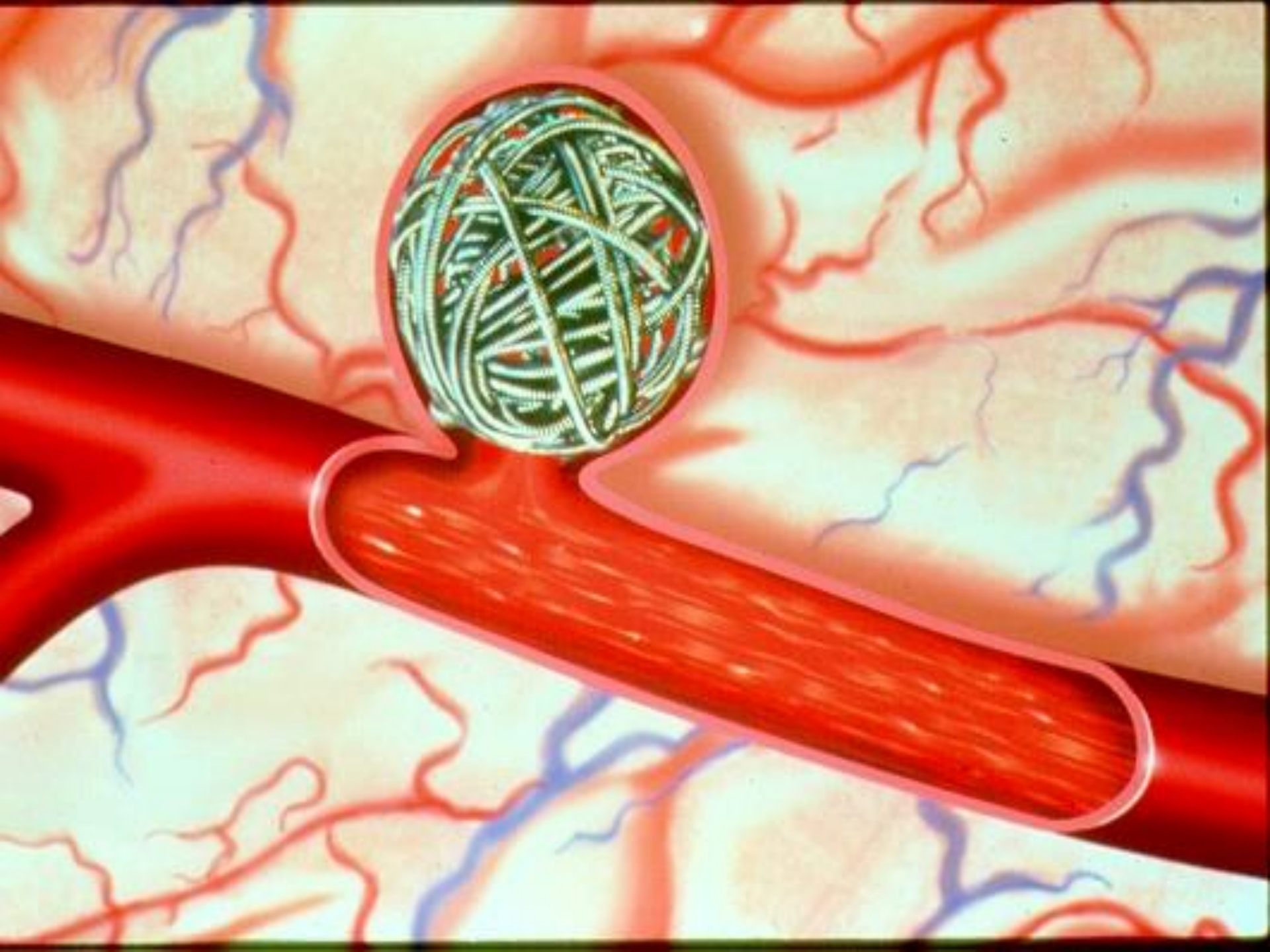



Internal carotid artery
Posterior communicating artery
© 199
Anterior choroidal artery
Anterior cerebral artery
Middle cerebral artery
Heubner artery
Aneurysm
Internal carotid
Posterior communicating artery
Anterior cerebral artery
Anterior choroidal artery
Middle cerebral artery
Heubner artery
Lenticulostriate arteries

Endovascular treatments of aneurysms

Intra-aneurysmal coiling





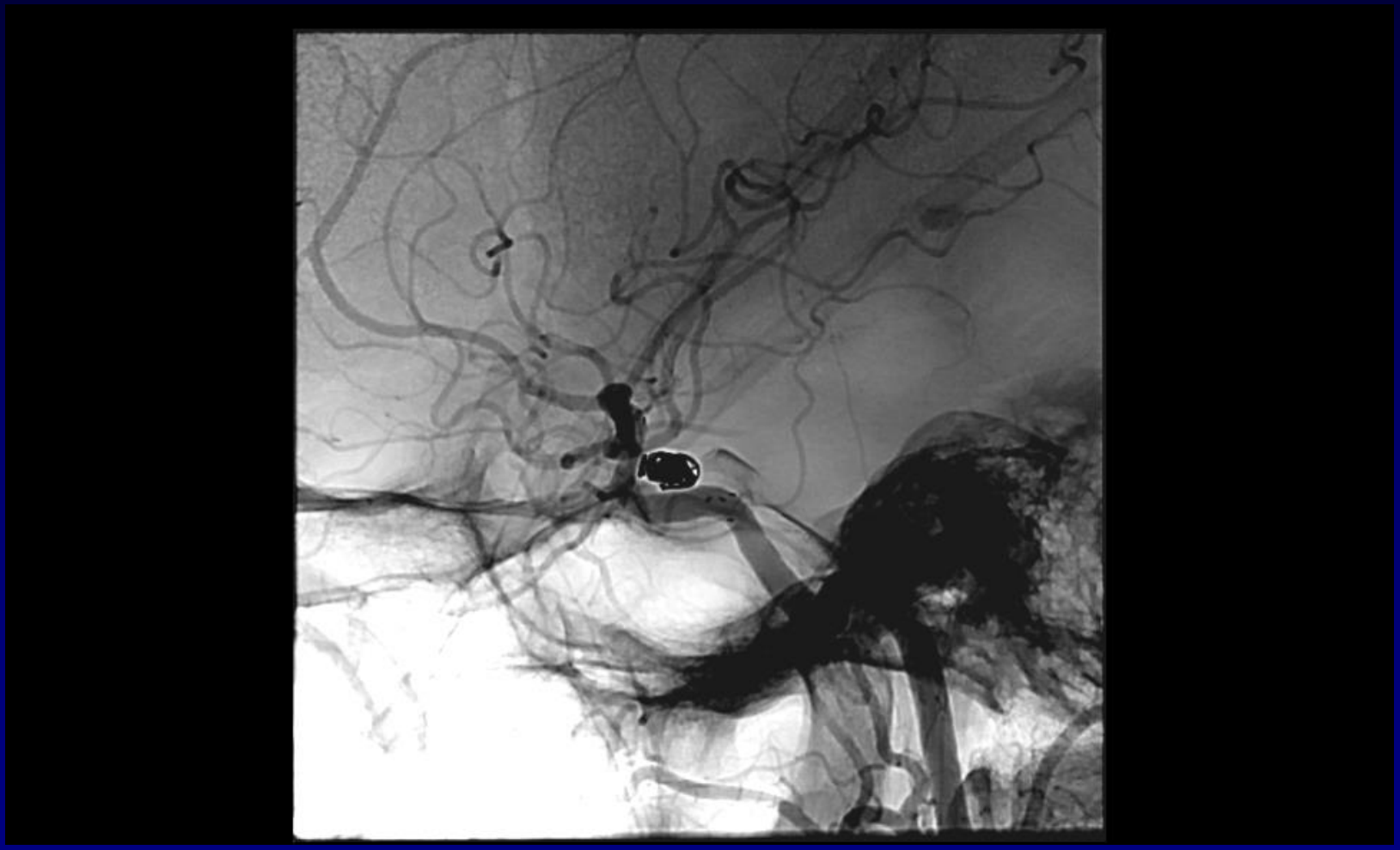
Endovascular Coiling

Endovascular Coiling

Stent-Assisted Coiling

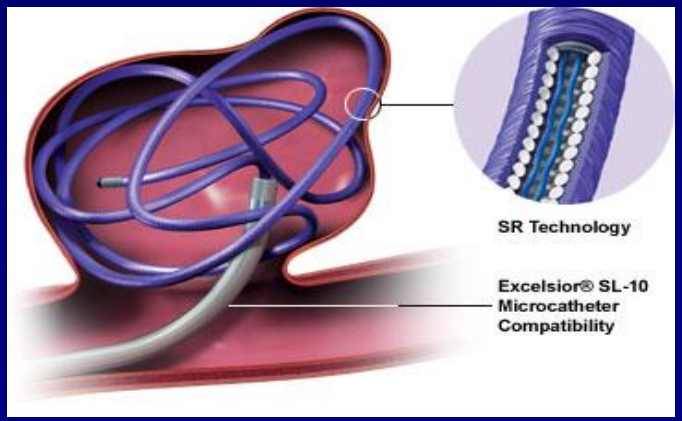
www.bostonscientific.com

Aneurysm-stent and coiled



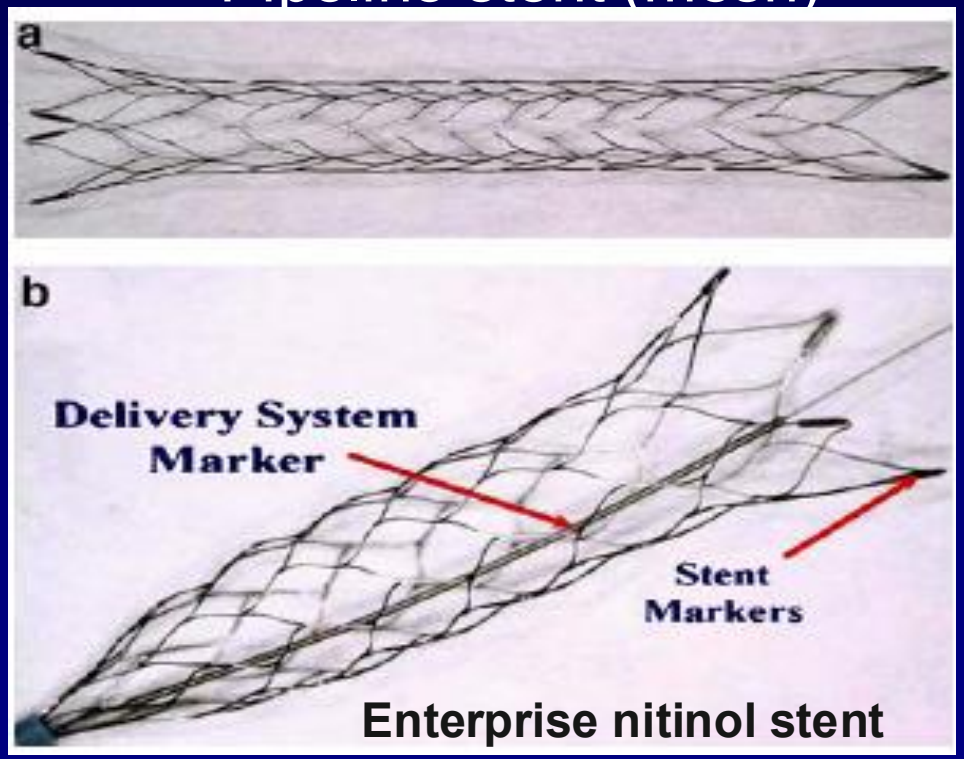
Advances in neurovascular disease over the past 20 years: MATERIALS/ENGINEERING

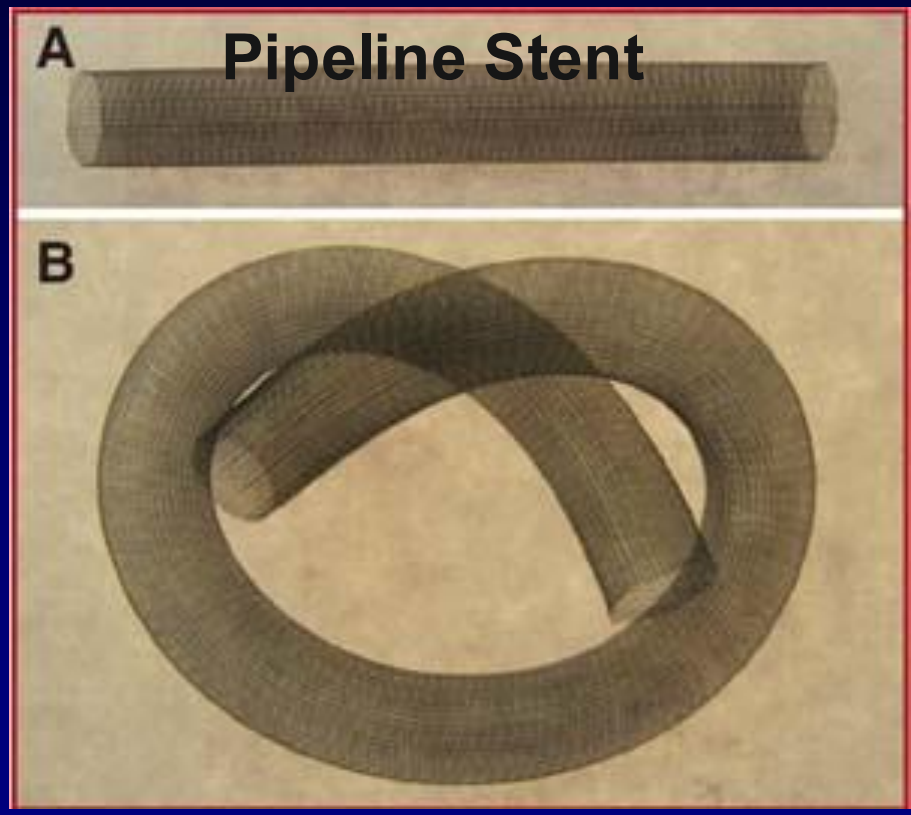
2. Materials/engineering
   - Embolization glue agents
   - Clot retrieval
   - Coils
     - Complex shape
     - Coated coils



Advances in neurovascular disease over the past 20 years: MATERIALS/ENGINEERING

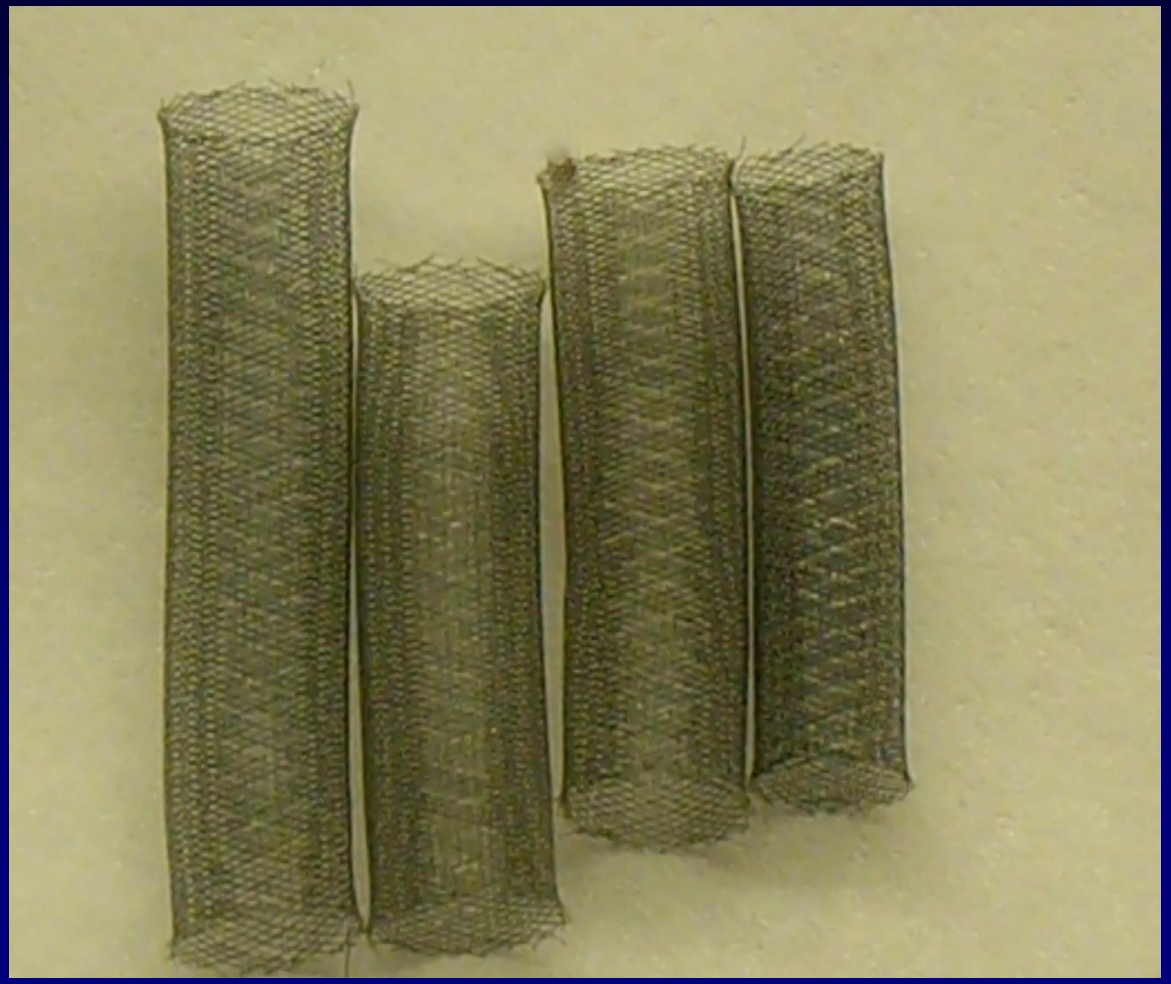
2. Materials/engineering
   - Stents
     - Pipeline stent (mesh)



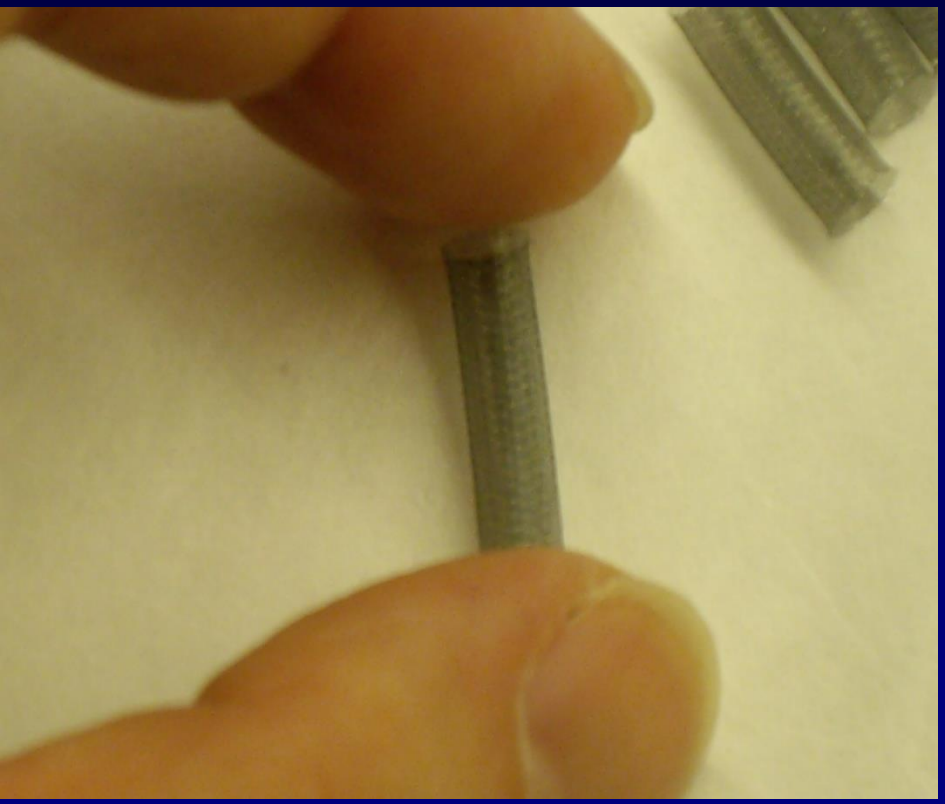


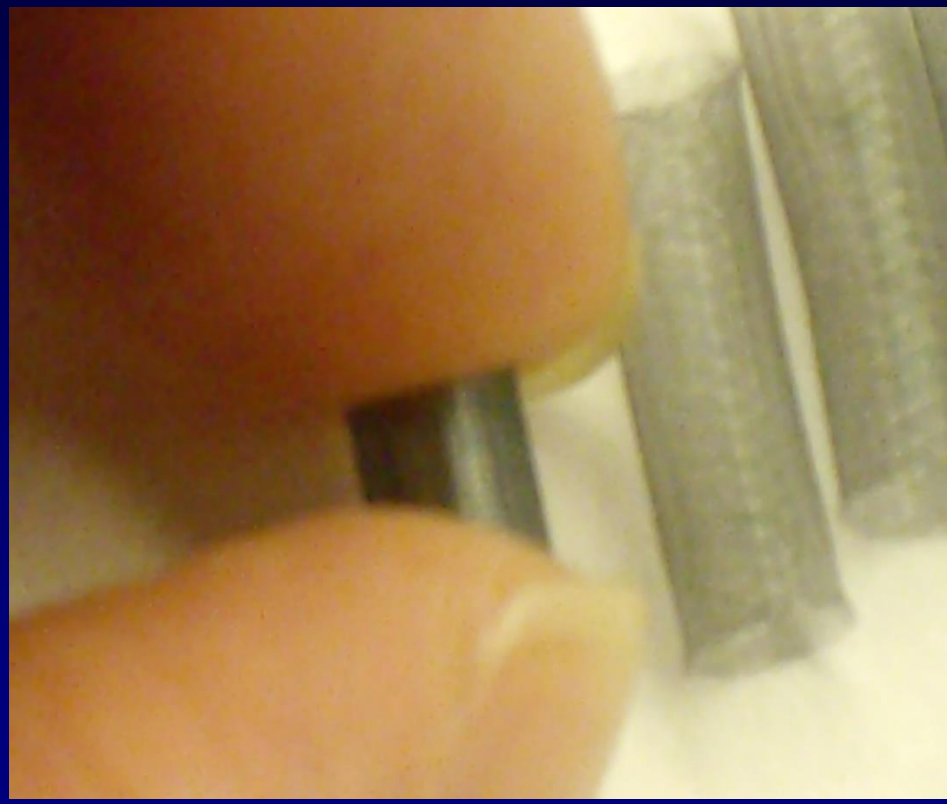
Flow diversion for aneurysmal treatment/thrombosis

Pipeline endovascular device

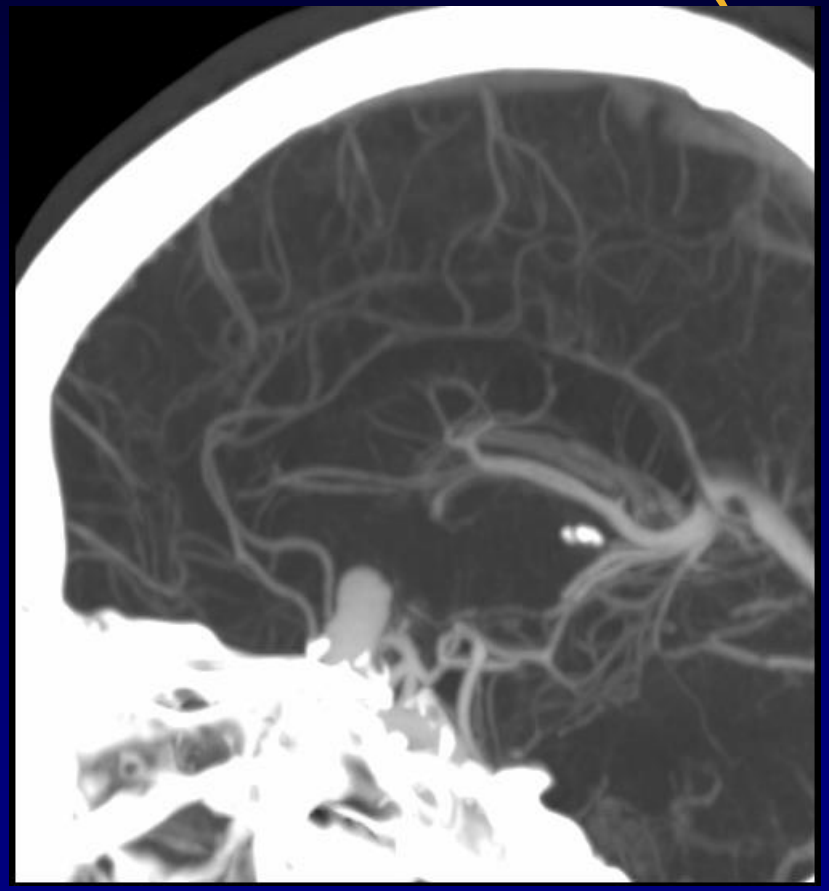


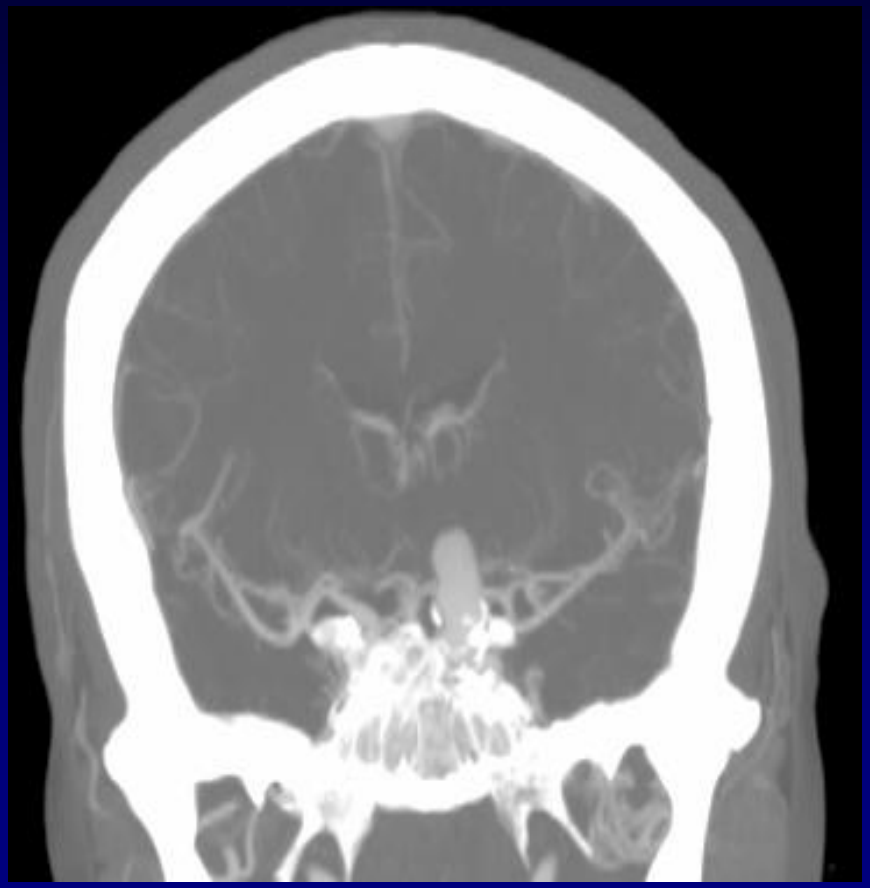
Pipeline endovascular device



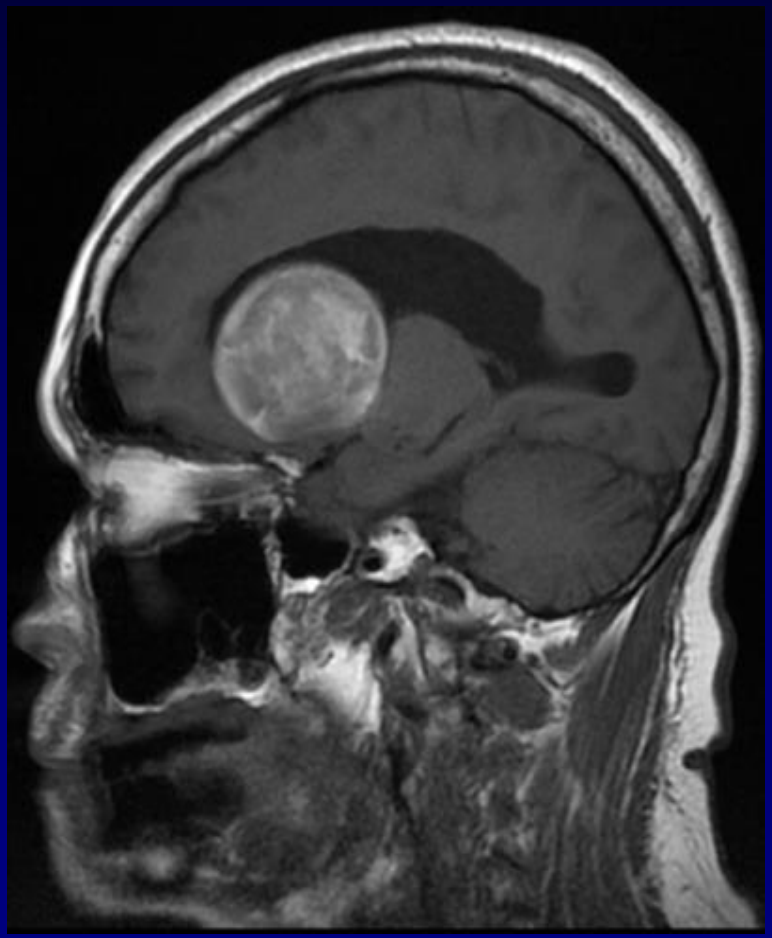


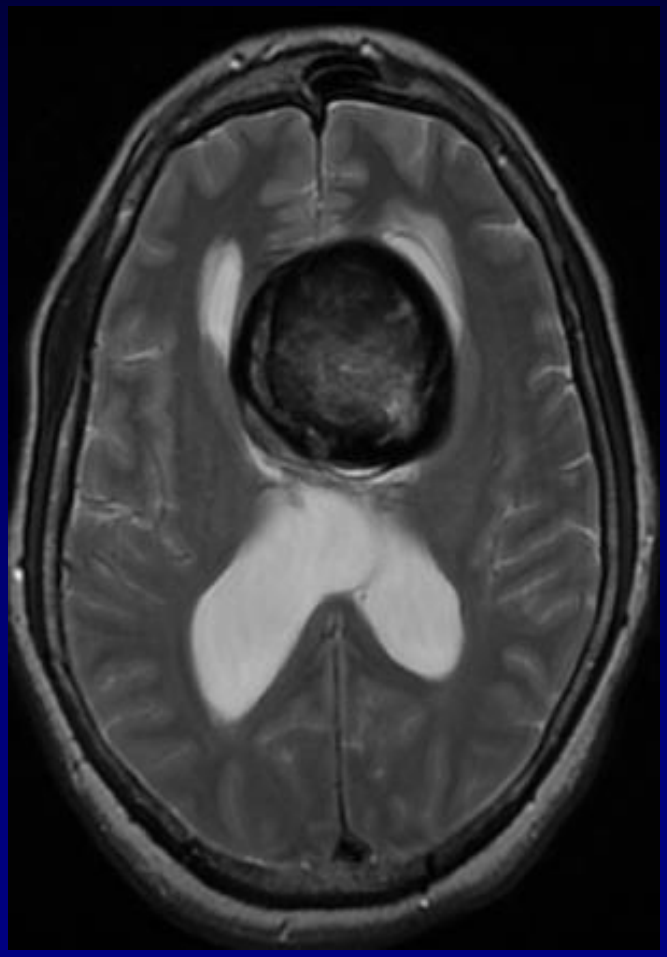
51 Year old with headaches (2004)



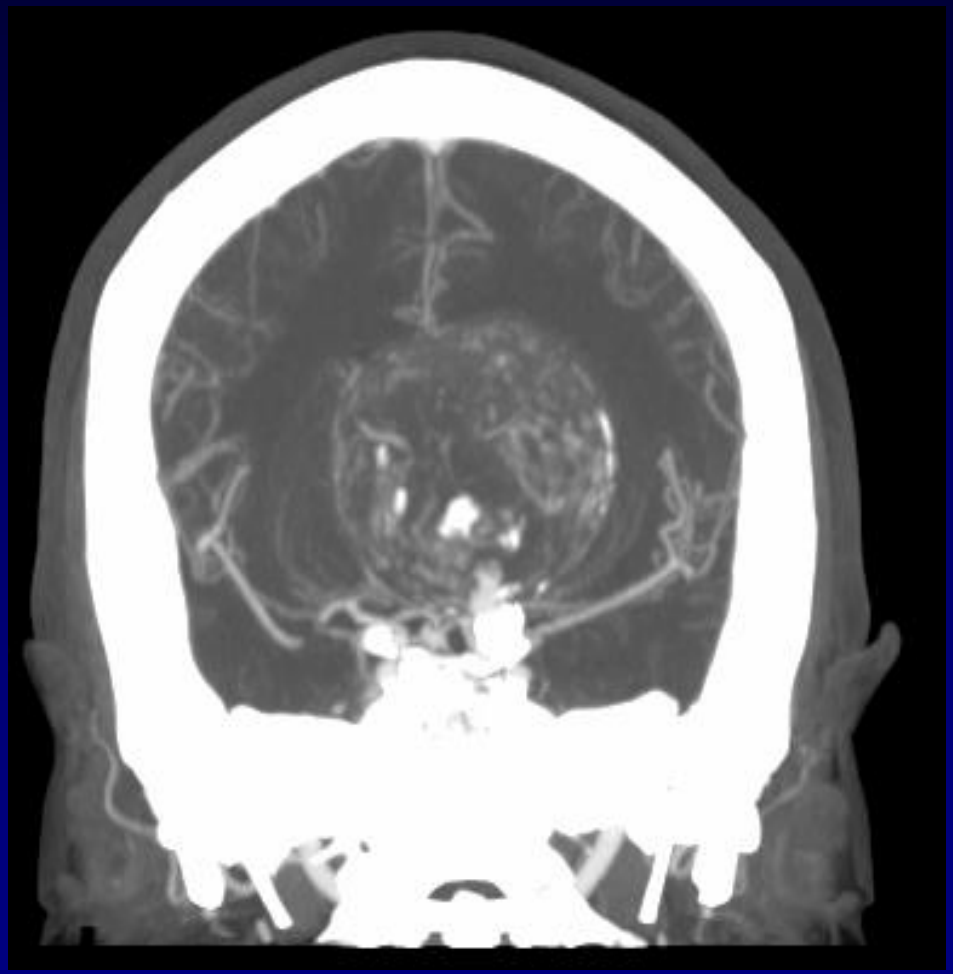


2010- Pt with gait difficulty and hydrocephalus





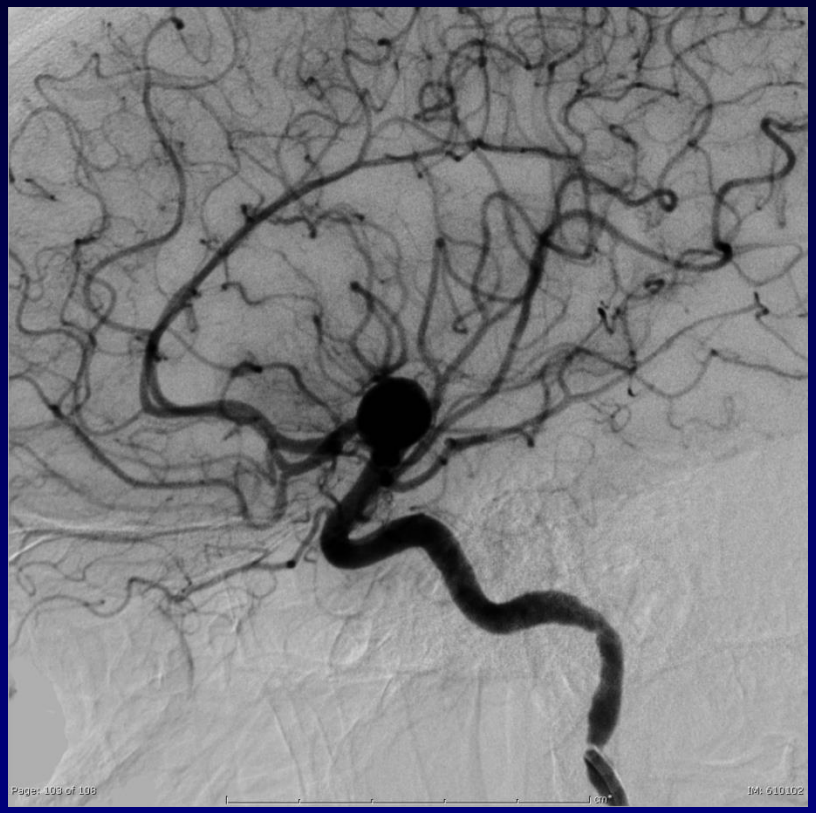
CTA after shunt placement and symptom resolution



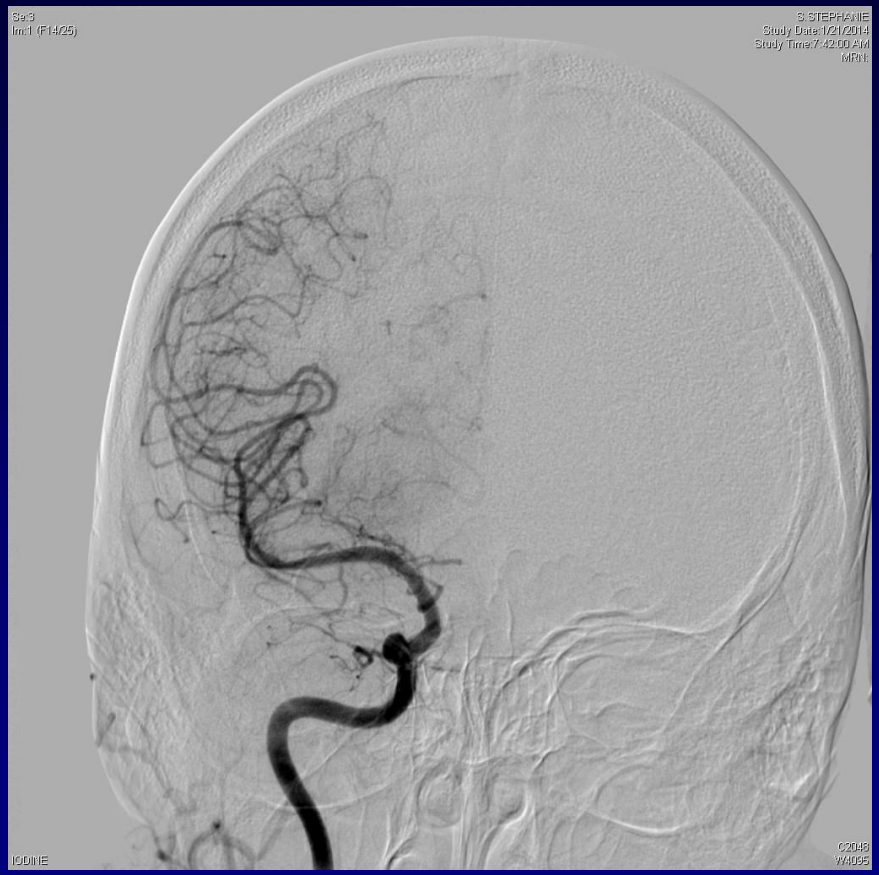
Pre treatment angiogram

3 months post 2 pipeline devices

42 year old- growing aneurysm pre-op



6 months after flow diversion



TREATMENT RISKS

- Patient specific factors:
  - Age
  - Medical comorbidities
- Lesion specific factors:
  - Size
  - Location
  - Calcification
  - Local anatomy details (parent vessel, perforators)

Treatment Risk
Changing the risk landscape…

- As with natural history, ***THERE IS STRATIFICATION OF TREATMENT RELATED RISKS***
- Highly specific treatment selection of surgical or endovascular therapy can be used based on patient and aneurysm characteristics.
- Treatment risk is not static, but changes as specialty progresses…

In each unruptured aneurysm patient encountered, an analysis can be done incorporating lesion and patient specific factors

Decision to treat unruptured aneurysm

Previous studies of treatment related risks for unruptured aneurysms

- Most reports are of surgical *or* endovascular outcomes
- Often couched in terms of 'clip vs coil' or surgery vs endovascular
- True combined modality management outcomes are scarce

ORIGINAL ARTICLE
WORLD NEUROSURGERY ■: E1-E10, ■ 2019
https://doi.org/10.1016/j.wneu.2019.03.005

Surgical and Endovascular Comprehensive Treatment Outcomes of Unruptured Intracranial Aneurysms: Reduction of Treatment Bias

Christopher S. Ogilvy, Noah J. Jordan, Luis C. Ascanio, Alejandro A. Enriquez-Marulanda, Mohamed M. Salem, Justin M. Moore, Ajith J. Thomas

658 aneurysms in 553 patients treated between 2014-2017- Endovascular AND Surgical treatment;
950 patients evaluated during this inteval and offered no treatment

Patient population

- 658 aneurysms in 553 patients treated between 2014-2017 at BIDMC
- Techniques used
  - Open surgical techniques (mostly direct clipping)
  - Endovascular techniques
    - Direct coiling
    - Stent assisted coiling
    - Balloon assisted coiling
    - Flow diversion

Treatment modality

- Chosen based on predicted risk for that patient (aneurysm specific and patient specific risks) for endovascular or surgical obliteration
- ‘Selection bias’- During this interval of treatment 950 patients were evaluated with unruptured lesions and were not treated based on aneurysm size, patient comorbidity or age

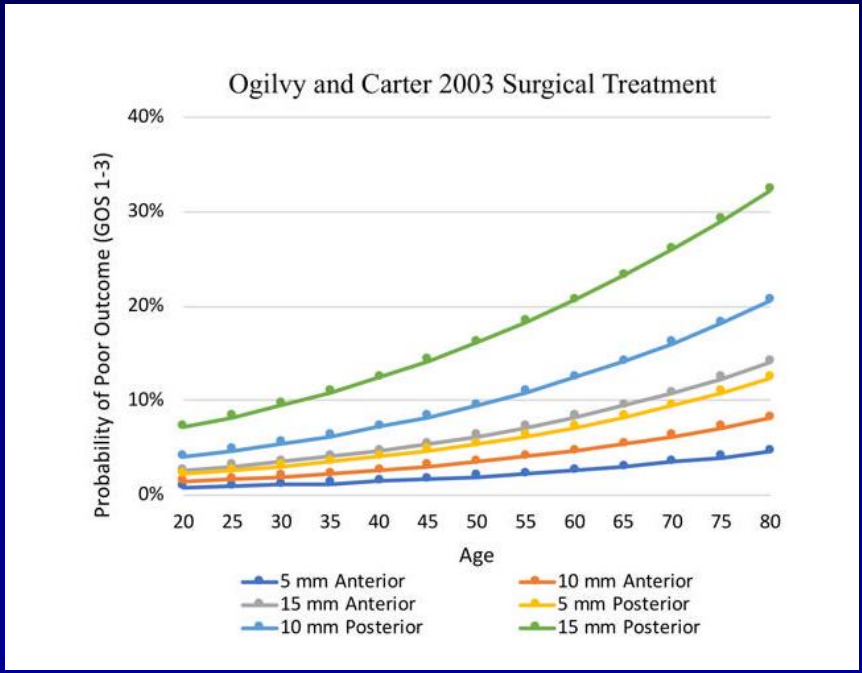
Analysis

Based on the final model, predicted probability curves for outcome were generated.

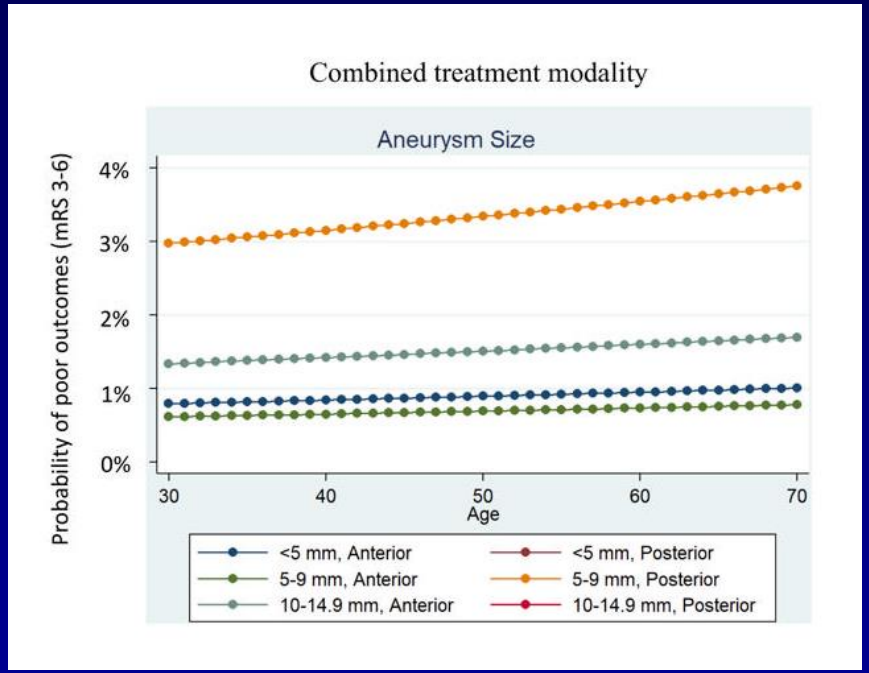
Comparison to similar previous analysis of surgical results

- Ogilvy and Carter, Neurosurgery 52:82-88, 2003
- 604 aneurysms in 493 patients
- Similar distributions of age and aneurysm sizes
- Results reported as GOS, current study results reported as mRS

2003

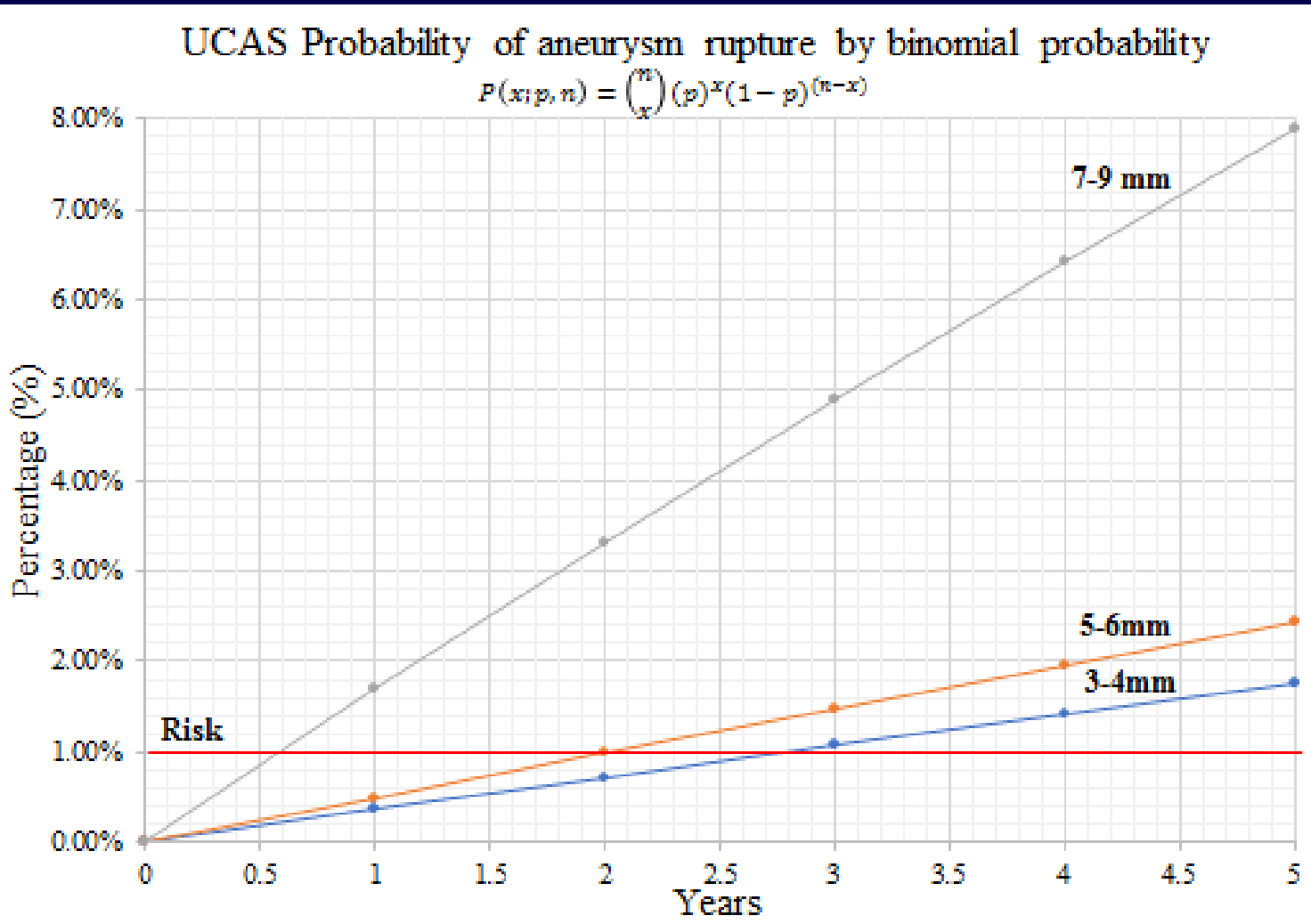

Ogilvy and Carter 2003 Surgical Treatment
Probability of Poor Outcome (GOS 1-3)
40%
30%
20%
10%
0%
20 25 30 35 40 45 50 55 60 65 70 75 80
Age
5 mm Anterior
10 mm Anterior
15 mm Anterior
5 mm Posterior
10 mm Posterior
15 mm Posterior

2018


Combined treatment modality
Aneurysm Size
Probability of poor outcomes (mRS 3-6)
4%
3%
2%
1%
0%
30 40 50 60 70
Age
<5 mm, Anterior
<5 mm, Posterior
5-9 mm, Anterior
5-9 mm, Posterior
10-14.9 mm, Anterior
10-14.9 mm, Posterior

Conclusions

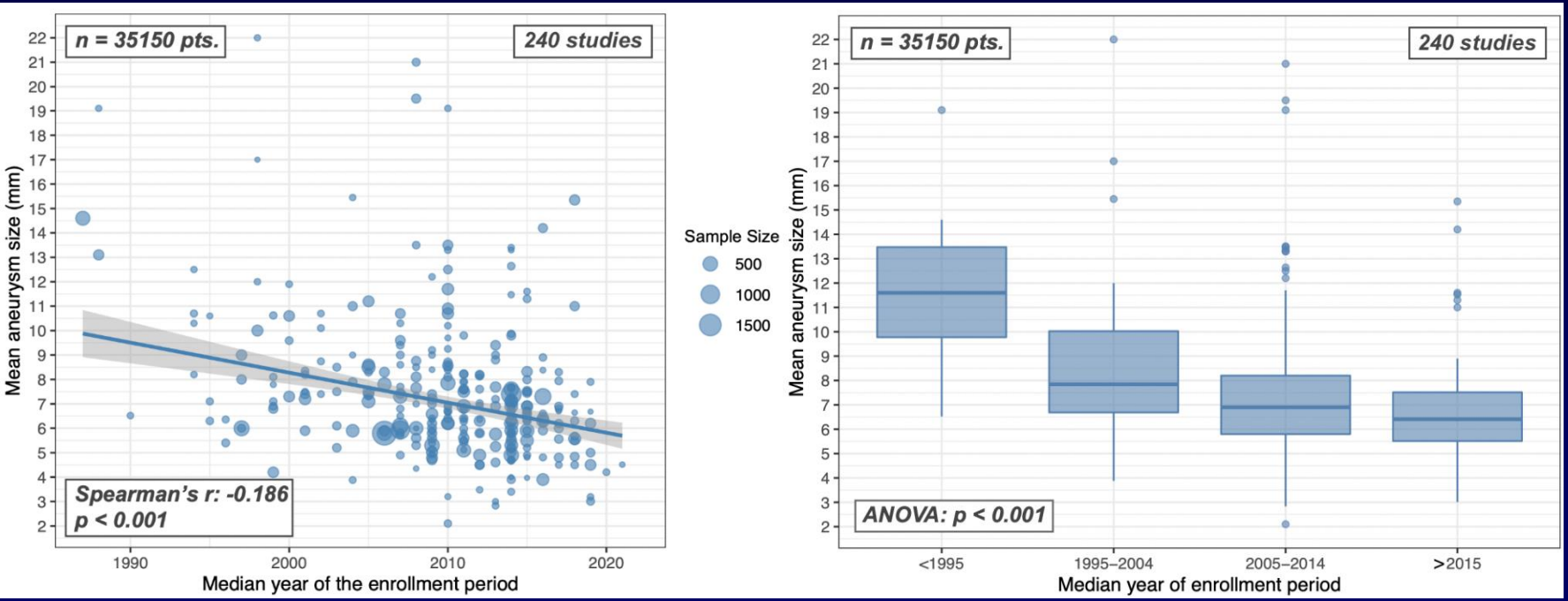
- Synergistic utilization of surgical and endovascular techniques reduces overall risk of treatment of unruptured aneurysms
- High ‘selection bias’ in who was treated – even ‘older’ patients had low co-morbidities and projected good life expectancy
- Given lower risks, treatment may be considered in patients with older age and smaller lesions


UCAS Probability of aneurysm rupture by binomial probability
$P(x;p,n) = \binom{n}{x}(p)^x(1-p)^{(n-x)}$
8.00%
7.00%
6.00%
5.00%
4.00%
3.00%
2.00%
1.00%
0.00%
Percentage (%)
7-9 mm
5-6mm
3-4mm
Risk
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
Years

Are current results with treatment changing size of aneurysms being treated or age of patients?

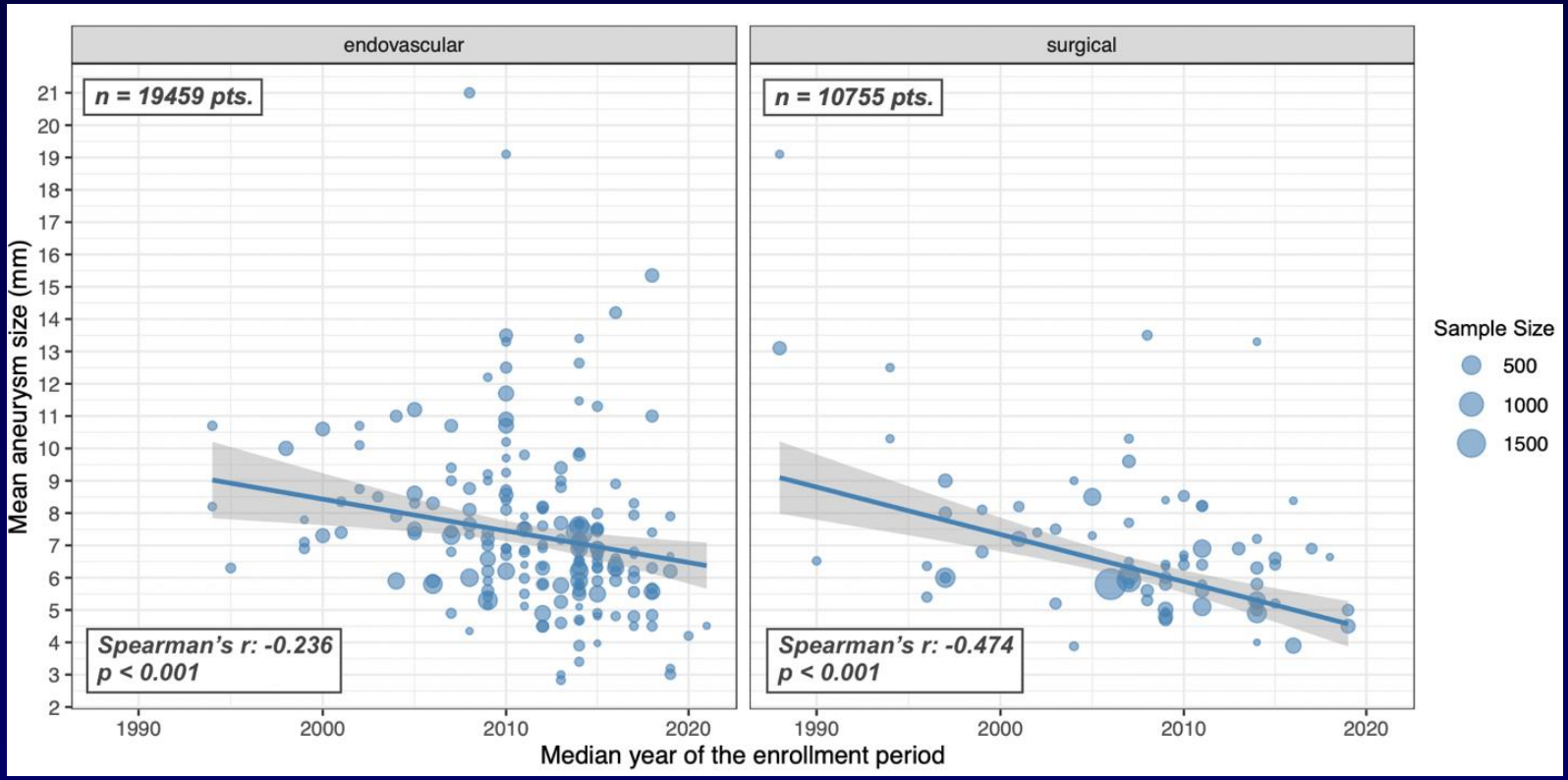
Reported size of aneurysms treated over time - literature search

- Weighted regression analysis suggests that the annual mean treated UIA dome size in the literature surpassed below 7mm in 2012



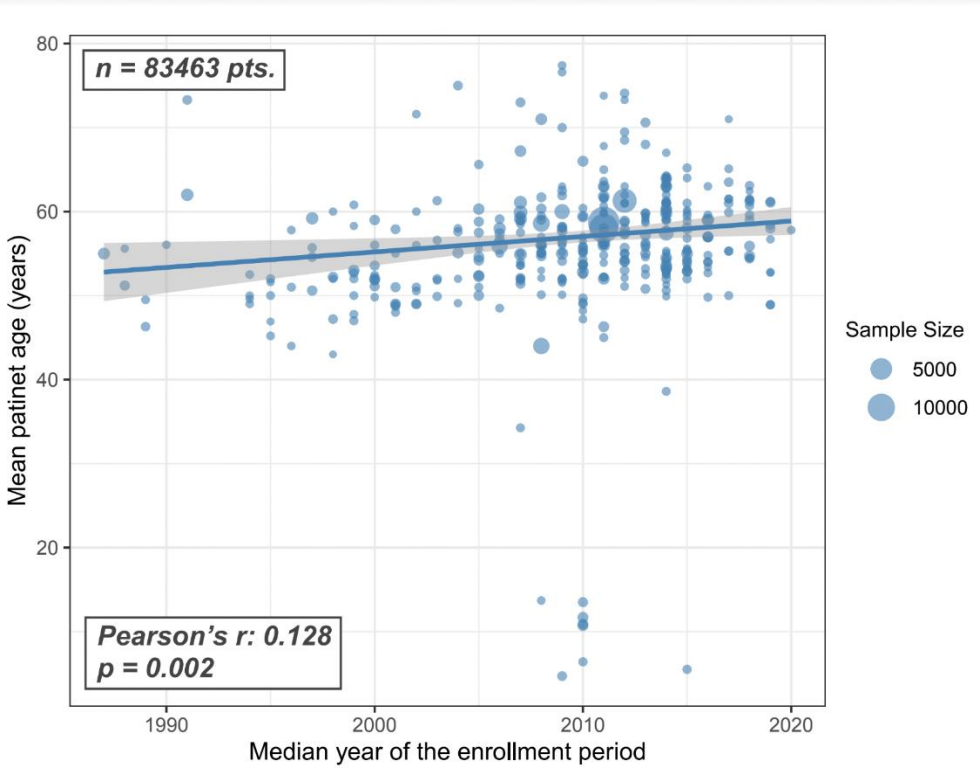
Endovascular and Surgical Treatment

- The rate of decrease in average size of the treated UIAs was 0.65 mm per every 5-year in the surgical group compared to 0.51 mm in the endovascular group



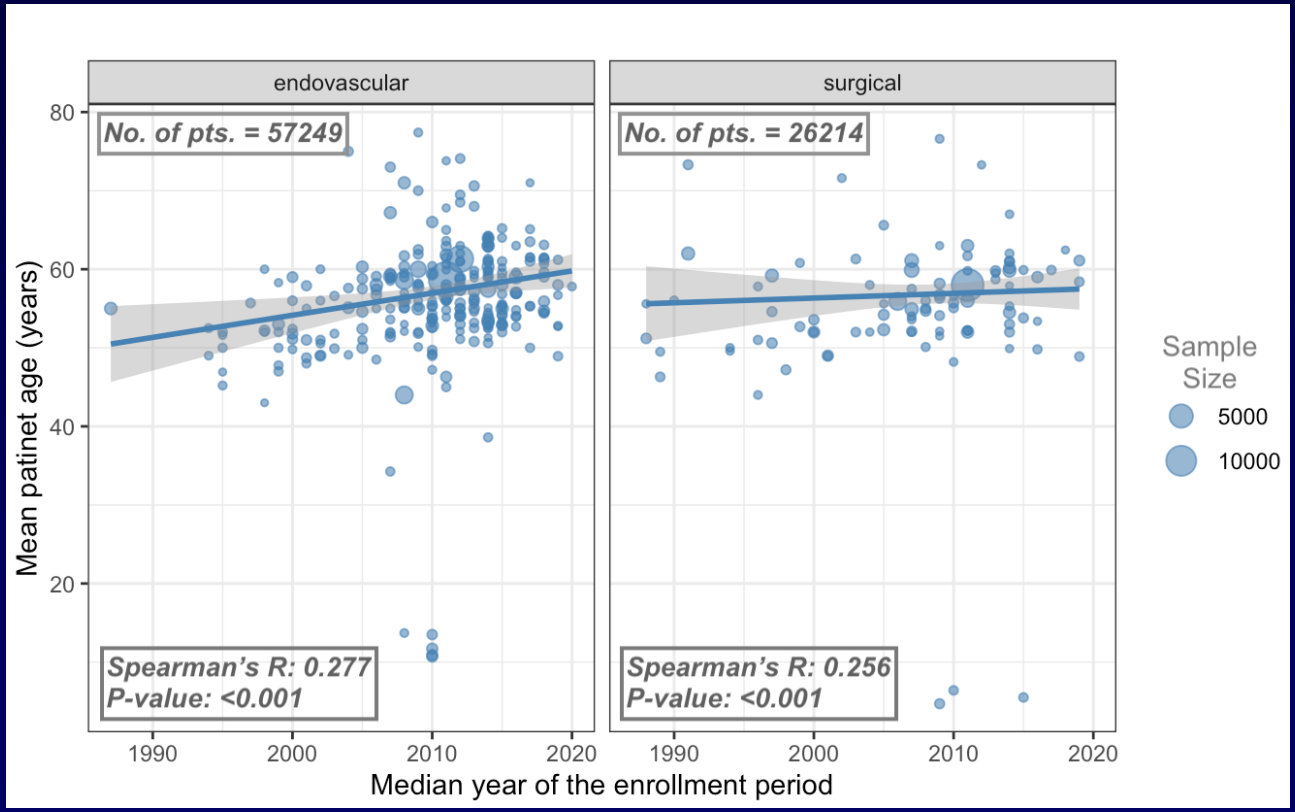
Trends in the age of treated patients

- The rate of increase in the average age of the patients treated is roughly 0.2 years per annum



Patient Age - Endovascular and Surgical Treatment

- The rate of increase in the average age of the patients treated endovascularly is roughly 0.29 years per annum compared to 0.07 per annum in those treated via clipping

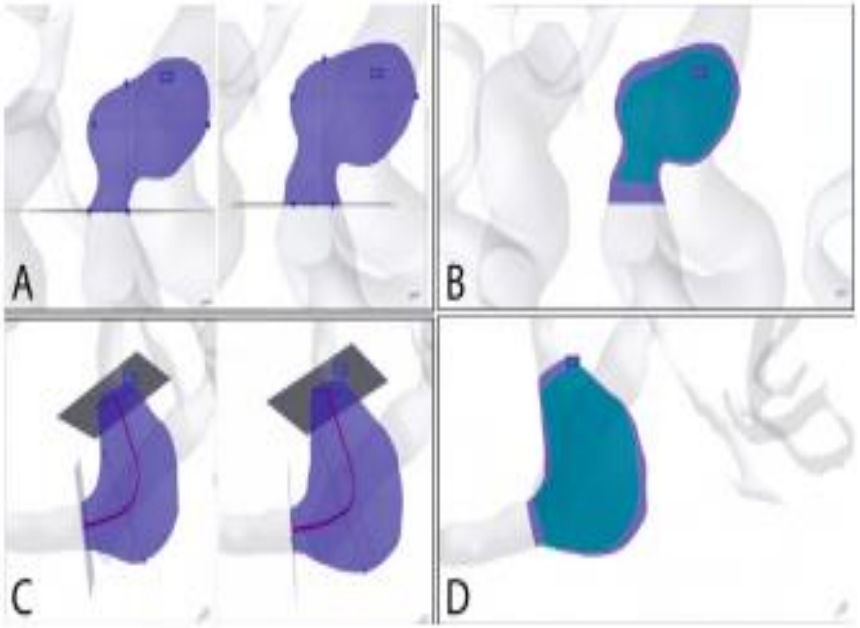


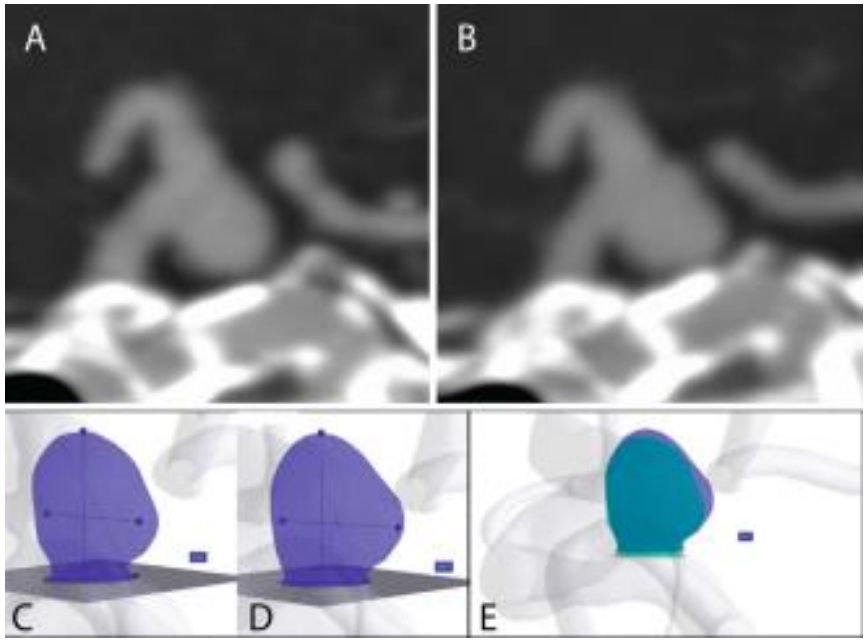
Trends

- Smaller aneurysms in older patients are being treated
- With lower risks of treatment and more information about small aneurysm natural history, these treatments can be justified

Artificial intelligence in unruptured aneurysm detection and follow-up

- Once an aneurysm is detected in scanner it can be sent directly to neurologist/neurosurgeon cell phone
- AI can measure volume, not just size of aneurysms (small or large)


A
B
C
D


A
B
C
D
E

Other factors to consider for unruptured aneurysm patients

- If an aneurysm is not treated- should it be "followed" with annual or every 5 year radiographic studies
- What activity level is appropriate for the patient with the small, untreated unruptured aneurysm?

SCREENING

Screening

Screening recommended (per AHA guidelines)

Class I

- ≥2 family members with aneurysm or SAH
- h/o ADPKD, particularly with family history

Class IIA

- Reasonable to screen patients with aortic coarctation and primordial dwarfism

Note: Initial screening in young adulthood: age 25-30 y.o.

Should repeat screening at 7-10 year intervals

Thompson et al, Stroke, 2015;46:2368-2400

Prevalence/Screening

- Women 30-60 smokers-19.1% (cost effective to screen) -1.9% in nonsmokers
- Familial 2 or more relatives-19%- (cost effective to screen)
- Men 20-80 smokers- 1.8% (??cost effective)
- ADPKD is approx 11.5% (cost effective to screen)
- Single unruptured aneurysms- 5% (not cost effective to screen)

GENERAL thoughts at present

- Younger (<60 yrs) patients with aneurysms larger than 4-6 mm generally considered for treatment.
- The younger the patient, the stronger the consideration for treatment.
- Input from several physicians working together (Neurology, radiology, neruorvascular neurosurgeon) is EXTREMELY helpful: Weekly conference.

For unruptured aneurysms

- At present, patients are evaluated on a case by case basis trying to incorporate true morbidity of treatment balanced against best estimates of the natural history for that individual. In addition, psychological and social factors are often important in the final decision of if and how to treat an unruptured aneurysm.

Thank you