REGULATORY CHALLENGES: NEW DEVICES FOR COMPLEX CEREBRAL ANEURYSMS

SPEAKERS

- Italo Linfante- President, Society of Vascular and Interventional Neurology
- Adam Arthur – President-Elect, Society for Neurointerventional Surgery
- Robert Harbaugh- Past-President, American Association of Neurological Surgeons
- David Fiorella – Sociert for Neurointerventional Surgery
- J Mocco – Chair-Elect, Joint Cerebrovascular Section

Italo Linfante MD, FAHA

DIRECTOR
INTERVENTIONAL NEURORADIOLOGY
MIAMI CARDIAC AND VASCULAR INSTITUTE
CLINICAL PROFESSOR
HERBERT WERTHEIM COLLEGE OF MEDICINE
PRESIDENT
SOCIETY OF VASCULAR AND INTERVENTIONAL NEUROLOGY

Subarachnoid Hemorrhage (SAH)

- Incidence of aSAH in the US: **9.7** per 100 000
- Median mortality rate from SAH in the US: **40%**
  - **15%** die before reaching the hospital
    - **Two-thirds** of survivors have permanent neurological morbidity
- Median age of subarachnoid hemorrhage is **50**

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Unruptured Intracranial Aneurysms (UIA)

- Estimated that **1 in 50** people harbor an unruptured cerebral aneurysm
- Can we predict the risk of rupture for UIA?
- Several epidemiological studies of UIA (ISUIA Lancet 2003, NEJMED 1998 and others) have attempted to predict risk of aneurysmal rupture

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Risk Factors for Rupture (ISUIA and others)

- Previous SAH
- Location (posterior circulation)
- Morphology: irregular shape, daughter sacs
- Enlargement on f/u imaging
- Patient features: age, race, female, smoking, family history of ruptured aneurysms
- Smoking: Adjusted RR of cigarette smoking for aneurysm rupture was 3.0 (95% CI, 1.2–7.7) if the patient continued smoking during follow-up
- **Size**

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Risk Factors: Size

- Aneurysmal size is a powerful independent predictor of rupture
- Larger UIAs have greater risk for rupture
- “Small” UIAs?
- Defining a critical size threshold for “small” aneurysms at risk for rupture remains difficult

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High Variability Between Studies in Relative Risk of Rupture for Small Aneurysms

- ISUIA
  - In 7-12 mm group:
    - RR for anterior circulation UIAs: 0.52% per five-year
    - RR for posterior circulation UIAs: 2.9% per five-years
- Juvela et al. :
  - < 10 mm: **0.9% to 2.3% for aneurysms PER YEAR**

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Aneurysmal SAH

- All studies of subarachnoid hemorrhage have shown that the vast majority of aneurysms that rupture are SMALL

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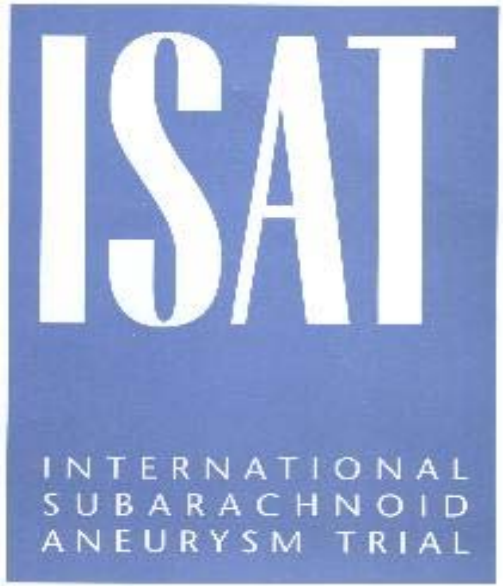

Multicentric prospective RCT comparing Endovascular coiling and Neurosurgical clipping for ruptured intra-cerebral aneurysms.

Lancet. 2002;360:1267–1274

Funding agencies: UK Medical Research Council
Canadian Institute of Health Research
French Health Ministry
Stroke Association of the UK for
Neuropsychological assessments

ISAT

- ISAT was a multicenter, prospective, randomized controlled trial of patients with aSAH
- **2143** patients with ruptured intracranial aneurysms randomly assigned to microsurgical clipping or endovascular embolization

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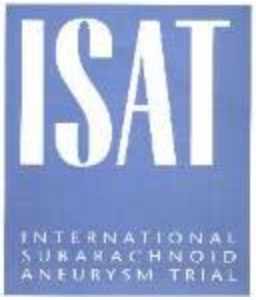
ISAT Multicentric prospective RCT comparing Endovascular coiling and Neurosurgical clipping for ruptured intra-cerebral aneurysms. Lancet. 2002;360:1267–1274



2143 patients with ruptured intracranial aneurysms

95% of the aneurysms were < 10 mm in size

54% (1,157) were < 5 mm in size !

Small aneurysms account for the ~~MAJORITY~~ of aSAH

- CLARITY: 782 ruptured aneurysms **90%** were ≤ 10 mm
- PRESAT: 534 ruptured aneurysms **86%** were < 10 mm
- Ohashi et al: 280 ruptured aneurysms **74%** were < 10 mm
- Lin Zao et al **1256** ruptured aneurysms: **47.1 %** were between **2 mm–5 mm; 39.7%** between 5 mm–10 mm.

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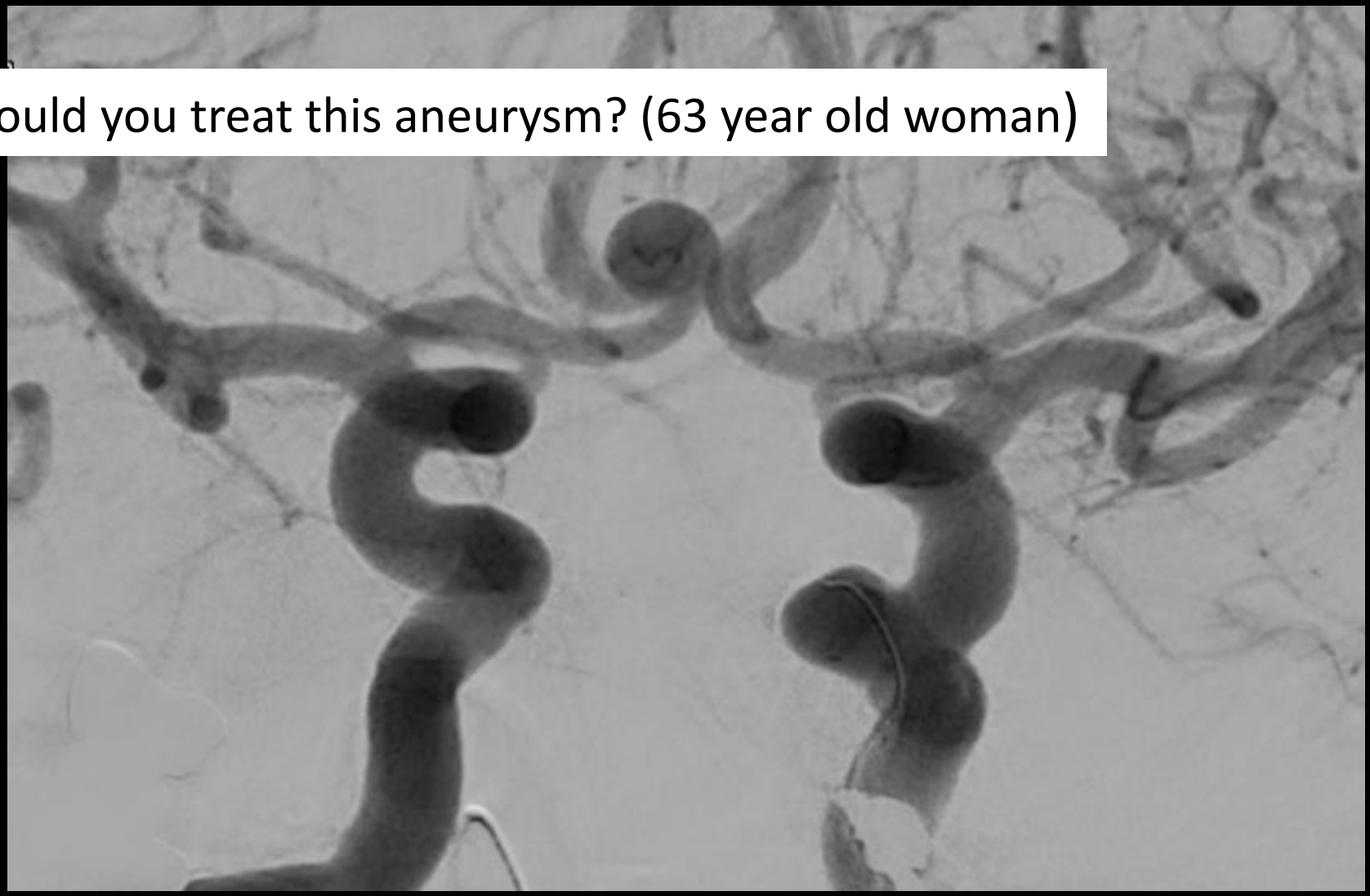
Would you treat this aneurysm? (63 year old woman)



Patient

- 63 year-old woman who developed “The Worst Headache of Her Life” with nausea and vomiting
- Presented to the ER with poor responsiveness
- Intubated

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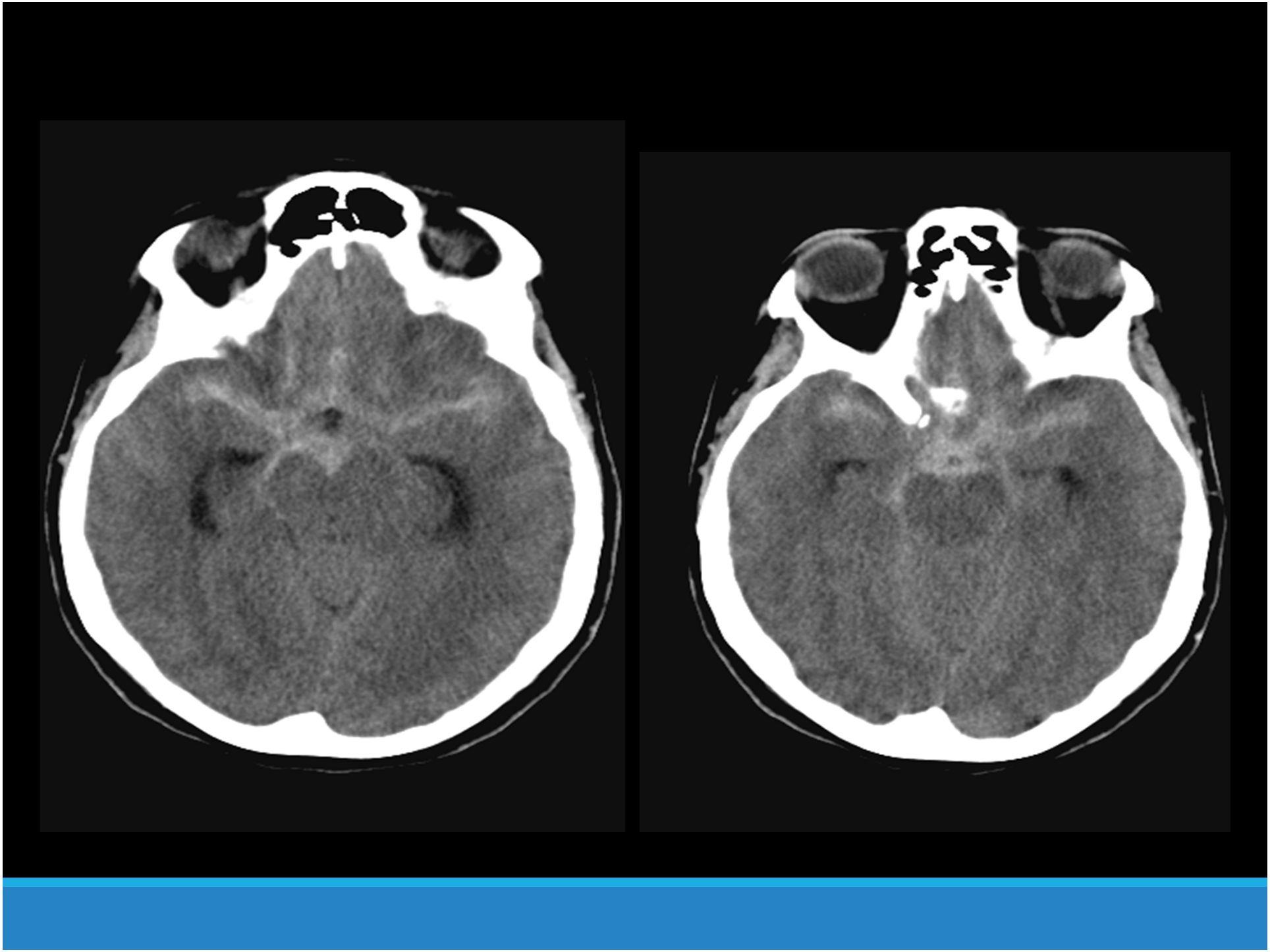
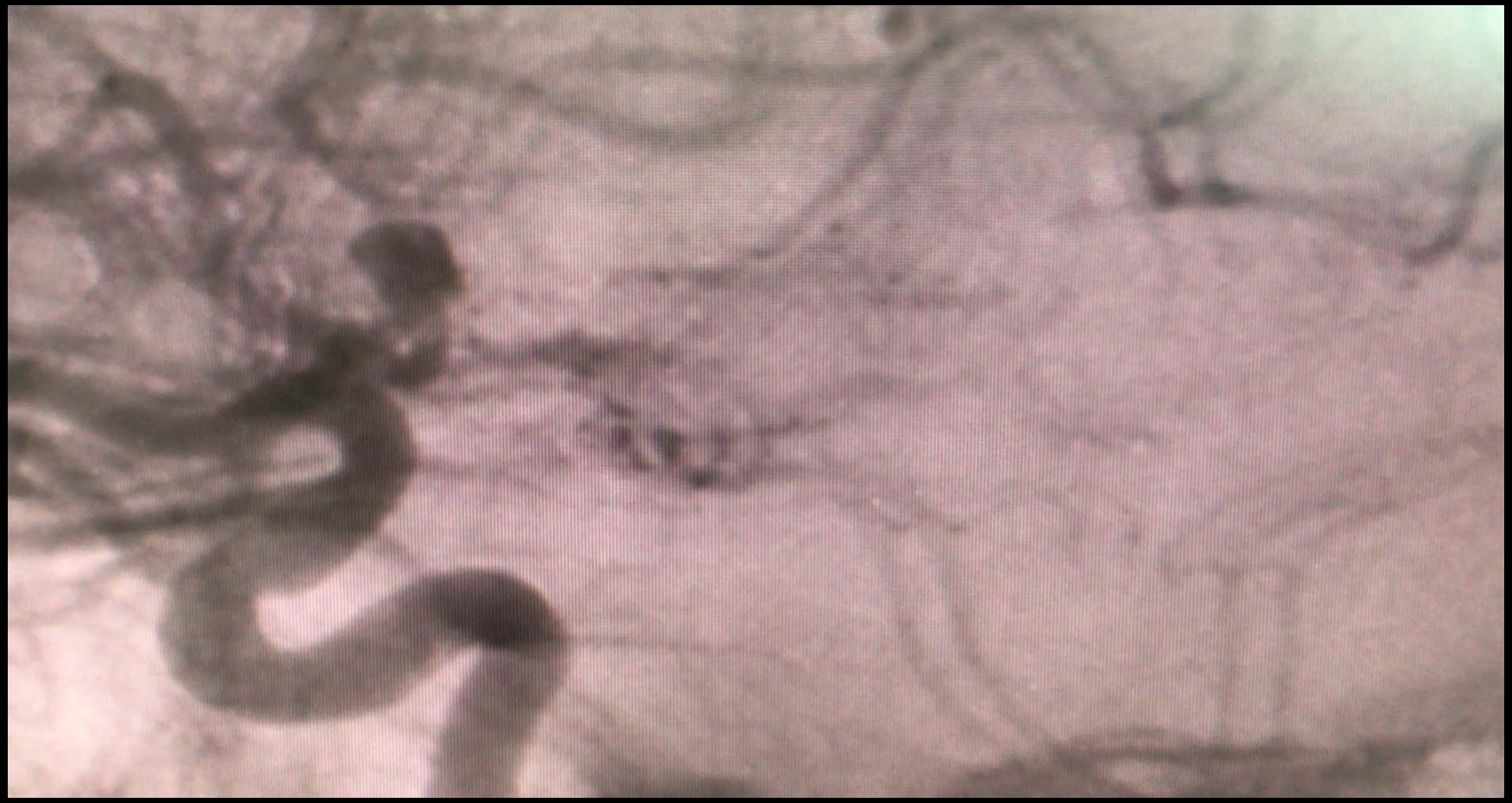
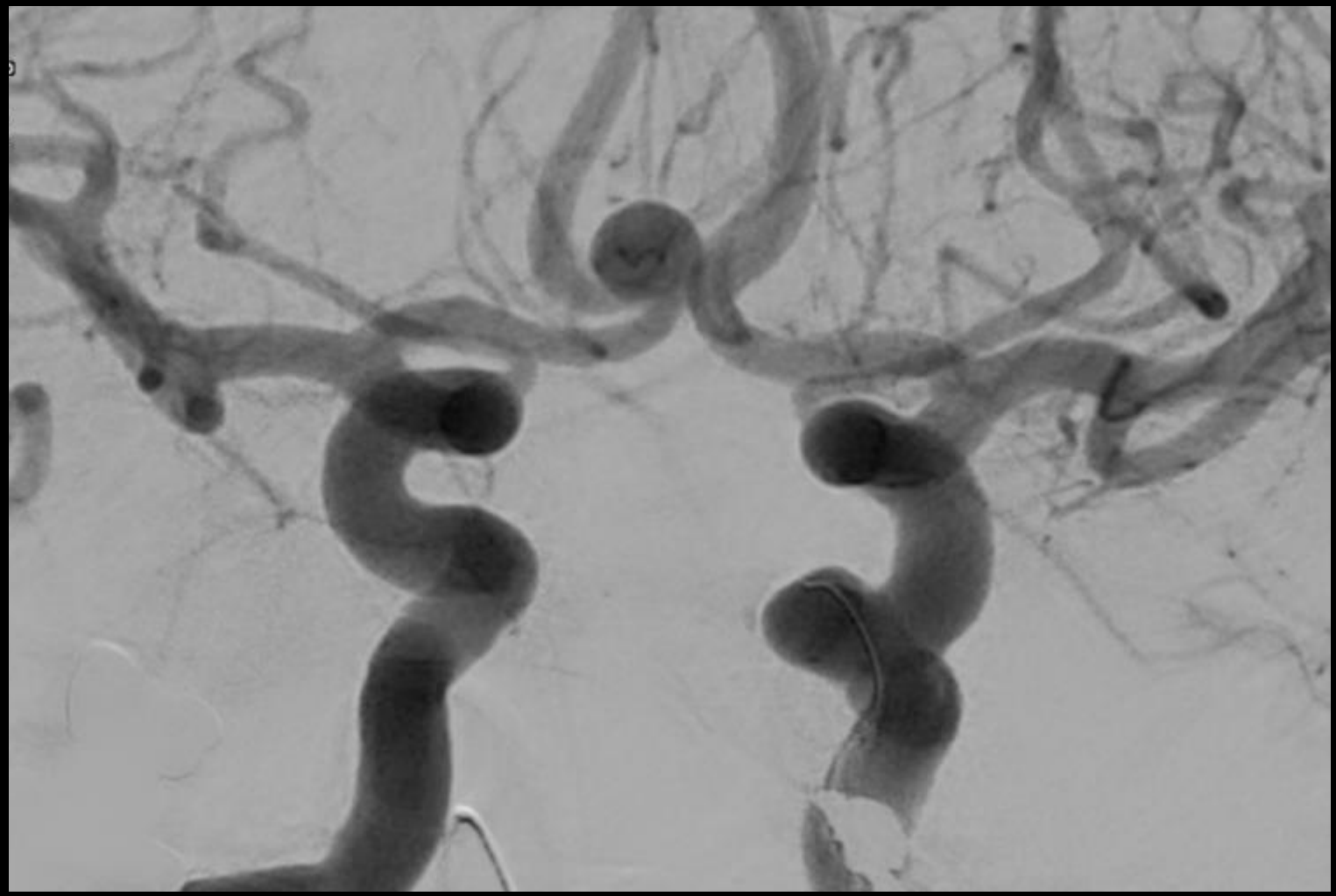
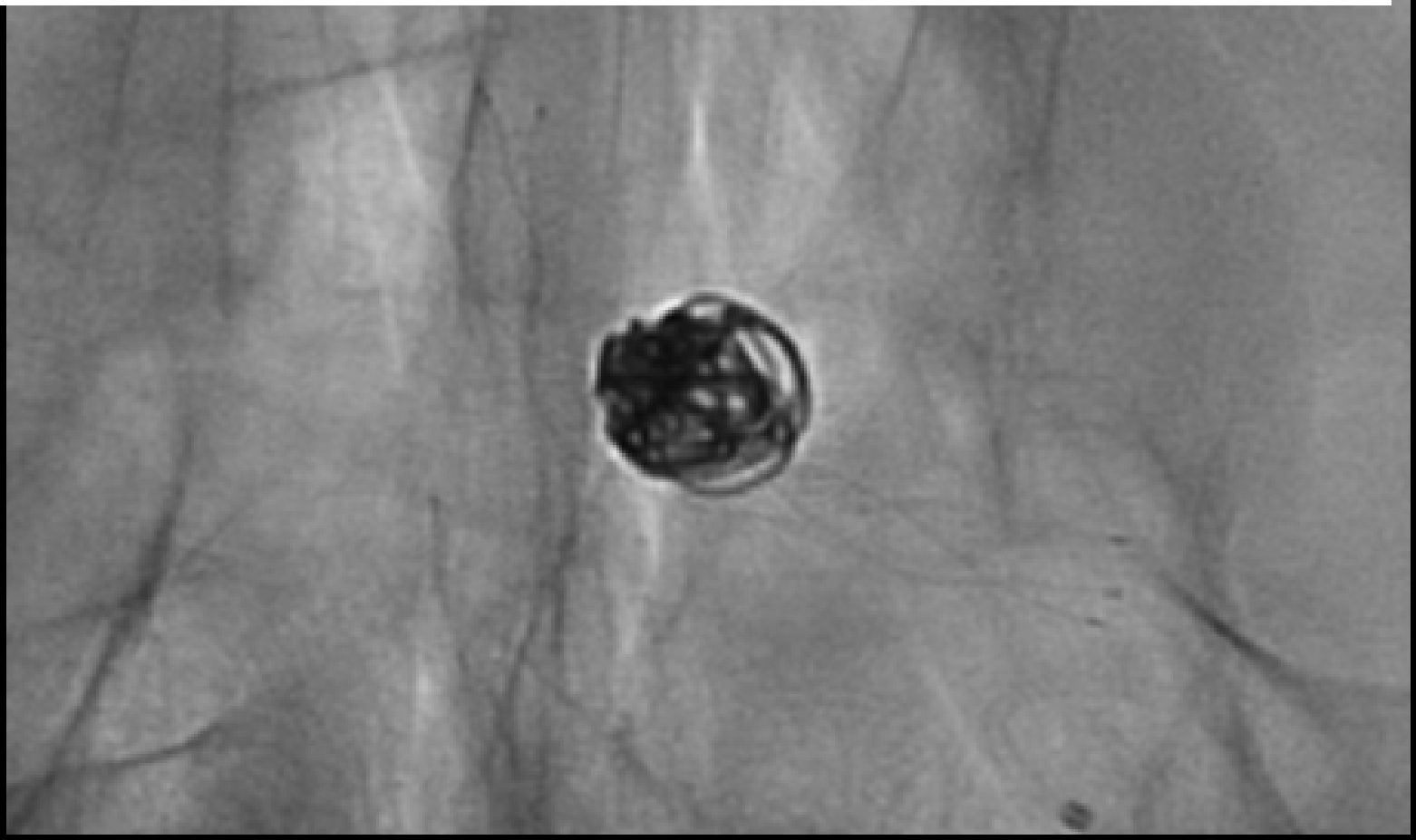
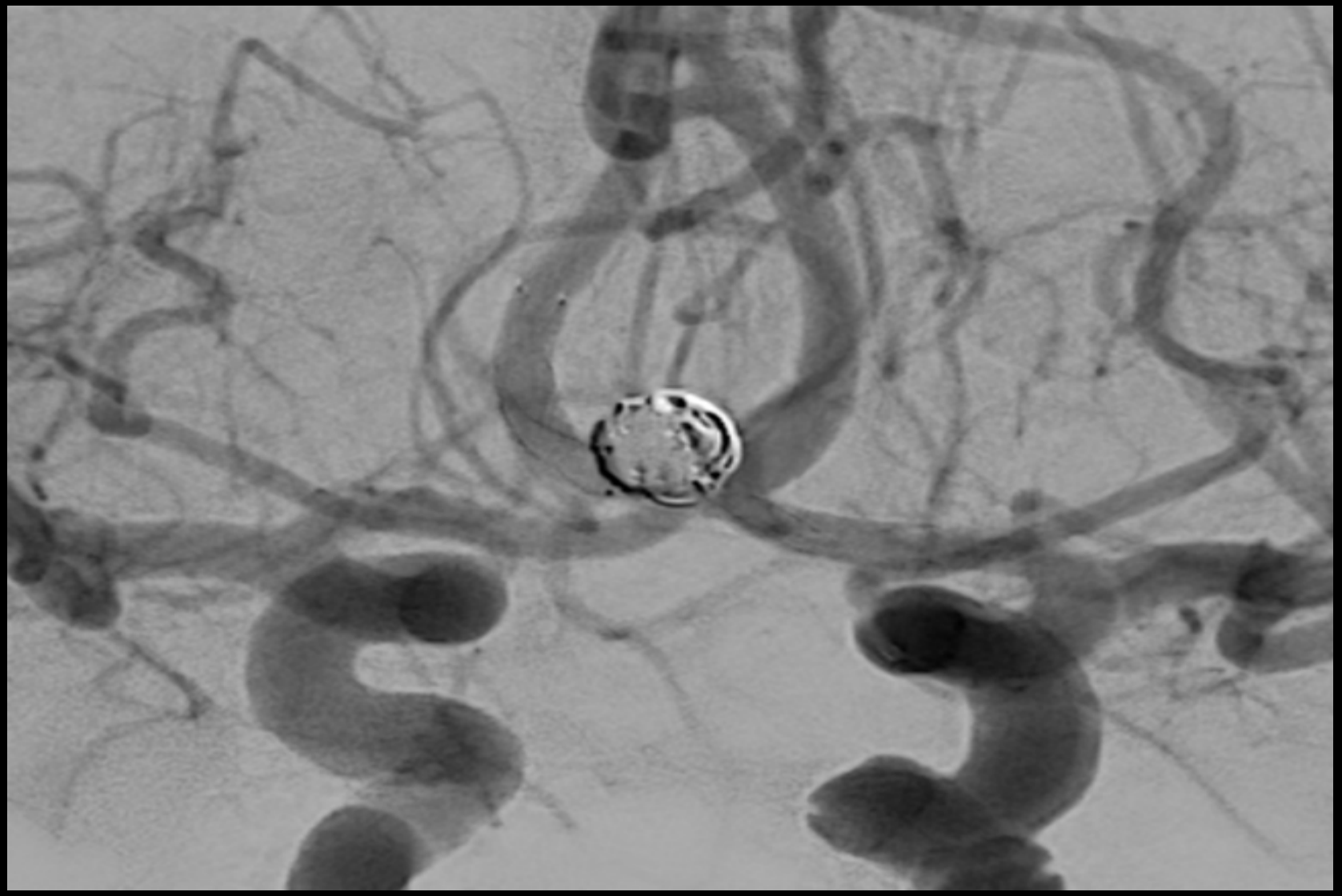


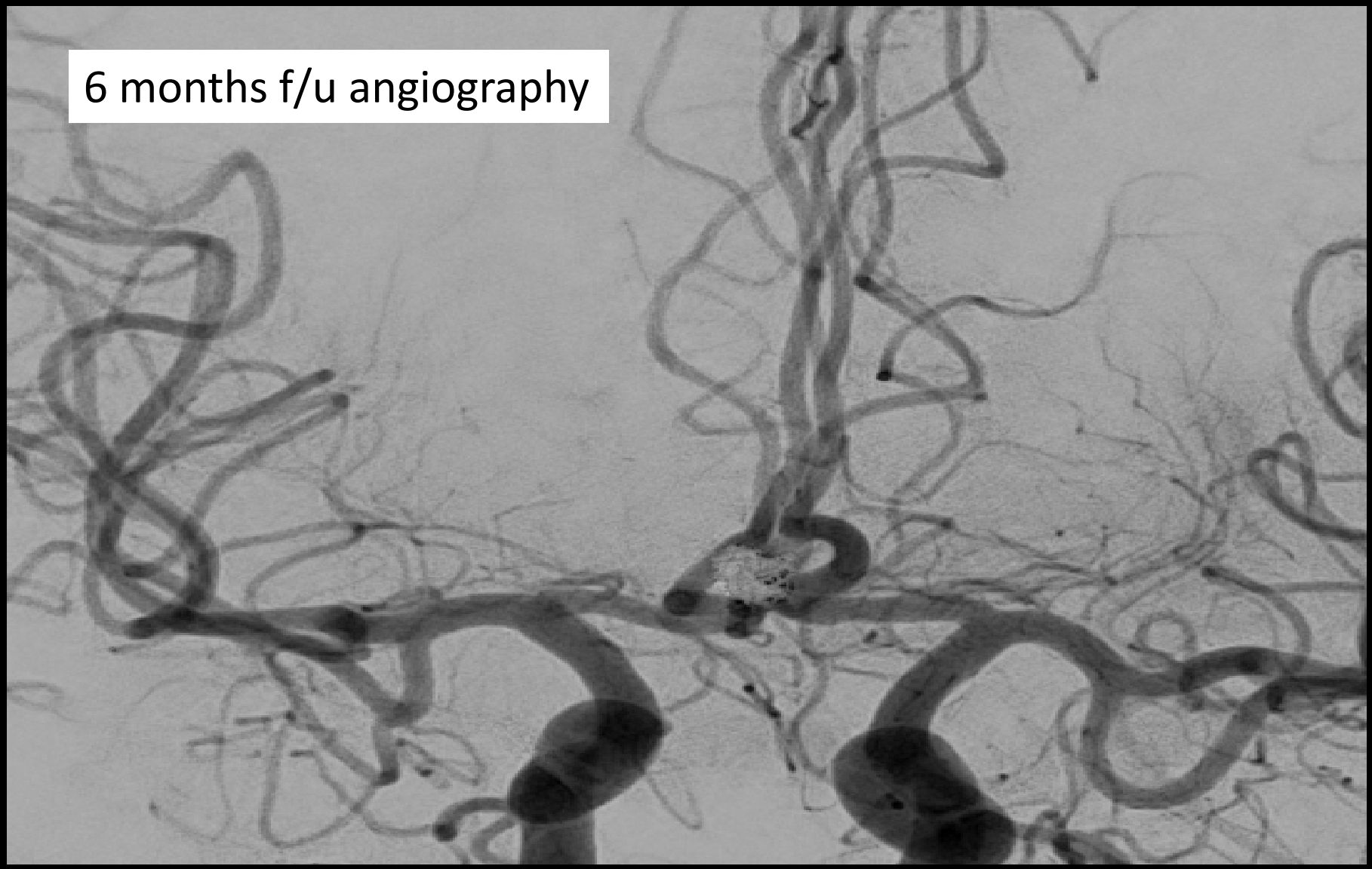




Balloon assisted, followed by stenting






6 months f/u angiography

Summary

- Subarachnoid hemorrhage is a **DEVASTATING DISEASE**
  - Affects patients of **ALL AGES** (median age 50)
- Although size is directly related to rupture risk, **MOST ruptured aneurysms are small**

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Summary

- It is very difficult to predict the rupture risk of a given aneurysm in a given patient
- Treatment decisions are **complex and multifactorial** and patient-specific
- Therefore, a “one size fits all” approach for aneurysms and aneurysmal subarachnoid hemorrhage is not appropriate
- Treatment decisions are made by the patient in consultation with their physicians after careful evaluation of all risk factors

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Innovation in Medicine

- Unquestionably the FDA has a challenging task
- Physicians appreciate and share the need for proof of safety and effectiveness of devices used to treat cerebral aneurysms

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Conclusion

- Undoubtedly, thanks to innovation and FDA Endovascular approach has revolutionized the treatment of ruptured and unruptured cerebral aneurysms
- Endovascular technology and innovation is expanding and so we need to **expand the armamentarium** of devices which will allow aneurysms to be treated as safely and effectively as possible

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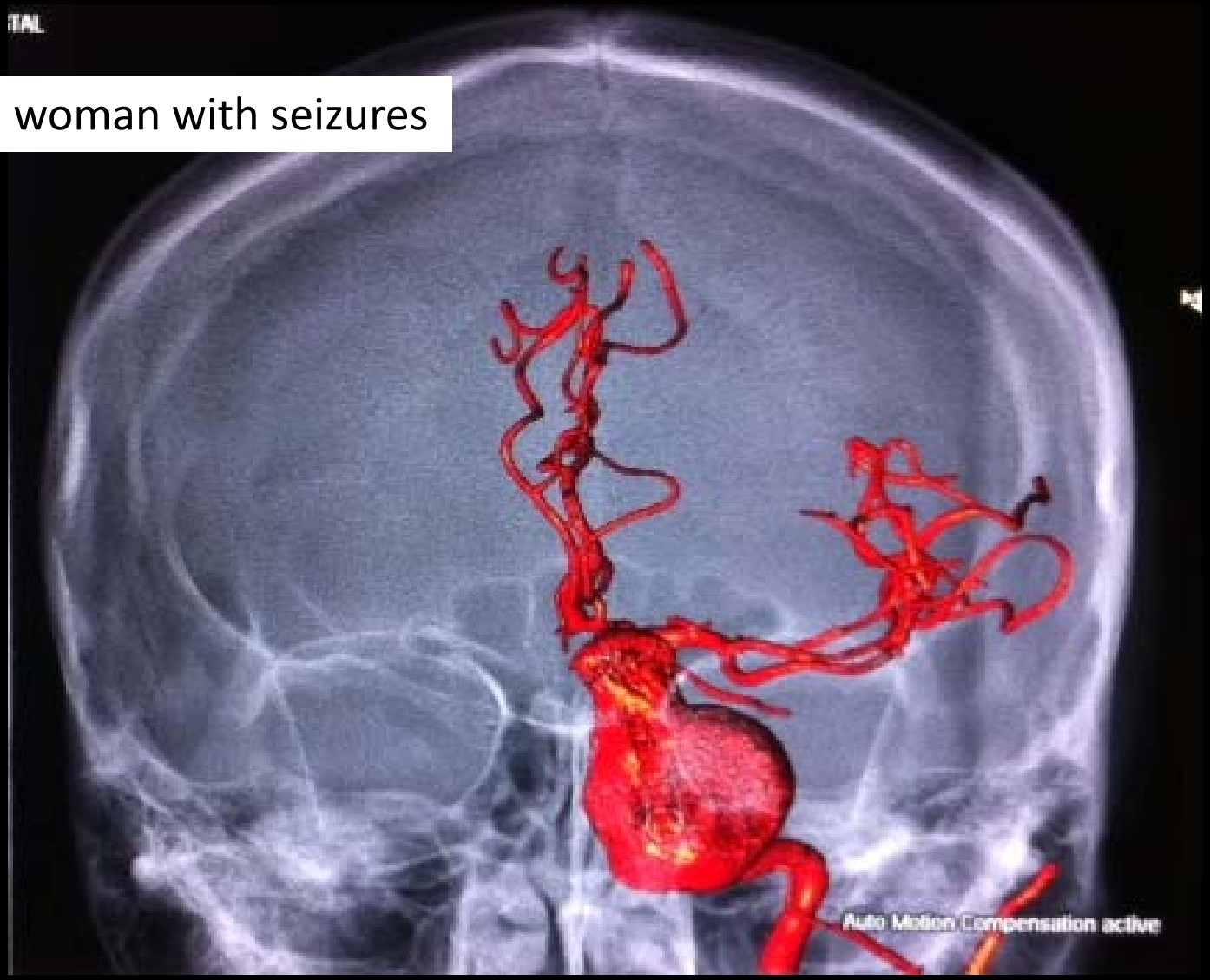
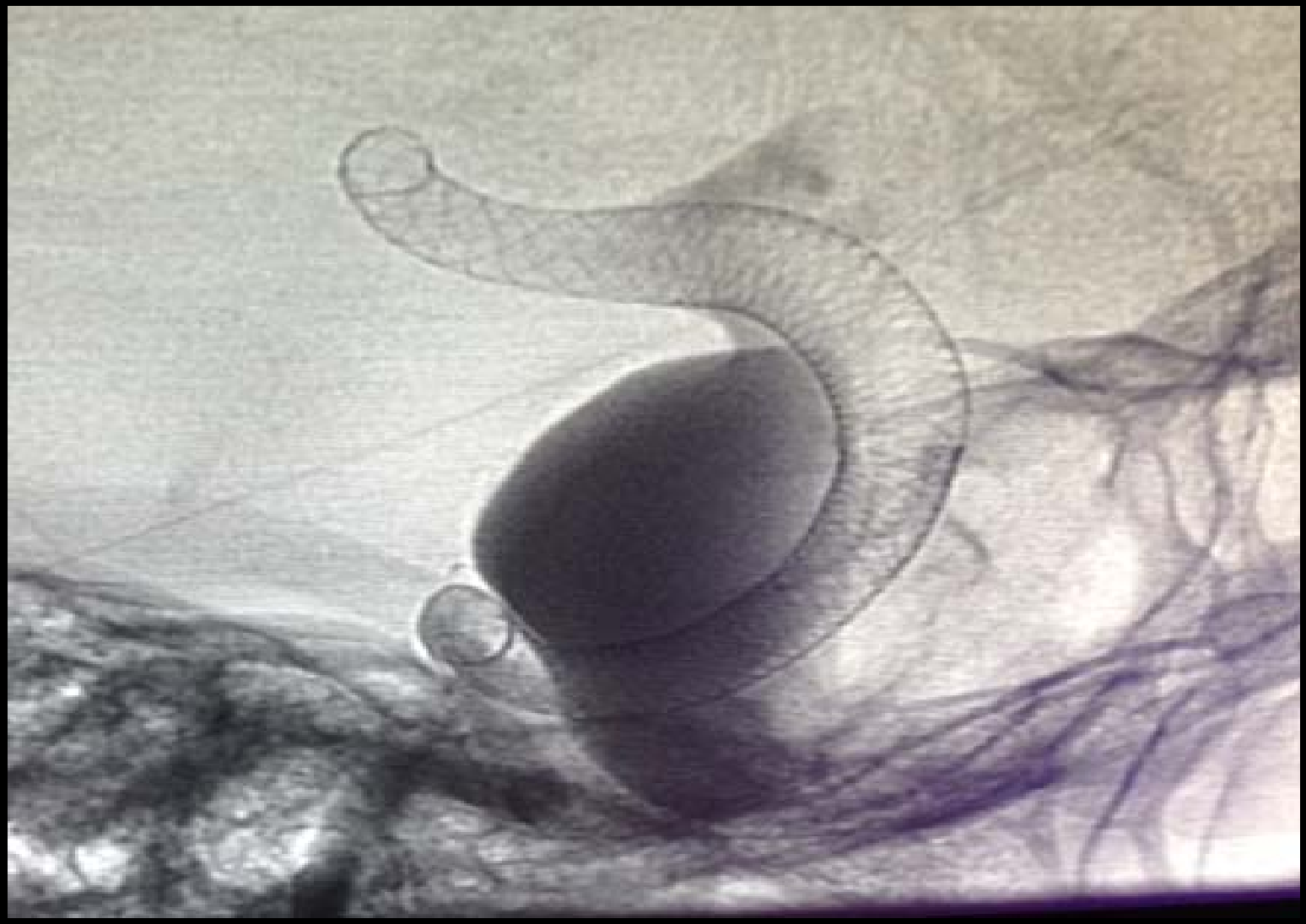
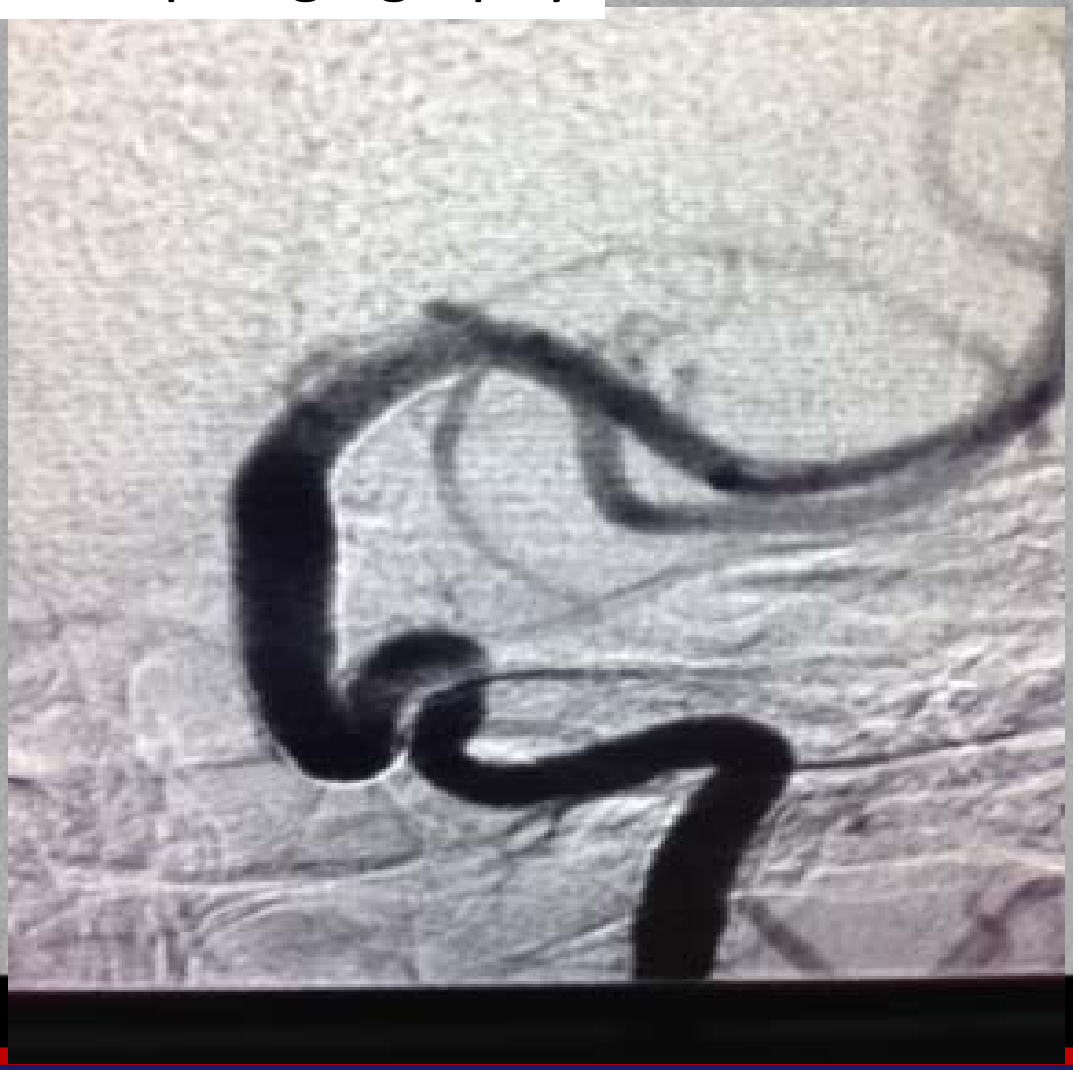
16 year old woman with seizures





3 year follow-up angiography



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5 years later….

THANK YOU !

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NEUROENDOVASCULAR DEVICE TRIAL DESIGN

Adam S. Arthur MD MPH FAANS FACS FAHA

Director of Cerebrovascular Neurosurgery

Professor of Neurosurgery

University of Tennessee Health Sciences Center

Semmes-Murphey Neurologic and Spine Clinic

Memphis, Tennessee

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NEUROENDOVASCULAR THERAPY

- The United States is the world leader in neuroendovascular innovation

- US patients should have access to the safest and most effective treatment options available to treat cerebral aneurysms

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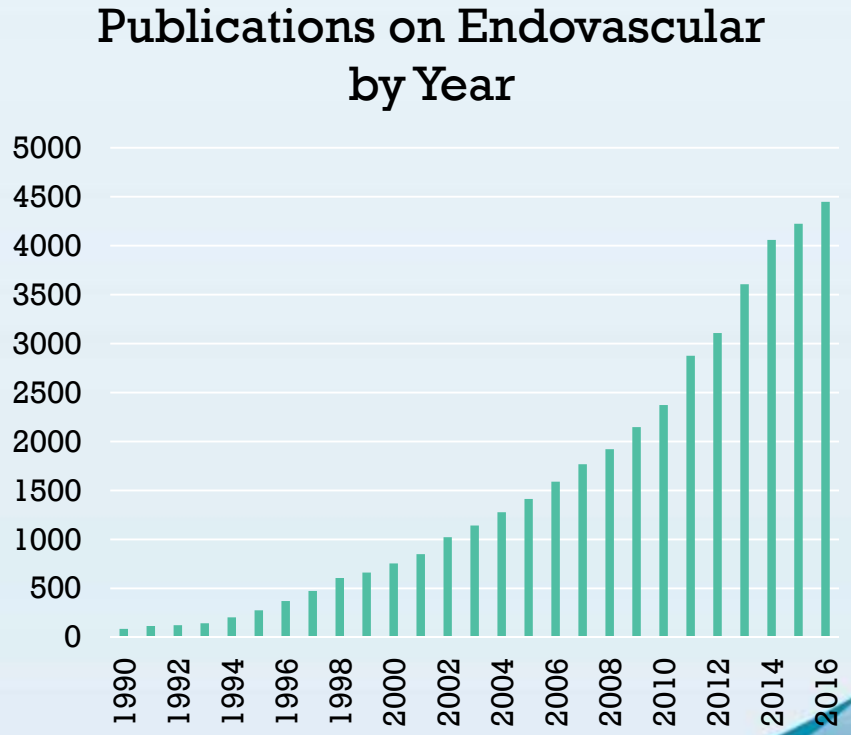
EVOLUTION AND CLINICAL EVIDENCE

- Neuroendovascular therapies are evolving at an exponentially increasing pace
- This growth and come with a strong foundation of concordant, high level, supportive clinical evidence
  - Thrombectomy in acute ischemic stroke
  - Endovascular aneurysm treatment vs. surgical clipping



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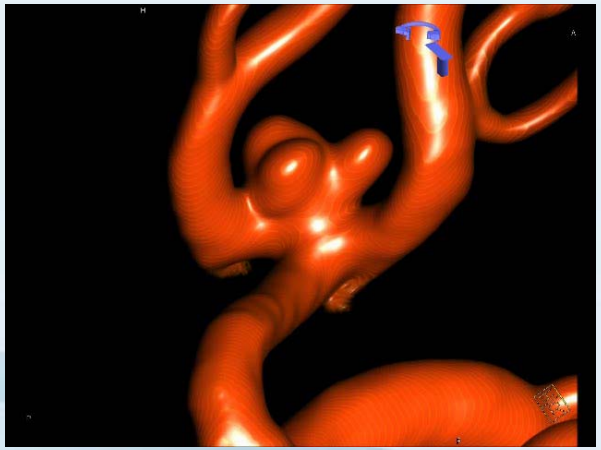
THE CHALLENGE VS. THE OPPORTUNITY

- The Agency is now being confronted with an increasing number of new applications for device clearance



- Pragmatic and efficient strategies for regulatory evaluation are absolutely essential
  - To ensure that US patients will have access to the safest and most effective new technologies
  - To allow the US maintains its role as the leader in innovation

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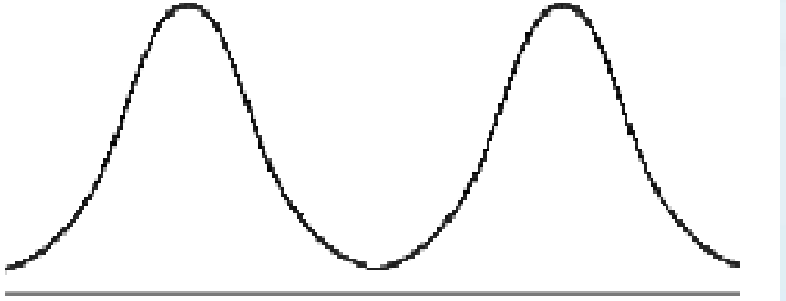
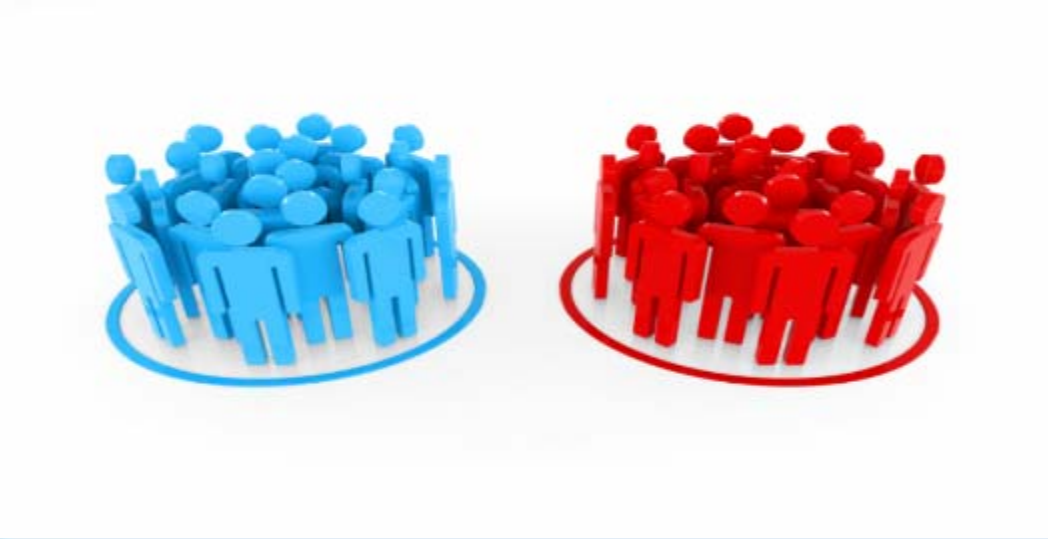
KEY ISSUES

- Regulatory Trial Designs
  - RCT's vs. OPCs/PGs
- Trial Endpoints
  - Need to be relevant and reasonable
- Indications for Use ≠ Treatment Recommendations



TRIALS OF NEW THERAPIES

- Randomized Controlled Trials (RCTs)
  - Highest Level of Clinical Evidence
  - Not always feasible or necessary



FACTORS LIMITING FEASIBILITY OF RCTS IN NEUROENDOVASCULAR THERAPEUTICS

- **Low Prevalence of Diseases**
  - Cerebrovascular diseases **comparatively rare** vs. peripheral and cardiac disease
- **Decentralization of Care**
  - Proliferation of hospitals offering a CV service line results in the **decentralization of cases** across centers
  - This can make it difficult to train enough centers and operators enroll patients in large trials

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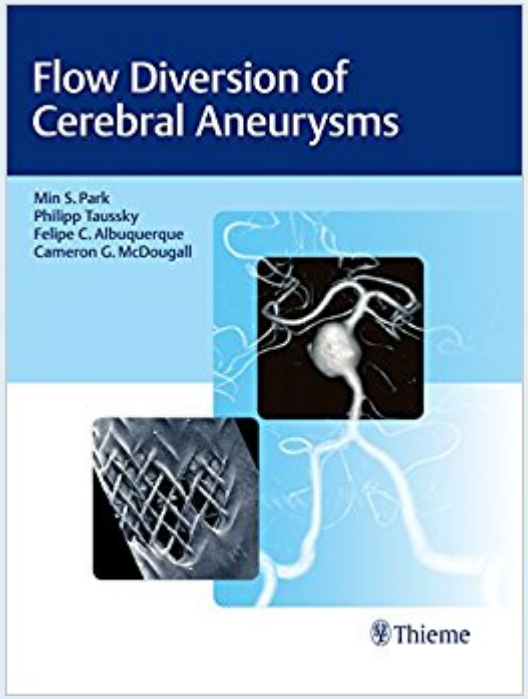
FACTORS LIMITING FEASIBILITY OF RCTS

- **Prohibitive Sample Sizes**
- Example: New Flow Diverter Device
  - Active Comparator: Pipeline vs. New FD
    - Assume 80% effectiveness of both the control (Pipeline) and the new FD device
    - 1:1 Randomized Controlled Trial
    - 80% power, 10% non-inferiority margin

= 504 patient study



FACTORS LIMITING FEASIBILITY OF RCTS

- **Absence of a suitable control arm**
  - No FDA cleared device for the same indication (e.g. a given type of aneurysm)
  - No relevant endovascular or surgical treatment option available for the same indication (e.g., Pipeline/PUFs)

FACTORS LIMITING FEASIBILITY OF RCTS

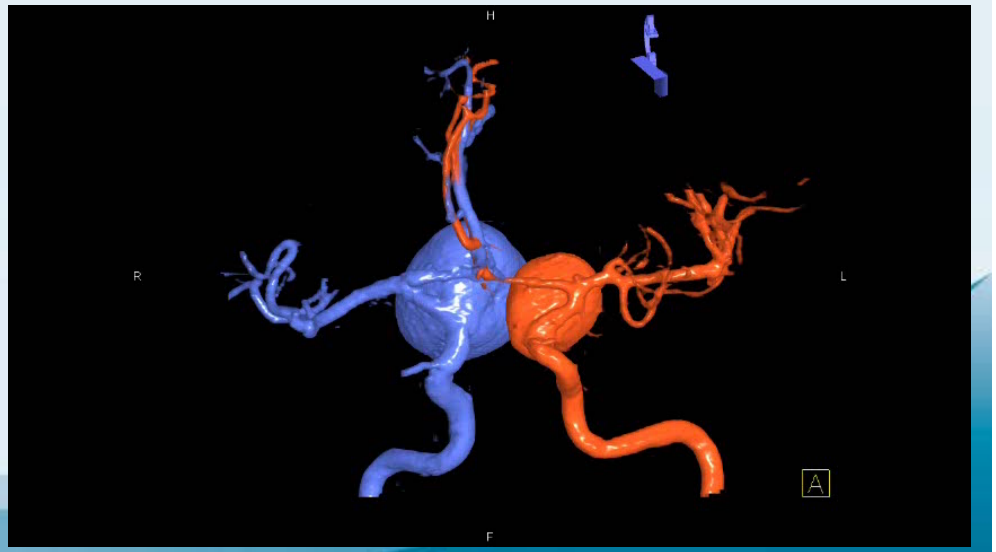
- **Challenges in enrolling patients**
  - Patients are often reluctant to participate in trials in which treatment decisions are based upon a **"coin flip"**
    - TEAM trial
  - Patients are often unwilling to undergo a random treatment allocation if **one treatment is more invasive** than the alternative
  - Physicians are often **unwilling to urge patients to participate** in randomization to a technology that is more challenging to use or more invasive
    - COCOA – coiling vs. Pipeline
    - LARGE TRIAL – stent coiling/deconstruction vs. Pipeline

FACTORS LIMITING NECESSITY OF RCTS

- New device is performing a **similar function** in a **well defined disease state**
  - Efficacy and safety endpoints **well defined** in prior high quality studies (no need for active comparator)
    - Thrombectomy for ELVO
      - E.g. new stent-retriever, new aspiration catheter
    - Flow Diversion for Side Wall Aneurysms
      - E.g., new flow diverter

IF RCTS ARE UNIVERSALLY REQUIRED…

- Approval studies
  - Require much **larger sample sizes**
    - **More sites, more operators to train**
  - Are **more expensive** to conduct
  - **Harder to enroll** patients
  - Take **longer** to complete
- **RESULT: U.S. PATIENTS ARE DENIED ACCESS TO NEW THERAPIES**



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RESULT: IF RCTS ARE UNIVERSALLY REQUIRED

- Disincentive for new companies to participate in the US neurovascular market
  - Regulatory process too expensive, process too lengthy
  - Prohibitive barrier for competitive devices (i.e., “regulatory monopoly”)
  - Innovation and iteration are stifled, creating a barrier to continued progress in the field
- Comparatively smaller space with “orphan diseases” (e.g., AVM, dural AVFs, etc) = not worth the investment

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THE ALTERNATIVE

- Well developed literature-based Objective Performance Criteria and Performance Goals
- OPC and methodology can be peer-reviewed
  - Defines and reviews “state of the field”
  - Establishes a consistent, level playing field

Hemorrhagic stroke
Review

How safe and effective are existing treatments for wide-necked bifurcation aneurysms? Literature-based objective performance criteria for safety and effectiveness

David Fiorella[1], Adam S Arthur[2], Richard Chiacchierini[3], Evelyne Emery[4], Andy Molyneux[5], Laurent Pierot[6]

Author affiliations

Abstract

Introduction Wide-necked bifurcation aneurysms (WNBAs) present unique technical challenges for both endovascular and surgical treatments which aim to achieve complete occlusion of the aneurysm without compromising the patency of the incorporated regional parent vessels. We present a meta-analysis of traditional therapies for WNBAs to provide critical benchmarks for safety and effectiveness.

Methods Following a systematic search of the literature and the application of pre-specified appropriateness criteria, 43 (including 2794 aneurysms treated) and 65 (including 5366 patients treated) references with sufficient detail were identified to include in a meta-analysis of efficacy and safety, respectively. Effectiveness endpoints of both complete and adequate occlusion were assessed. A composite safety endpoint was based upon commonly applied metrics for major adverse events. Fleiss analyses were performed for both effectiveness and safety endpoints for the entire group, and then parsed separately by treatment modality (surgical clipping (SC) or endovascular therapy (EVT)) and location (anterior or posterior circulation).

Results Using the above methods, the core laboratory adjusted rate of complete occlusion was 46.3% (standard error 3.6%), 39.8% (3.7%), and 52.5% (9.6%) for all therapies, EVT, and SC, respectively. The rate of adequate occlusion was 59.4% (12.2%), 43.8% (5.3%), and 69.7% (14.3%) for all therapies, EVT, and SC, respectively. The rates of occurrence for pre-specified safety endpoints were 18.7% (2.9%), 21.1% (2.8%), and 24.3% (4.9%) for all therapies, EVT, and SC, respectively.

Conclusions Conventional therapies for WNBAs are associated with relatively low rates of complete occlusion and peri-procedural complications are not uncommon. As new treatment technologies are investigated, it is important that the available data regarding predicate treatments is understood.

http://dx.doi.org/10.1136/neurintsurg-2017-013223

Statistics from Altmetric.com

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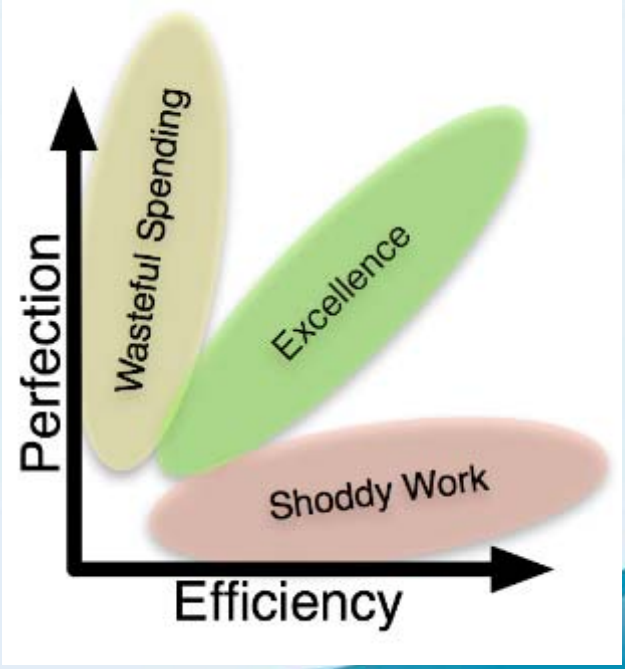
IMPROVING OPCS/PGS

- Progressive improvement with the proliferation of prospective, core lab adjudicated, externally monitored, GCP device trials
    - Sidewall Aneurysms: PUFS, PREMIER, ASPIRE (FRED, SURPASS)
    - WNBA: WEB, LVIS (subset), Atlas (subset) Pulse Rider, Barrel, and others to follow
- This ***HAS ALREADY*** resulted in much better data for endovascular therapy than exists for open surgical clipping

ADVANTAGES: SINGLE ARM TRIAL AGAINST OPC/PG

- Smaller sample sizes
- Allows conservation of enrolled patients
  - 100% allocated to treatment device
- Faster, less expensive and more efficient trials



DURATION OF FOLLOW-UP

- If a given aneurysm treatment can demonstrate:
  - adequate aneurysm occlusion (Raymond I or II equivalent) that is stable for a cohort of patients at one year,
  - Significant architectural advantages over coils
- The likelihood of significant aneurysm regrowth is ***low***.

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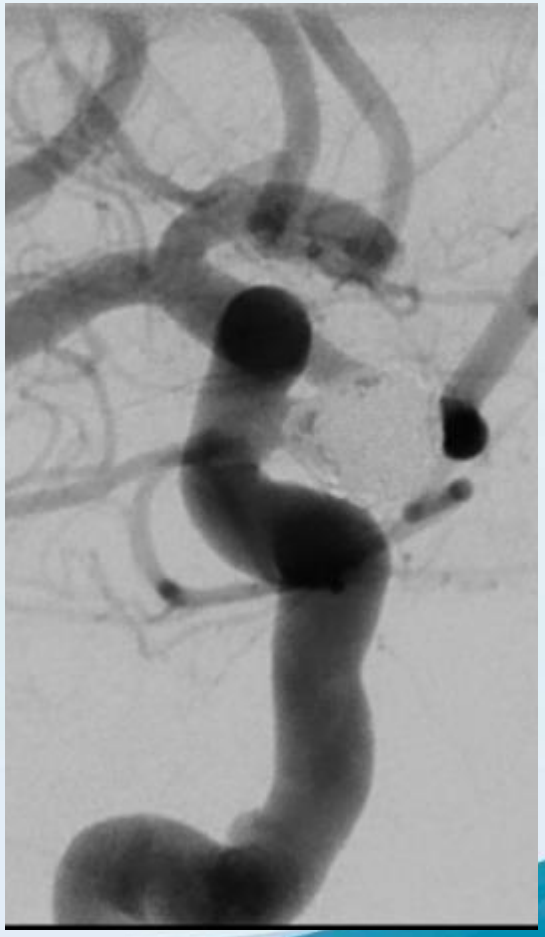
WORSENING IN RAYMOND GRADE

- The Raymond score system is specific to coils only.
- Clinically, worsening in Raymond scale does not mandate retreatment and does not constitute a treatment failure in and of itself.



“INSURANCE POLICY”

- Post-Market Surveillance Studies
  - Enrich under represented subsets
  - Evaluate for continuing safety and efficacy
  - Monitor for any “signals” in pivotal trial

Evidence Based Medicine and Intracranial Aneurysms

Robert E. Harbaugh, MD, FAANS, FACS, FAHA
Director, Neuroscience Institute
University Distinguished Professor & Chair, Department of Neurosurgery
Professor, Engineering Science and Mechanics
Penn State University - Milton S. Hershey Medical Center

Unruptured Intracranial Aneurysms: Who and How to Treat?

- Many intracranial aneurysms are found incidentally
  - Imaging studies - 0.5 - 2% of population
  - Autopsy studies - 1 - 9% of population
- Unruptured intracranial aneurysms (UIAs) may remain asymptomatic.
- If there is an aneurysm rupture there is a 30-50% one month mortality.
- All aneurysm treatments carry a risk of morbidity and mortality.
- How can we choose which UIAs to treat?

Estimating Risk of Rupture

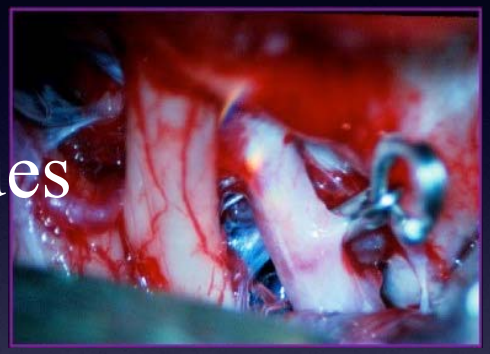
Risk factor	Key findings	Investigators
Size	Larger UIAs have greater RR Aneurysm size is an independent predictor of RR Defining a critical size threshold remains difficult	ISUIA investigators Wiebers et al. 2003 Ishibashi et al. 2009
Enlargement	IAs are often larger at time of rupture than at diagnosis Larger UIAs are more likely to grow Larger UIAs → greater growth risk → increased RR	Yasui et al. 1996 Burns et al. 2009 Matsubara et al. 2004
Previous SAH	Prior history of aneurysmal SAH increases RR Aneurysms <7mm have greater RR with prior history of SAH	ISUIA investigators Wiebers et al. 2003
Location	Posterior circulation aneurysms are more hazardous Intracavernous IAs are more benign	Weir et al. 2002 Wermer et al. 2007 Kupersmith et al. 1992
Patient	Age, sex and co-morbidities influence aneurysmal RR Female sex and cigarette smoking are independent predictors of aneurysm formation, growth and rupture	Nahed et al. 2005 Juvela et al. 2001
Morphology	Multiple lobulations or loculations increase RR High dome:neck ratio increases RR Aneurysm angle from parent vessel is a predictor of rupture	Hademenos et al. 1998 Beck et al. 2003 Dhar et al. 2008
	Quantified irregular aneurysm shape is a predictor of rupture	Harbaugh, Raghavan et al. 2004, 2005, 2015
	Aneurysm shape determines hemodynamic stress and is associated with biological behavior of aneurysm wall	Raghavan, Harbaugh, Laaksamo et al. 2007, 2010, 2012, 2014

What ISUIA Did and Didn't Tell Us

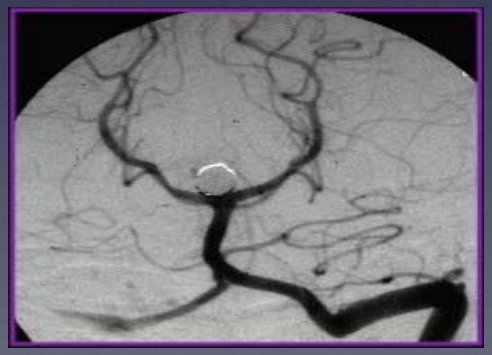
- In ISUIA, if the neurovascular specialists who evaluated the patients deemed the risk of treatment to be less than the risk of rupture, treatment was recommended.
- If they deemed the risk of rupture to be less than the risk of treatment, observation was recommended.
- Patients with small aneurysms, for whom observation was recommended, had a low risk of rupture.
- The most parsimonious explanation is that the physicians selected UIAs with a low risk of rupture for observation.
- ISUIA tells us nothing about what would have happened to the aneurysms chosen for treatment had treatment not occurred.

How Do We Gather Further Data?

- Decision Analysis to clarify the issues



- Then
  - A Randomized Controlled Trial or
  - An Observational Database?



Decision Analysis for UIAs

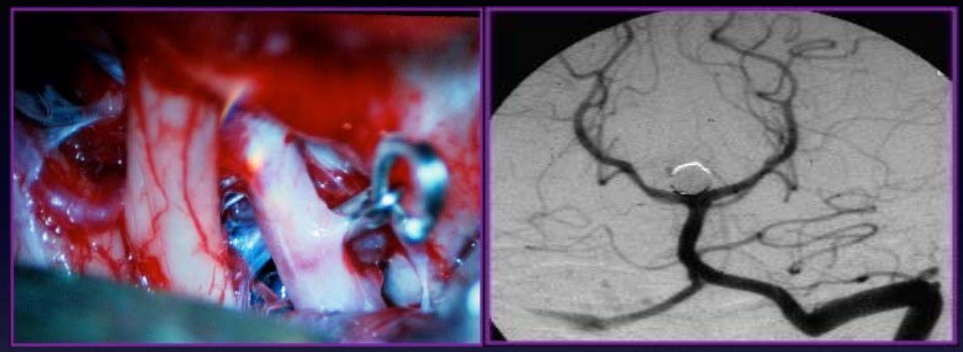
- Patients start out neurologically well at age 40
- Natural history annual rupture rate is 1.46%
- Clipping has 11.2% morbidity/mortality, decreases risk of hemorrhage by 95%
- Coiling has 5.6% morbidity/mortality, decreases risk of hemorrhage by 75%
- Actuarial risks from U.S. Health Statistics
- Standard discount rate for later years of life
- QALYs assigned via Monte Carlo method

Decision Analysis Results

One year from entry
- Observe - 0.93 QALY
- Coil - 0.87 QALY
- Clip - 0.75 QALY

Five years from entry
- Coil - 4.77 QALY
- Clip - 4.72 QALY
- Observe - 4.52 QALY

Lifetime
- Clip - 32.17 QALY
- Coil - 30.62 QALY
- Observe - 27.75 QALY



Crossover point for clipping vs. coiling is 10.5 years

How reliable are the data on which the model is based?

Are the results patient and surgeon specific?

Problems with RCTs

Intention to treat and crossovers

RCT surgeons and patients may not be representative and surgical expertise has profound effects on study outcome.

RCTs are very expensive and labor intensive.

As technology changes results of RCTs may be invalidated

Lack of equipoise

Lack of Equipoise

Concerns

- 40 year old woman, positive FH of aneurysm rupture, cigarette smoker, 10 mm, irregular, basilar apex aneurysm - would you randomize?

- 65 year old woman, no FH of aneurysm rupture, non-smoker, 7 mm, regular, ophthalmic artery aneurysm - would you randomize?

- Duration of study - 2 years? 5 years? 15 years?

Observational Database Designed for Propensity Score Analysis

- An RCT differs from an observational study in one design issue: the use of randomization to allocate patients to treatment and control groups.
- Randomization ensures that treatment status, within the trial, will not be confounded by measured or unmeasured baseline characteristics - so treatment effect can be determined by directly comparing outcomes.
- In an observational study, treatment selection is influenced by covariates that may differ among groups - so we must account for these differences when determining treatment effect.

Observational Database Designed for Propensity Score Analysis

What is Propensity Analysis?

- The propensity score is the probability of treatment assignment due to baseline covariates.
- Patients with the same propensity score have the same distribution of covariates and differ only in regard to the intervention being studied.
- Propensity analysis allows a properly designed, non-randomized observational study to mimic an RCT.

Observational Database Designed for Propensity Score Analysis

- What randomized experiment do we want to model?
- Who are the decision makers for treatment assignment?
- What are the key covariates used to assign treatment?
- Can we measure the key covariates well?
- What clinically meaningful outcomes will we measure?
- What sample sizes will be needed?

- If we address the issues above we will be able to draw reliable causal inferences from the data. This may correct some of the inadequacies of the present EBM algorithm.

Designing an Observational Database for Treatment of UIAs

What randomized experiment do we want to model?

Observation vs invasive treatment for patients with UIAs

Who are the decision makers for treatment assignment?

Physicians, patients and family members

What key covariates do they use to decide?

Patient-specific factors (patient age, prior aneurysm rupture, co-morbidities, social history, family history, patient preferences) aneurysm-specific factors (aneurysm size, shape and location) and physician-specific factors (endovascular specialist, open surgical specialist, both, neither, years of experience, practice setting)

Are the key covariates well measured?

Define and quantify key covariates

What are the clinically meaningful outcomes we want to measure

Mortality, aneurysm rupture, functional health status, QOL

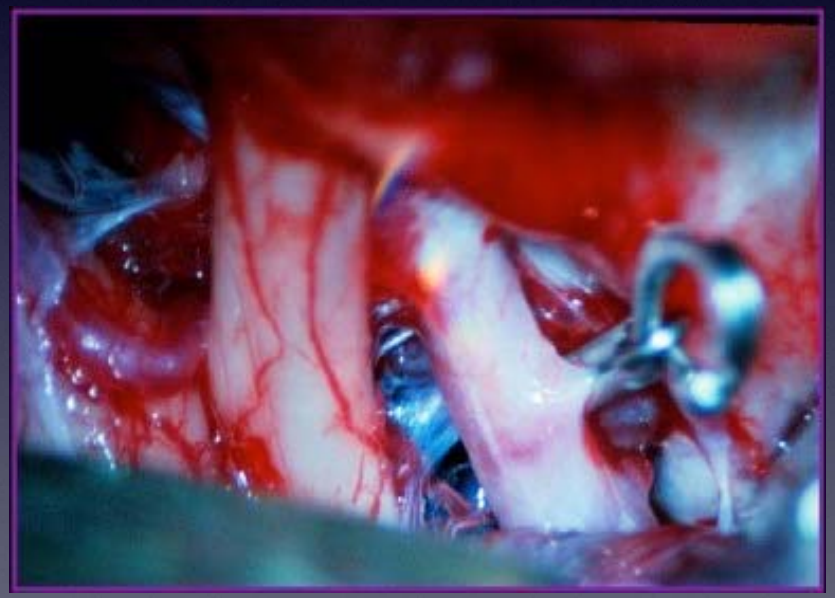
What sample sizes will be needed?

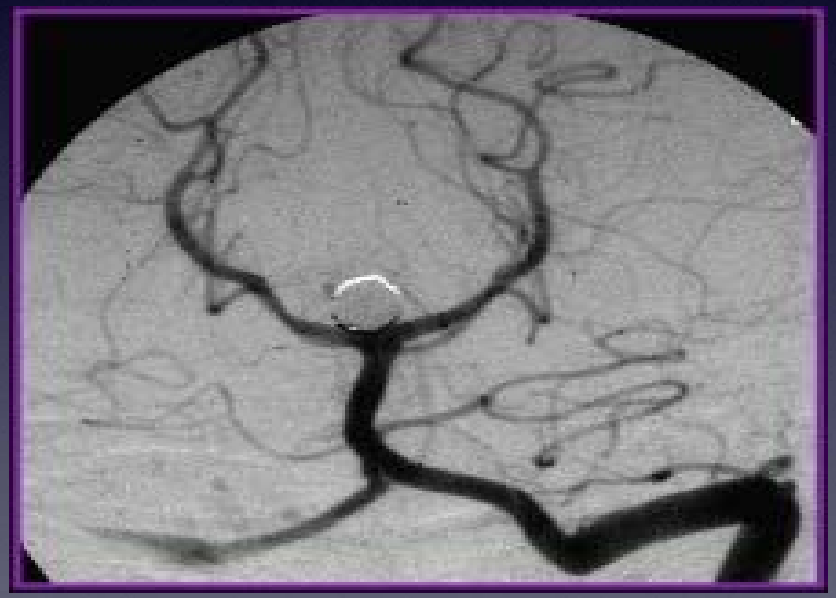
Traditional power calculations

Post Market Observation Database

- UIA-POD would provide a multicenter registry designed to allow propensity matching of patients evaluated for unruptured intracranial aneurysms.
- It will allow patients with the same propensity score to be evaluated for outcomes with observation, endovascular and open treatment.
- Comparisons of outcomes for patients with the same propensity score except for treatment assignment will allow us to draw causal inferences regarding treatment effects from an observational study.
- This approach combines some of the best features of registries and RCTs.

Thank You for Your Attention





Endpoints for Neuroendovascular Device Trials

David Fiorella, MD PhD
Director of the Cerebrovascular Center
Professor of Neurosurgery and Neuroradiology
State University of NY at Stony Brook
Stony Brook, NY

SNIS Society of NeuroInterventional Surgery

Trial Endpoints: Aneurysm

- The Raymond Scale was created to assess the occlusion of **coiled aneurysms**
- This scale has been recently applied to all aneurysm devices
  - "Complete Occlusion" (Raymond Scale Grade 1) has become the accepted primary effectiveness endpoint

Trial Endpoints: Aneurysm

- "One-size fits all" scale is not appropriate
  - Very heterogeneous disease process
  - Different EV device morphologies and mechanisms of action

Trial Endpoints: Aneurysm

- Effectiveness endpoints need to be appropriately matched to devices and anatomy
- Key Considerations Differ
  - Coils (+/- Stent)
  - Intra-Saccular Braided Devices
  - Flow Diverter

Trial Endpoints: Aneurysm

- Effectiveness endpoints need to be appropriately matched to devices and anatomy
- Key Considerations Differ
  - **Coils (+/- Stent)**
  - Intra-Saccular Braided Devices
  - Flow Diverter

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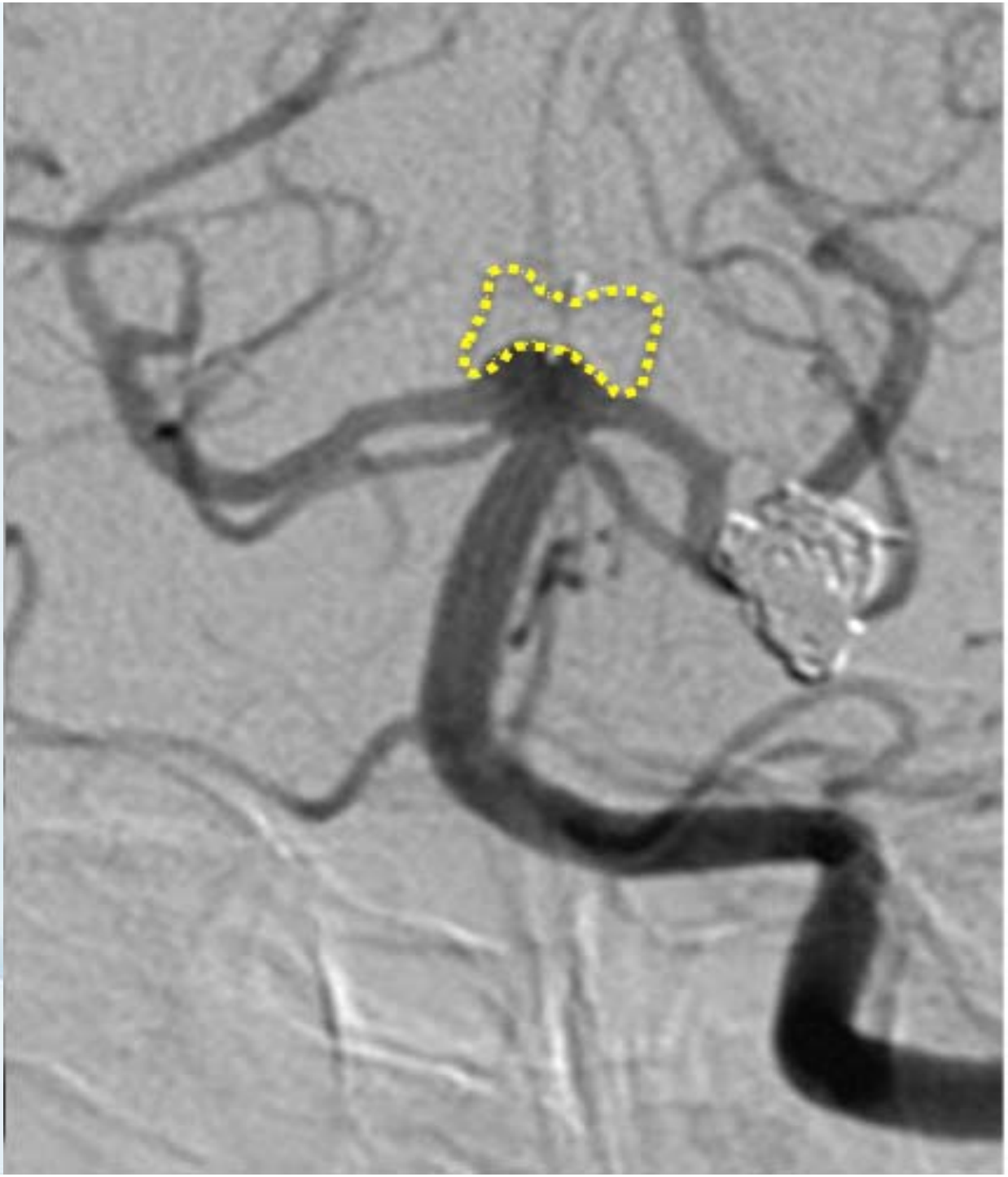
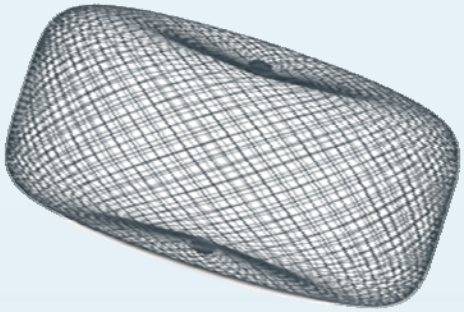
Coils (+/- Stent or BAT)

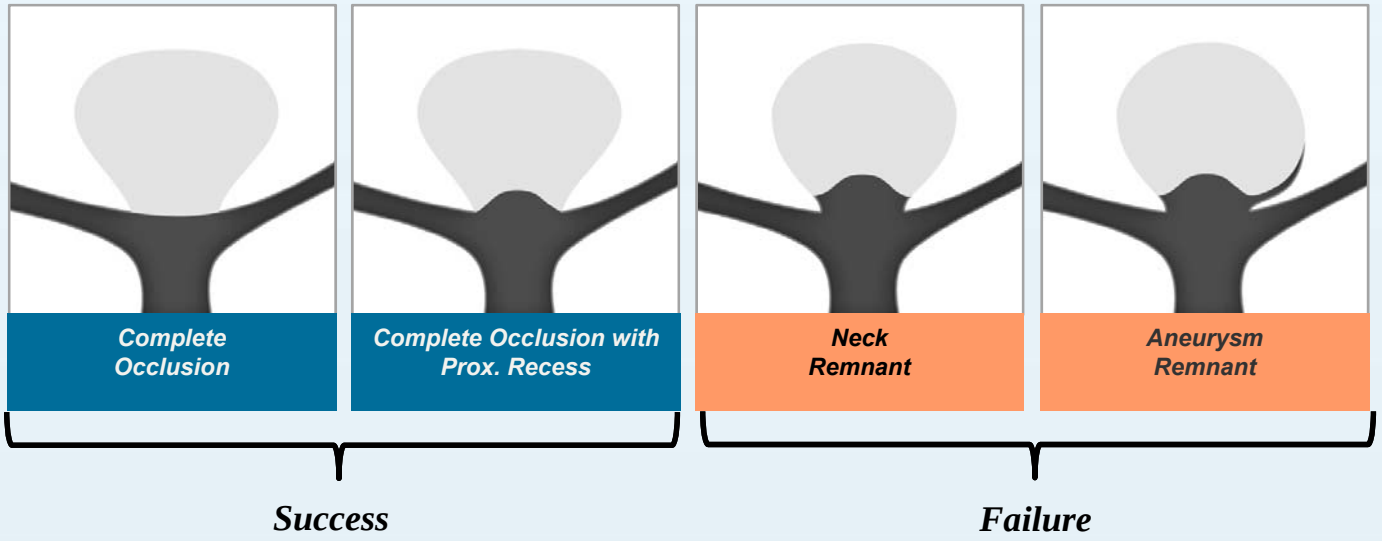
- Coils fill the aneurysm and reconstruct an irregular mass at the aneurysm-parent artery interface (even in Raymond 1)
  - Particularly evident in wide-necked aneurysms
- **Raymond scale is appropriate for the assessment of effectiveness**
  - Designed and validated for coils (+/- stents or BAT)

Trial Endpoints: Aneurysm

- Effectiveness endpoints need to be appropriately matched to devices and anatomy
- Key Considerations Differ
  - Coils (+/- Stent)
  - **Intra-Saccular Braided Devices**
  - Flow Diverter







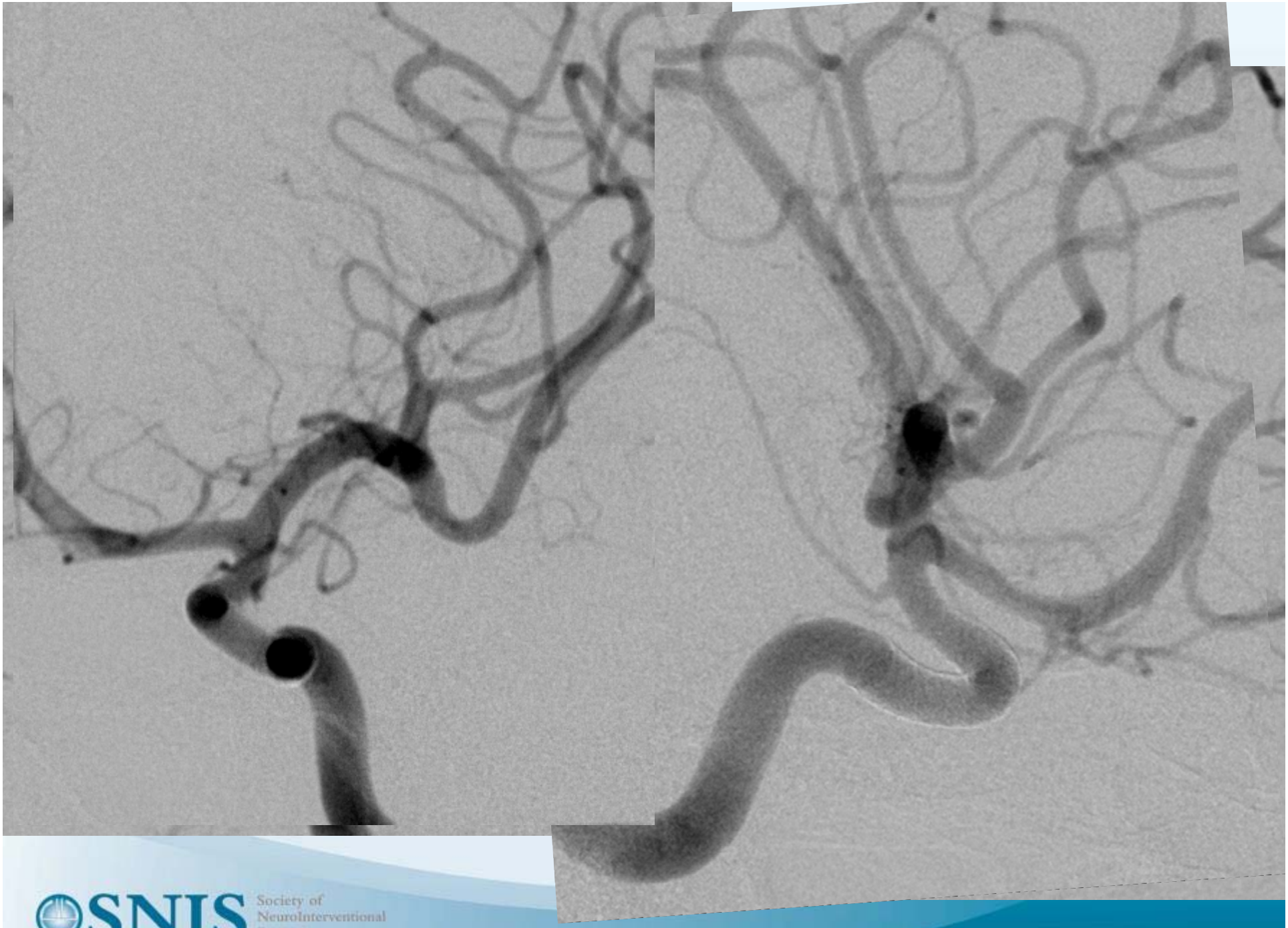
- Developed and validated a modification of the Raymond Scale (WEB Occlusion Scale)
  - Validated histology
  - Validated inter and intra-observer variabiltiy
  - Documented Stability

Braided Intra-Saccular Devices

- Very analogous to coils, so **Raymond Scale is a good starting point**
  - **May need to be modified** based upon the shape and mechanism of the particular intra-saccular device

Trial Endpoints: Aneurysm

- Effectiveness endpoints need to be appropriately matched to devices and anatomy
- Key Considerations Differ
  - Coils (+/- Stent)
  - Intra-Saccular Braided Devices
  - **Flow Diverter**



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Intra-vascular Flow Diverters

- **Raymond Scale NOT relevant**
  - Binary result = complete occlusion or not

Trial Endpoints: Aneurysm

- The “best-achievable” angiographic result

- The most ≠ appropriate angiographic effectiveness endpoint

Trial Endpoints: Aneurysm

- Effectiveness endpoints need to be **clinically appropriate** and matched to devices, anatomy and mechanism

Trial Endpoints: Flow Diversion

- **Complete occlusion**

  = the most clinically appropriate angiographic effectiveness endpoint **for intra-vascular flow diverters**

Trial Endpoints: Flow Diversion

- Aneurysm regression and physiological remodeling typically requires complete occlusion
- (Often times) nothing is placed in the saccular component (e.g., coils)
- Complete occlusion is a safely achievable endpoint in a high percentage of cases

Trial Endpoints: Intra-Saccular Devices

- **Adequate occlusion (complete + near complete occlusion)**

  = the most clinically appropriate angiographic effectiveness endpoint **for intra-saccular aneurysm devices**

Why is “near complete occlusion” an acceptable endpoint for intra-saccular devices

- ISAT (and BRAT) demonstrated **durably better outcomes** for EVT in comparison to surgery for ruptured aneurysms
  - **~ 6-7%** absolute benefit for coiling in both studies **(OR 1.3)**
    - ISAT follow up now >10 years
    - BRAT follow up now 6 years

Why is “near complete occlusion” an acceptable endpoint for intra-saccular devices

- Complete occlusion rates in ISAT and BRAT were lower for EVT (~50%) than surgery (~80-95%)

Why is “near complete occlusion” an acceptable endpoint for intra-saccular devices

- Rates of death or disability from re-bleeds were **EXCEEDINGLY LOW in both studies**
  - ISAT
    - 6 coil (0.072%) = 1/1397 pt-yrs
    - 4 clip (0.049%) = 1/2041 pt-yrs
  - BRAT
    - **No delayed re-bleed in any coiled** patient at 6 years

Why is “near complete occlusion” a pragmatic and acceptable endpoint for intrasaccular devices

- Aneurysm re-bleeding was **not a major cause of morbidity or mortality** in ISAT patients
  - **> 40x** more likely to die from another cause
  - **6 patients** (4 coil/2 clip) died from re-bleed vs. **232** from other causes (cancer and CV disease)

What about future re-treatments?

- Aneurysm re-treatment was not a major cause of death or disability in either ISAT or BRAT
  - Zero death or disability from late re-treatment in BRAT through 6 years
  - Zero death or disability from late re-treatment in ISAT

Complete occlusion is a potentially sub-optimal endpoint

- Encourages Over-aggressive treatment (particularly within approval trials)
  - Use of **too many** implants
  - Use of **oversized** intra-saccular devices
- Could lead to higher rates of complications

Complete occlusion is a potentially sub-optimal endpoint

- Undue emphasis on low rates of "complete occlusion"
  - Could potentially delay, or lead to inappropriate non-clearance, of safe and effective devices

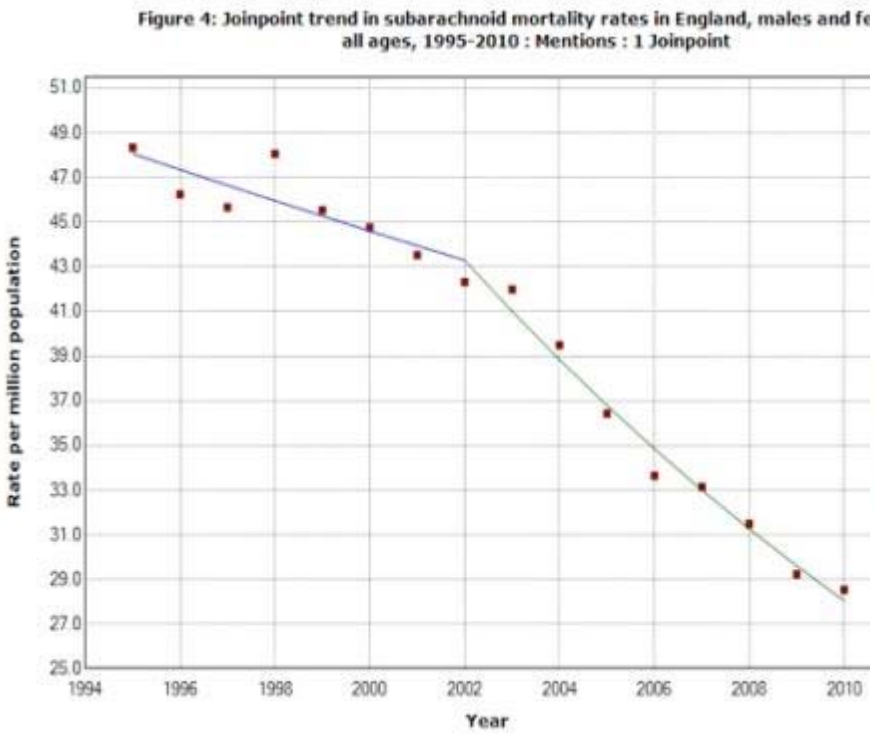
For aneurysms amenable to EVT…

- EVT provides excellent protection against death and disability from the re-rupture in previously ruptured aneurysms
  - and in all probability, rupture in unruptured aneurysms
- **Adequate occlusion (C + NC) of aneurysms after intra-saccular EVT is effective**
- EVT has a superior safety profile to surgery with better clinical outcomes

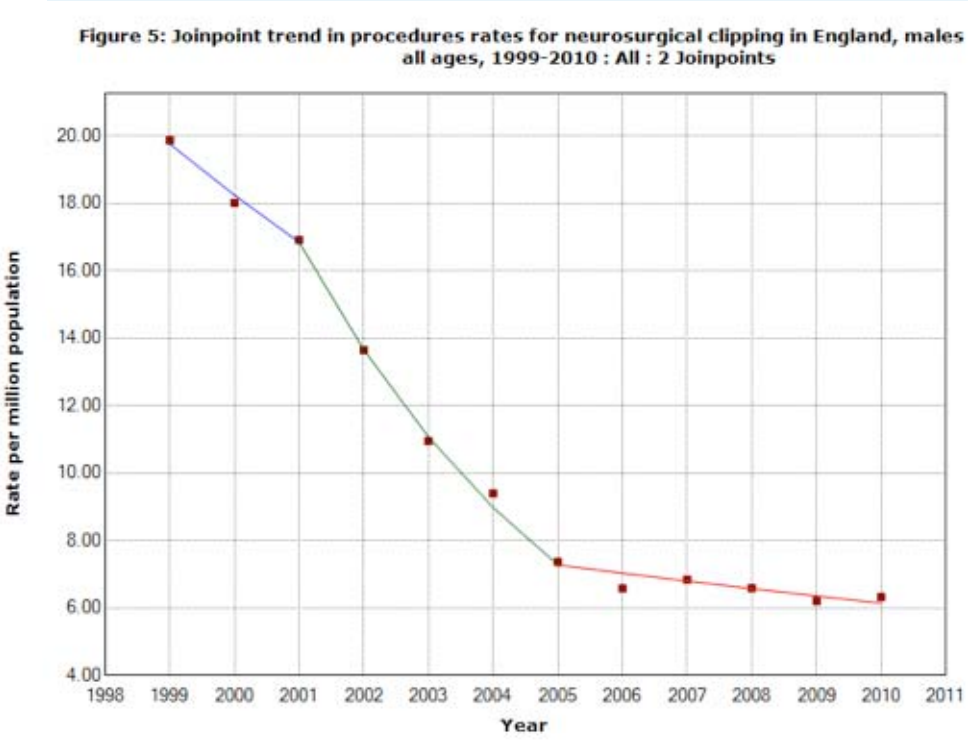
Small aneurysm neck remnants after EVT **are generally not the problem**

- How can FDA **improve outcomes** for aneurysm patients ?
  - Provide access to innovative EV therapies
    - which make treatments **less invasive, easier and safer**
    - which **extend the spectrum of aneurysms that can be treated with minimally invasive EVTs**

Population Mortality Trends in England 1995-2010 for SAH



Clipping rates of ruptured cerebral aneurysm 1999 – 2010



Rates per million population

Currently estimated that 90% of aneurysms are treated with EVT

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Slide courtesy of Dr. Andy Molyneaux

FDA Aneurysm Panel

J Mocco, MD, MS, FAANS, FAHA
Professor and System Vice Chair
Director of The Cerebrovascular Center
Department of Neurological Surgery
Mount Sinai Health System

Question 1

1. Typically, aneurysm device trial primary safety endpoints have focused on death and major ipsilateral stroke (defined as an increase in the National Institutes of Health Stroke Scale (NIHSS) by 4 points at the time of stroke event within 1 year after treatment). Additional safety events (adverse events or AEs) that are considered in our safety assessment of new devices include:

Question 1

Access Site Issues (e.g., Dissections, Hematomas)
Aneurysm Leak, Rupture, or Contrast Extravasation
Distal Embolic Phenomenon
Dual Antiplatelet Therapy (DAPT) Related AEs
Mechanical Device Failures and/or Acute or Delayed Device Migration or Embolization
Minor Ipsilateral Strokes (NIHSS Change < 4)
Transient Ischemic Attacks (TIAs)

Question 1

Please address the following:

a. Is the AE list above complete? If not, what AE(s) should be added?

b. Are there specific rates of AEs that would raise serious concerns about the safety of any specific device?

Question 1

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a. Is the AE list above complete? If not, what AE(s) should be added?

Some simple additions: intraprocedural thrombotic events, delayed access site infection, cranial neuropathy

Question 1

Please address the following:

a. Is the AE list above complete? If not, what AE(s) should be added?

World Health Organization

Guidelines for Good Clinical Practice

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Please address the following:

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Guidelines for Good Clinical Practice

Any untoward medical occurrence in a clinical trial subject…

it does not necessarily have a causal relationship with the treatment.

Question 1

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World Health Organization

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Question 1

Please address the following:

b. Are there specific rates of AEs that would raise serious concerns about the safety of any specific device?

Question 1

Please address the following:

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No

Question 1

Please address the following:

b. Are there specific rates of AEs that would raise serious concerns about the safety of any specific device?

No

Any untoward medical occurrence in a clinical trial subject…

it does not necessarily have a causal relationship with the treatment.

Question 1

Please address the following:

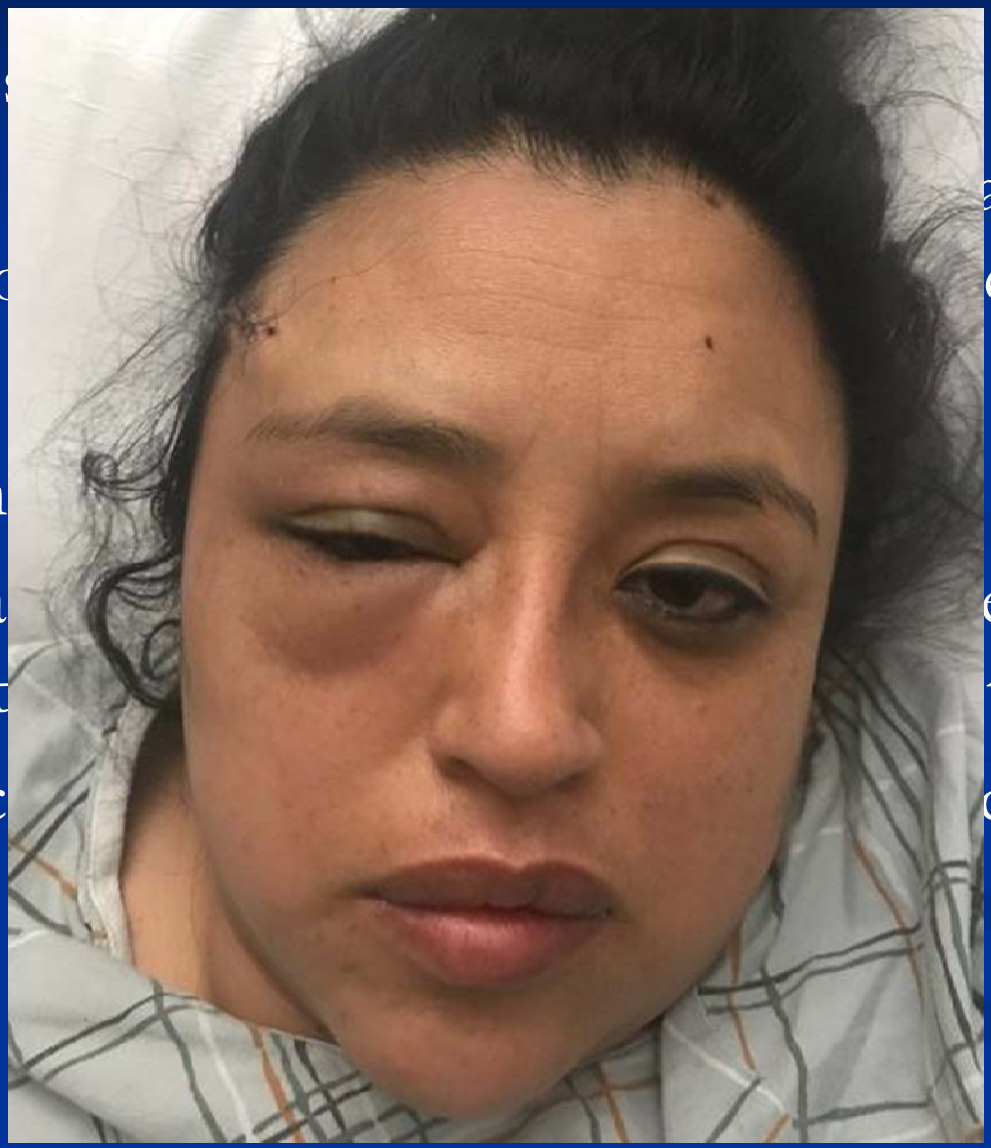
b. Are there specific rates of AEs that would raise serious concerns about the safety of any specific device?

AE's demonstrate:

1) A wide variety of causes, often due to a patients: pre-morbid state, unrelated procedural events, and patient tolerance of stress

2) Variable consistency in reporting. No fixed denominator.

Question 1



Please addres

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AE's demon

1) A wide va ents: pre-morbid state, unrelat tolerance of stress

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Question 1

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AE's demonstrate:

1) A wide variety of causes, often due to a patients: pre-morbid state, unrelated procedural events, and patient tolerance of stress

2) Variable consistency in reporting. No fixed denominator.

Safety should be driven by fixed endpoint, known denominator, validated assessments

Question 2

2. The modified Rankin Scale (mRS) has often been incorporated as a secondary endpoint. Can the mRS at 1 year also be a potential primary safety outcome measure for all endovascular device trials? If yes, what magnitude of decline in the mRS and for what percentage of treated subjects with a decline in the mRS at 1 year follow-up would raise serious concerns about the safety of the device? If no, what alternative primary safety outcomes are possible and for what duration of time.

Question 2

2. The modified Rankin Scale (mRS) has often been incorporated as a secondary endpoint. Can the mRS at 1 year also be a potential primary safety outcome measure for all endovascular device trials?

For UIA – Yes

For SAH – No

Question 2

2. If yes, what magnitude of decline in the mRS and for what percentage of treated subjects with a decline in the mRS at 1 year follow-up would raise serious concerns about the safety of the device?

UIA

ISUIA 1 yr mRS 3-6 rate = 6.6% (clipping 7.1%)

- Baseline mRS of 0-2 population

Therefore: mRS 3-6 rate in mRS 0-2 population >10% would raise serious concern

Question 3

3. Considering the AE list above and any additional AEs specified in response to question #1.a., what patient characteristics (e.g., malignancy, advanced age, aneurysm size) justify foregoing treatment for an aneurysm that would otherwise be considered for treatment?

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Life Expectancy <1yr

Question 3

3. Considering the AE list above and any additional AEs specified in response to question #1.a., what patient characteristics (e.g., malignancy, advanced age, aneurysm size) justify foregoing treatment for an aneurysm that would otherwise be considered for treatment?

Life Expectancy <1yr

Age >85?

Actuarial Life Table

Period Life Table, 2014

	Male			Female		
Exact age	Death probability [a]	Number of lives [b]	Life expectancy	Death probability [a]	Number of lives [b]	Life expectancy
70	0.023380	73,427	14.32	0.015612	82,818	16.53
71	0.025549	71,710	13.66	0.017275	81,525	15.78
72	0.027885	69,878	13.00	0.019047	80,117	15.05
73	0.030374	67,930	12.36	0.020909	78,591	14.34
74	0.033099	65,866	11.73	0.022939	76,947	13.63
75	0.036254	63,686	11.11	0.025297	75,182	12.94
76	0.039882	61,377	10.51	0.028045	73,280	12.26
77	0.043879	58,930	9.93	0.031131	71,225	11.60
78	0.048256	56,344	9.36	0.034582	69,008	10.96
79	0.053123	53,625	8.81	0.038467	66,621	10.33
80	0.058711	50,776	8.28	0.043008	64,059	9.73
81	0.065081	47,795	7.76	0.048175	61,304	9.14
82	0.072139	44,685	7.27	0.053772	58,350	8.58
83	0.079912	41,461	6.80	0.059770	55,213	8.04
84	0.088529	38,148	6.34	0.066367	51,913	7.52
85	0.098148	34,771	5.91	0.073828	48,467	7.01

Question 3

3. Considering the AE list above and any additional AEs specified in response to question #1.a., what patient characteristics (e.g., malignancy, advanced age, aneurysm size) justify foregoing treatment for an aneurysm that would otherwise be considered for treatment?

Aneurysm treatment is a complex and nuanced decision that is ultimately driven by patient choice with physician guidance.

We should resist creating well-intended but inappropriately restrictive external limits on patient characteristics.

Aneurysm Size

The New England
Journal of Medicine

VOLUME 339 DECEMBER 10, 1998 NUMBER 24

UNRUPTURED INTRACRANIAL ANEURYSMS — RISK OF RUPTURE AND RISKS OF SURGICAL INTERVENTION

THE INTERNATIONAL STUDY OF UNRUPTURED INTRACRANIAL ANEURYSMS INVESTIGATORS*

Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment

*International Study of Unruptured Intracranial Aneurysms Investigators**

Aneurysm Size

	<7 mm		7–12 mm	13–24 mm	⩾25 mm
	Group 1	Group 2			
Cavernous carotid artery (n=210)	0	0	0	3·0%	6·4%
AC/MC/IC (n=1037)	0	1·5%	2·6%	14·5%	40%
Post-P comm (n=445)	2·5%	3·4%	14·5%	18·4%	50%

AC=anterior communicating or anterior cerebral artery. IC=internal carotid artery (not cavernous carotid artery). MC=middle cerebral artery. Post-P comm=vertebrobasilar, posterior cerebral arterial system, or the posterior communicating artery.

Table 4: **5-year cumulative rupture rates according to size and location of unruptured aneurysm**

ISUIA writing group member

I have personally reviewed over 250 ISUIA angiograms… including all ruptured cases

J Neurointerv Surg. 2013 Aug 13. doi: 10.1136/neurintsurg-2013-010838. [Epub ahead of print]

An angiographic atlas of intracranial arterial diameters associated with cerebral aneurysms.

Mocco J[1], Huston J, Fargen KM, Torner J, Brown RD Jr; for the International Study of Unruptured Aneurysms Investigators.

Transl Stroke Res. 2014 Apr;5(2):252-9. doi: 10.1007/s12975-014-0330-5. Epub 2014 Jan 31.

Aneurysm Shape Reconstruction from Biplane Angiograms in the ISUIA Collection.

Raghavan ML[1], Sharda GV, Huston J 3rd, Mocco J, Capuano AW, Torner JC, Saha PK, Meissner I, Brown RD Jr; International Study of Unruptured Intracranial Aneurysms Investigators.

ISUIA writing group member

I have personally reviewed over 250 ISUIA angiograms… including all ruptured cases

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Raghavan ML[1], S

Aneurysms Investi

Inruptured Intracranial

Aneurysm Morphology and Prediction of Rupture: An International Study of Unruptured Intracranial Aneurysms Analysis

J. Mocco, MD, MS*
Robert D Brown, Jr, MD, MPH‡
James C. Torner, PhD§
Ana W. Capuano, PhD¶
Kyle M. Fargen, MD, MPH‖
Madhavan L. Raghavan, PhD#
David G. Piepgras, MD**
Irene Meissner, MD‡‡
John Huston III, MD##
on behalf of the International Study of Unruptured Intracranial Aneurysms Investigators

*Department of Neurosurgery, Mount Sinai Medical Center, New York, New York; ‡Department of Neurology, Mayo Clinic, Rochester, Minnesota; §Department of Epidemiology, University of Iowa, Iowa City, Iowa; ¶Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL; ‖Department of Neurosurgery, Wake Forest University, Winston-Salem, North Carolina; #Department of Biomedical Engineering, University of Iowa, Iowa City, Iowa; **Department of Neurosurgery, Mayo Clinic, Rochester, Minnesota; ‡‡Department of Radiology, Mayo Clinic,

BACKGROUND: There are conflicting data between natural history studies suggesting a very low risk of rupture for small, unruptured intracranial aneurysms and retrospective studies that have identified a much higher frequency of small, ruptured aneurysms than expected.

OBJECTIVE: To use the prospective International Study of Unruptured Intracranial Aneurysms cohort to identify morphological characteristics predictive of unruptured intracranial aneurysm rupture.

METHODS: A case-control design was used to analyze morphological characteristics associated with aneurysm rupture in the International Study of Unruptured Intracranial Aneurysms database. Fifty-seven patients with ruptured aneurysms during follow-up were matched (by size and location) with 198 patients with unruptured intracranial aneurysms without rupture during follow-up. Twelve morphological metrics were measured from cerebral angiograms in a blinded fashion.

RESULTS: Perpendicular height ($P = .008$) and size ratio (ratio of maximum diameter to the parent vessel diameter; $P = .01$) were predictors of aneurysm rupture on univariate analysis. Aspect ratio, daughter sacs, multiple lobes, aneurysm angle, neck diameter, parent vessel diameter, and calculated aneurysm volume were not statistically significant predictors of rupture. On multivariate analysis, perpendicular height was the only significant predictor of rupture (Chi-square 7.1, *P*-value .008).

CONCLUSION: This study underscores the importance of other morphological factors, such as perpendicular height and size ratio, that may influence unruptured intracranial aneurysm rupture risk in addition to greatest diameter and anterior vs posterior location.

KEY WORDS: Aneurysm, Cerebrovascular circulation, Subarachnoid hemorrhage, Morphology, Cerebral aneurysm, Hemorrhagic stroke, Natural history, Unruptured

Neurosurgery 0:1–6, 2017 DOI:10.1093/neuros/nyx226 www.neurosurgery-online.com

Weir et al.

J Neurosurg 96:64–70, 2002

Sizes of ruptured and unruptured aneurysms in relation to their sites and the ages of patients

BRYCE WEIR, M.D., LEW DISNEY, M.D., PH.D., AND THEODORE KARRISON, PH.D.

Section of Neurosurgery, and the Department of Health Studies, University of Chicago, Illinois; and University of Alberta, Edmonton, Alberta, Canada

Object. The authors explore the risk of rupture in aneurysms categorized by size.

Methods. A computerized database of 945 patients with aneurysms treated between 1967 and 1987 was retrospectively established. All available clinical and radiological studies were abstracted. Because of the recent interest in the size of intracranial aneurysms in relation to their likelihood of rupture, the database was searched with respect to this parameter. In 390 patients representing 41% of all cases, aneurysms were measured by neuroradiologists at the time of diagnosis. In 78% of the 945 patients there was only one aneurysm, and of the 507 aneurysms that were measured, 60% were solitary. Of all patients, 86% had ruptured aneurysms. The average age of all patients was 47 years, and for those with ruptured aneurysms it was 46 years. Of the ruptured aneurysms, 77% were 10 mm or smaller, compared with 85% of the unruptured aneurysms. It was found that 40.3% of the ruptured aneurysms were on the anterior cerebral artery or anterior communicating artery, compared with 13% of the unruptured aneurysms. None of the cavernous internal carotid artery (ICA) aneurysms were ruptured and 65% of the ophthalmic artery (OphA) aneurysms were. Of the unruptured aneurysms, 15% were located in the cavernous ICA or the OphA. Of the ruptured aneurysms, 29% were on the middle cerebral artery, compared with 36% of the unruptured aneurysms. The mean size of ruptured and unruptured aneurysms showed no statistically significant increase with patient age, although the difference in size between the ruptured and unruptured aneurysms decreased with increasing age. The mean size of all ruptured aneurysms (10.8 mm) was significantly larger than the mean size of all unruptured aneurysms (7.8 mm, $p < 0.001$); the median sizes were 10 mm and 5 mm, respectively. The size of ruptured aneurysms in patients who died in the hospital was significantly larger than those in the patients who survived (12 mm compared with 9.9 mm, $p = 0.004$). Symptomatic unruptured aneurysms were significantly larger than incidental unruptured aneurysms (14.6 mm compared with 6.9 mm, $p = 0.032$), which were, in turn, larger than aneurysms that were unruptured and part of a multiple aneurysm constellation. Both ruptured and unruptured aneurysms were larger in male than in female patients, but not significantly.

Conclusions. Site and patient age, as well as lesion size, may affect the chance of rupture.

Weir et al.

945 patients (86% of which were ruptured)

Of those with ruptured aneurysms 77% were <10mm

40.3% of ruptured aneurysms were on the ACA or Acom

Only 13% of unruptured aneurysms were ACA/Acom

Carter et al.

Wolters Kluwer Health | Lippincott Williams & Wilkins

NEUROSURGERY Online

Epidemiology of the Size Distribution of Intracranial Bifurcation Aneurysms: Smaller Size of Distal Aneurysms and Increasing Size of Unruptured Aneurysms with Age

Author(s): Carter, Bob S. M.D., Ph.D.; Sheth, Sunil A.B.; Chang, Eric M.D.; Sethl, Manish M.D.; Ogilvy, Christopher S. M.D.

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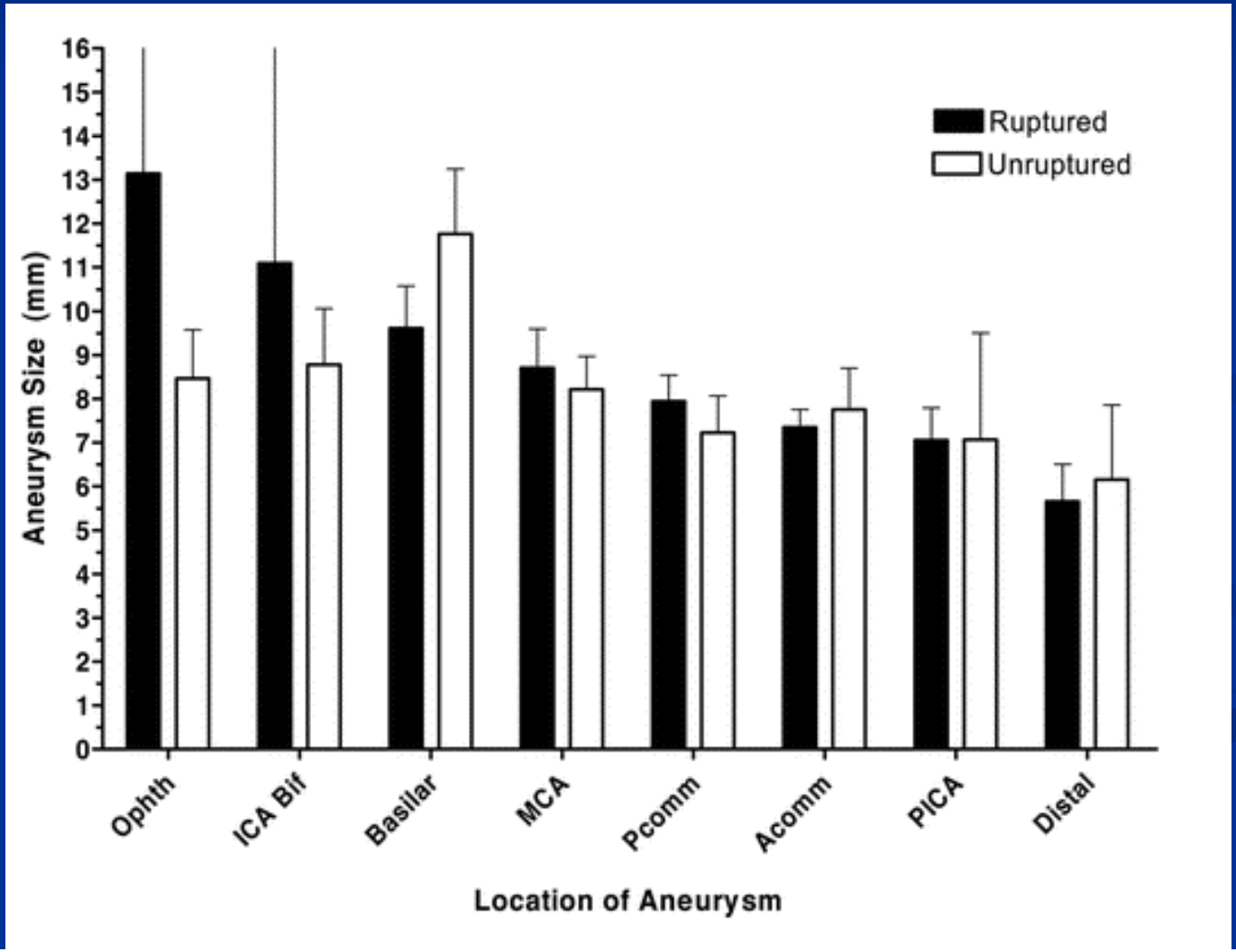
Carter et al.


Ruptured
Unruptured
Aneurysm Size (mm)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
Ophth
ICA Bif
Basilar
MCA
Pcomm
Acomm
PICA
Distal
Location of Aneurysm

New Metrics

Size Ratio Can Highly Predict Rupture Risk in Intracranial Small (<5 mm) Aneurysms

Daina Kashiwazaki, MD; Satoshi Kuroda, MD, PhD; on behalf of the Sapporo SAH Study Group

Background and Purpose—Management strategies for unruptured intracranial aneurysms (UIAs) are controversial. This study aimed to identify surrogate parameters that highly predict the rupture risk of small (<5 mm) UIAs.

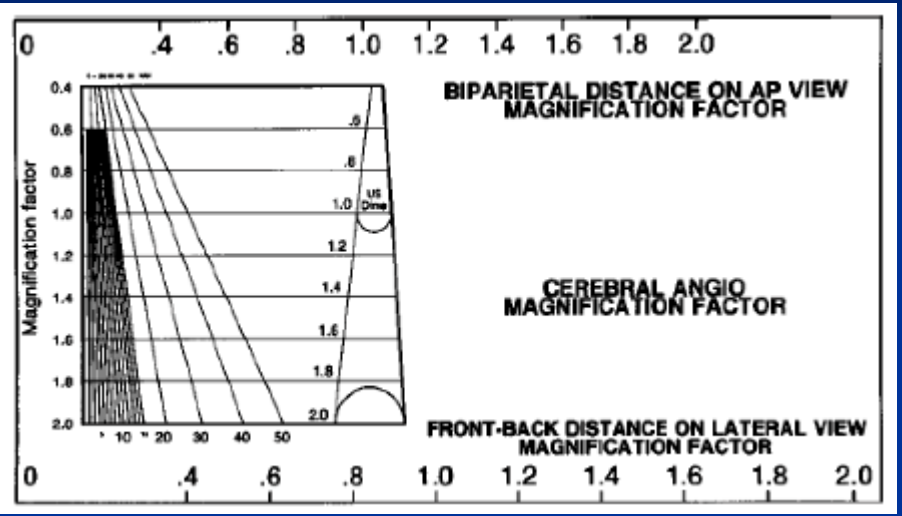
Methods—Radiological data were collected from 854 patients with aneurysmal subarachnoid hemorrhages who were enrolled in the Sapporo SAH Study. They had a total of 854 ruptured intracranial aneurysms and 180 UIAs. The size, aneurysm-to-vessel size ratio, and distribution were precisely compared between ruptured intracranial aneurysms and UIAs.

Results—For all aneurysms, the size was significantly larger in ruptured intracranial aneurysms (7.0±1.3 mm) than in the UIAs (3.7±1.2 mm; $P<0.001$). Size ratio was also significantly higher in ruptured intracranial aneurysms (4.3±1.9) than in the UIAs (2.2±1.6; $P<0.001$). Multivariate logistic analysis showed that size and size ratio were correlated with aneurysm rupture. However, in small aneurysms, multivariate logistic regression revealed that only size ratio was associated with ruptured aneurysms ($P=0.008$; odds ratio, 9.1). There were no significant differences in size or aneurysm location. A receiver operating characteristic analysis was performed for size ratio in small aneurysms, and the threshold separating ruptured and unruptured groups was 3.12 and the area under the curve was 0.801.

Conclusions—This study revealed that the size ratio, and not the absolute size, may highly predict the risk of rupture in small UIAs. Size ratio measurements are very simple and provide useful information for determining treatment and follow-up strategies for patients with small UIAs. (***Stroke*. 2013;44:2169-2173.**)

How reliable is <5 or 7 mm

How reliable is <5 or 7 mm



A special ruler called the cerebral angiogram magnification/minification ruler was devised by one of the authors

Interobserver Variability in Angiographic Measurement and Morphologic Characterization of Intracranial Aneurysms: A Report from the International Study of Unruptured Intracranial Aneurysms

Glenn Forbes, Allan J. Fox, John Huston III, David O. Wiebers, and James Torner

How reliable is <5 or 7 mm

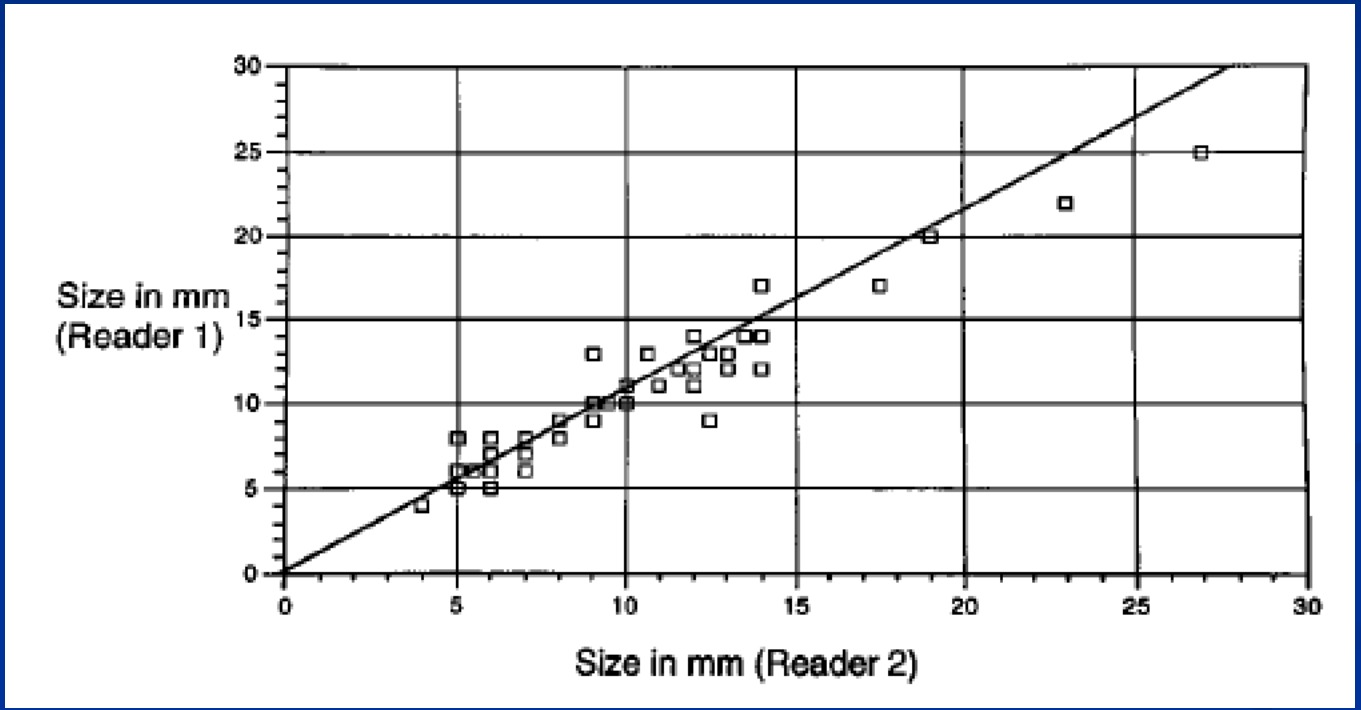
How reliable is <5 or 7 mm

Analysis of Skull Anthropometric Measurements in Patients with Neurofibromatosis Type-1

FRANCIS J. DiMARIO, Jr., MD,* PETER BOWERS, MD,* BIPIN JAGJIVAN, MD,† JOSEPH BURLESON, PhD,‡ SHARON LANGSHUR, MS,* AND ROBERT M. GREENSTEIN, MD*

Retrospective analysis of 58 NF patient X-rays, as well as 200 normal adults

How reliable is <5 or 7 mm



Aneurysm Growth

Aneurysm Growth

Acta Neurochir (2013) 155:211–216
DOI 10.1007/s00701-012-1566-z

CLINICAL ARTICLE - VASCULAR

Incidence of growth and rupture of unruptured intracranial aneurysms followed by serial MRA

K. Matsumoto · S. Oshino · M. Sasaki ·
K. Tsuruzono · S. Taketsuna · T. Yoshimine

Received: 12 May 2012 / Accepted: 13 November 2012 / Published online: 30 November 2012

3.9% per year

Aneurysm Growth

J Neurosurg 117:20–25, 2012

Annual rupture risk of growing unruptured cerebral aneurysms detected by magnetic resonance angiography

Clinical article

Takashi Inoue, M.D., Ph.D.,[1] Hiroaki Shimizu, M.D., Ph.D.,[1] Miki Fujimura, M.D., Ph.D.,[2] Atsushi Saito, M.D., Ph.D.,[1] and Teiji Tominaga, M.D., Ph.D.[3]

[1]Department of Neurosurgery, Kohnan Hospital; [2]Department of Neurosurgery, Sendai Medical Center; and [3]Department of Neurosurgery, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan

Object. In this paper, the authors' goals were to clarify the characteristics of growing unruptured cerebral aneurysms detected by serial MR angiography and to establish the recommended follow-up interval.

Methods. A total of 1002 patients with 1325 unruptured cerebral aneurysms were retrospectively identified. These patients had undergone follow-up evaluation at least twice. Aneurysm growth was defined as an increase in maximum aneurysm diameter by 1.5 times or the appearance of a bleb.

Results. Aneurysm growth was observed in 18 patients during the period of this study (1.8%/person-year). The annual rupture risk after growth was 18.5%/person-year. The proportion of females among patients with growing aneurysms was significantly larger than those without growing aneurysms ($p = 0.0281$). The aneurysm wall was reddish, thin, and fragile on intraoperative findings. Frequent follow-up examination is recommended to detect aneurysm growth before rupture.

Conclusions. Despite the relatively short period, the annual rupture risk of growing unruptured cerebral aneurysms detected by MR angiography was not as low as previously reported. Surgical or endovascular treatment can be considered if aneurysm growth is detected during the follow-up period.

(http://thejns.org/doi/abs/10.3171/2012.4.JNS112225)

1.8% per year

-> 18% per year rupture risk

Aneurysm Growth

Radiologic Surveillance of Untreated Unruptured Intracranial Aneurysms: A Single Surgeon's Experience

Mario Teo and Edward J. St George

Department of Neurosurgery, Institute of Neurological Science, Glasgow, United Kingdom

To whom correspondence should be addressed: Mario Teo, M.D., F.R.C.S. (SN)
[E-mail: marioteo@doctors.org.uk]

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Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

Mean size: 5.7 mm
3.4 yrs mean follow up
12% grew = 3.5% per yr
9% of those <7mm
- 2.6% per yr

Growth = 24 fold increase risk of SAH

Aneurysm Growth

Patient- and Aneurysm-Specific Risk Factors for Intracranial Aneurysm Growth

A Systematic Review and Meta-Analysis

Daan Backes, MD; Gabriel J.E. Rinkel, MD, FRCPE; Kamil G. Laban, MD; Ale Algra, MD, PhD; Mervyn D.I. Vergouwen, MD, PhD

Background and Purpose—Follow-up imaging is often performed in intracranial aneurysms that are not treated. We performed a systematic review and meta-analysis on patient- and aneurysm-specific risk factors for aneurysm growth.

Methods—We searched EMBASE and MEDLINE for cohort studies describing risk factors for aneurysm growth. Two authors independently assessed study eligibility and rated quality with the Newcastle Ottawa Scale. With univariable Poisson regression analysis, we calculated risk ratios (RRs) with corresponding 95% confidence intervals (95% CI) of risk factors for aneurysm growth. Heterogeneity was assessed with I^2.

Results—Eighteen studies on 15 patient-populations described 3990 patients with 4972 unruptured aneurysms. A total of 437 aneurysms (9%) enlarged during 13987 aneurysm-years of follow-up. Compared with aneurysms ≤4 mm, RRs were 2.56 (95% CI, 1.93–3.39; I^2=98%) for ≥5 mm, 2.80 (95% CI, 2.01–3.90; I^2=96%) for ≥7 mm, and 5.38 (95% CI, 3.76–7.70; I^2=97%) for ≥10 mm. Compared with aneurysms on the middle cerebral artery, the RR for basilar artery was 1.94 (95% CI, 1.32–2.83; I^2=57%). RRs were 2.03 (95% CI, 1.52–2.71; I^2=59%) for smoking at baseline, 2.04 (95% CI, 1.56–2.66; I^2=90%) for multiple unruptured aneurysms, 1.26 (95% CI, 0.97–1.62; I^2=59%) for women, 1.24 (95% CI, 0.98–1.58; I^2=40%) for hypertension, and 2.32 (95% CI, 1.46–3.68; I^2=91%) for irregular aneurysm shape. Compared with other regions, RR was 0.75 (95% CI, 0.58–0.96) for Japan and 0.64 (95% CI, 0.45–0.90) for Finland.

Conclusions—Most risk factors for aneurysm growth are consistent with risk factors for rupture. In contrast with rupture, the risk of growth was smaller in Japanese and Finnish cohorts compared with other regions. Pooling of individual patient data from low- and high-risk geographical regions is needed to assess independent predictors of aneurysm growth. (***Stroke***. 2016;47:951-957. DOI: 10.1161/STROKEAHA.115.012162.)

2.8 yrs mean follow up

- 13,987 aneurysm years

9% grew

>3% per year

Aneurysm Growth

Social Security SEARCH MENU LANGUAGES SIGN IN / UP

Actuarial Life Table

Period Life Table, 2014

	Male			Female		
Exact age	Death probability [a]	Number of lives [b]	Life expectancy	Death probability [a]	Number of lives [b]	Life expectancy
35	0.001716	96,753	43.22	0.000932	98,266	47.25
36	0.001782	96,587	42.29	0.001005	98,175	46.29
37	0.001854	96,415	41.37	0.001082	98,076	45.34
38	0.001931	96,236	40.44	0.001160	97,970	44.39
39	0.002018	96,050	39.52	0.001243	97,856	43.44
40	0.002123	95,856	38.60	0.001336	97,735	42.49
41	0.002252	95,653	37.68	0.001442	97,604	41.55
42	0.002413	95,437	36.76	0.001562	97,463	40.61
43	0.002611	95,207	35.85	0.001698	97,311	39.67
44	0.002845	94,958	34.95	0.001849	97,146	38.74

Question 3

3. Considering the AE list above and any additional AEs specified in response to question #1.a., what patient characteristics (e.g., malignancy, advanced age, aneurysm size) justify foregoing treatment for an aneurysm that would otherwise be considered for treatment?

Aneurysm treatment is a complex and nuanced decision that is ultimately driven by patient choice with physician guidance.

We should resist creating well-intended but inappropriately restrictive external limits on patient characteristics.

THANK YOU

SNIS Society of NeuroInterventional Surgery

FDA Questions for Panel

- Question 4a:
  - Raymond Scale in NOT APPROPRIATE for all devices
    - FD: Binary Scale: Complete or Incomplete
    - Coils +/- Stent or BAT: Raymond Scale
    - Braided Intra-saccular Devices: Modified, Validated Raymond Scale (e.g., WOS)
    - Novel Aneurysm Device: TBD

FDA Questions for Panel

- Question 4b:
  - Regardless of rupture status
  - **Complete occlusion** is a reasonable and achievable effectiveness benchmark for FLOW DIVERSION
  - **Adequate occlusion** (Complete and near complete occlusion) is a reasonable and achievable effectiveness benchmark for Coils (+/- Stents or BAT) and Intra-saccular devices

FDA Questions for Panel

- Question 5:
  - Device effectiveness endpoints differ between devices and aneurysm types and must be based upon established OPCs
    - **OPCs continue to improve** as more high quality, prospective, GCP data become available
      - FD: PITA, PUFS, ASPIRE, PREMIER
      - Coils: ISAT, MAPS, CCT, HELPS, LVIS
      - Intra-saccular Devices: US WEB-IT, WEBCAST I and II, FROB

FDA Questions for Panel

- Question 6:
  - Angiographic Scales must be appropriate for the aneurysms treated and devices used
  - Nuances were addressed in the preceding slides

PANEL EXECUTIVE SUMMARY QUESTIONS

#7 Length of follow-up

For the purpose of evaluating the effectiveness of endovascular aneurysm treatments, one year of followup demonstrating stable adequate occlusion (Raymond I or II) is sufficient.

#8 Retreatment

Worsening Raymond scale alone does not constitute treatment failure.

Alternative Imaging Assessments

9. We consider digital subtraction angiography (DSA) to be the gold standard to assess aneurysm occlusion at follow-up. Can magnetic resonance angiography (MRA) or computed tomography angiography (CTA) serve as a surrogate follow-up examination and when should this take place?

- At least one follow-up angiogram within the first year following treatment is ideal

- Thereafter surveillance may employ either MRA with contrast or CTA depending on treatment modality

Journal of
NeuroInterventional Surgery

Neuroimaging
Original research

PDF

Multiparametric MRI of intracranial aneurysms treated with the Woven EndoBridge (WEB): a case of Faraday's cage?

Marie Teresa Nawka, Jan Sedlacik, Andreas Frölich, Maxim Bester, Jens Fiehler, Jan-Hendrik Buhk

Conclusions Signal intensity measurements in multiparametric MRI suggest that neither contrast-enhanced MRA nor morphological sequences are capable of revealing reliable information on the WEB lumen, presumably due to radio frequency shielding. MRI is therefore not suitable for confirming complete thrombus formation within the WEB.

Post Approval Studies

10. In some cases, a post-approval study may be warranted, for example when limited follow up exists for patients. What is a sufficient long term follow-up period for a post-approval study where the majority of patients have the following outcomes for ruptured or unruptured aneurysms?

    a. Raymond I

    b. Raymond II

    c. Raymond III

- Longitudinal post-approval studies should be conducted regardless of original Primary efficacy treatment outcome (Raymond Class) for both scientific validity and potential for delayed recanalization
- We propose 5 years

Labeling

11. What patient characteristics should be specified in the IFU (i.e., age, aneurysm morphology, location, size, Type 1 or Type 2 status, ruptured vs. unruptured)? For intraluminal flow diverters? And for endosaccular devices?

- IFU should be based on the device approval study with focus on
  - Aneurysm morphology (narrow or wide neck, fusiform, blister, berry etc.)
  - Location (sidewall versus bifurcation)

- IFU SHOULD NOT be based on
  - Age, prior rupture history

Labeling

11. What patient characteristics should be specified in the IFU (i.e., age, aneurysm morphology, location, size, Type 1 or Type 2 status, ruptured vs. unruptured)? For intraluminal flow diverters? And for endosaccular devices?

- IFU for intraluminal flow divertors should be based on range of vessel sizes in which they may be implanted

- IFU for endosaccular devices should be based on range of aneurysm sizes in which they may be implanted