

Title: The International Study of Unruptured Intracranial Aneurysms: Methodology

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Abstract

The current lack of consensus of how to manage patients with unruptured intracranial aneurysms (UIAs) reflects the need for a greater understanding of the natural history of these lesions and the risk of repairing them. The International Study of Unruptured Intracranial Aneurysms (ISUIA) was designed to define the natural history of UIAs; determine the risk factors associated with the development and rupture of UIAs; and assess the morbidity and mortality associated with repair of UIAs among UIA patients with and without a history of subarachnoid hemorrhage from a separate aneurysm.

Introduction

Unruptured intracranial aneurysms constitute a significant public health problem in the United States.¹ Approximately 10,000 patients are hospitalized annually in the United States with a diagnosis of unruptured intracranial aneurysm (UIA), and many others are diagnosed and followed as outpatients. In addition to the obvious impact on society in terms of disability and loss of life, the economic impact of these lesions is considerable.

The estimated lifetime cost of annual cases of UIA patients hospitalized in the United States--including the cost of hospitalization, surgery, morbidity, and mortality--is approximately \$522.5 million compared to an analogous figure of \$1,755 million per year for subarachnoid hemorrhage (SAH). These estimates include only hospitalized patients in nonfederal hospitals and, consequently, they are likely to be underestimates of the magnitude of the problem, particularly among UIA patients.

The management of patients with UIAs remains controversial. The issue has become more compelling in recent years as greater numbers of these lesions are diagnosed fortuitously with the widespread use of computed tomographic (CT) and magnetic resonance (MR) head scanning for various reasons and with the increased quality of these techniques. The advancing age of the population is also a factor in the increased number of UIAs.

Given the lack of consensus about managing these patients and the substantial and increasing magnitude of the problem, a new study group was formed called the International Study of Unruptured Intracranial Aneurysms. This group has undertaken an initial epidemiologic project to address the major issues involved in clinical decision making regarding patients with UIA.

Methods

1. Study Organization

The study involves participants from 60 medical centers in North America and Europe who have specific interest and expertise in intracranial aneurysms and aneurysmal SAH. The study has been coordinated clinically by a central office in the Department of Health Sciences Research at the Mayo Clinic in Rochester, Minnesota. The Methods Center is located at the University of Virginia in Charlottesville, Virginia, and The Statistical Center is at the University of Iowa in Iowa City, Iowa. All participating clinical centers have demonstrated the capability of identifying eligible patients and have demonstrated high-quality cerebral angiography and the capability of obtaining hard-copy arteriograms for patients with UIA at least 5 years earlier.

2. Study Objectives

Specific objectives of this study are 1) to better define the natural history of saccular UIAs in patients with or without a history of prior SAH, 2) to define whether there are subgroups of patients with a greater risk associated with subsequent aneurysmal rupture or surgical repair or both to better establish proper management of these patients, and 3) to test several hypotheses about pathophysiologic mechanisms underlying aneurysmal growth and rupture that resulted from prior natural history studies.^{2,3,4,5}

The primary hypotheses of this study are as follows. 1) Among patients without a history of SAH with UIA, there is a critical size above which there is a significant risk of subsequent aneurysmal rupture, with accompanying neurologic morbidity and mortality. 2) Among patients with UIAs and a history of SAH from another source, the risk of future rupture of UIA, disability, and death is greater

than in patients without a history of SAH and varies directly with aneurysmal size. 3) The risk of death and significant disability from surgery to isolate UIAs from the intracranial circulation varies according to the size and the location of the aneurysm, history of SAH from another source, and confounding variables such as age and co-morbid conditions.

3. Patient Identification and Recruitment

Patients have been identified in the retrospective group for the years 1970 to 1991 to provide maximum follow-up years and best quality of cerebral arteriograms. At each center, retrospective cases were allowed only as far back as hard copy arteriograms and medical records were available for all or virtually all patients. Medical center central records systems as well as log records from Radiology, Neurosurgery, Neurology, and Admissions have all served as sources for identifying potential patients. Prospective patients became eligible from November 1991. Patients found to be ineligible are entered in an ineligible log with the reason for ineligibility described. Detailed data are not collected on these patients. A total of 60 centers will contribute 5,500 patients with unruptured aneurysms. Fifteen hundred of these will be retrospective patients with unoperated UIA, approximately half with no history of SAH (Group I) and half with a history of SAH (Group II). Another 4,000 patients will be identified prospectively for a 1- to 9-year follow-up.

4. Patient Eligibility

To be eligible for the study, patients must satisfy the following clinical, radiologic, and exclusion criteria.

1) Clinical Inclusion Criteria.

Retrospective patients must have at least one UIA, which may or may not be symptomatic (e.g., cranial

nerve palsy). Patients may have had a ruptured aneurysm at another location that was clipped, trapped, or treated through endovascular obliteration and isolated from the circulation. They must be able to care for themselves after the aneurysmal treatment according to the Rankin scale (grade 1 or 2). These patients must have been observed at least 30 days from initial arteriographic demonstration of the UIA to operation.

Prospective patients must have at least one UIA, which may or may not be symptomatic. Patients who have had a ruptured aneurysm at another location that was isolated, trapped, clipped, or treated through endovascular obliteration must be able to care for themselves after the aneurysmal treatment (Rankin grade 1 or 2) according to a follow-up evaluation at 30 days post-treatment. Patients may or may not undergo surgical clipping or endovascular intervention at the investigator's discretion.

2) Exclusion Criteria. Patients with fusiform, traumatic, or mycotic aneurysms are not eligible for the study. Also, patients with saccular aneurysms less than 2 mm at the maximum diameter using the standard measuring device are excluded. SAH from a single ruptured aneurysm or unknown source with no other unruptured aneurysm visible on angiogram is an exclusion. All retrospective patients in whom the UIA was manipulated by wrapping, packing, coils, proximal arterial ligation, bypass, or balloon occlusion or clipped within 30 days of discovery before entry into the study are not eligible. Patients with a history of intracranial hemorrhage from any of the following are excluded: unrepaired underlying structural lesion, primary intracerebral hemorrhage without an underlying repaired lesion, or nonaneurysmal SAH of unknown etiology.

Retrospective patients with arteriograms performed before 1970 are deemed ineligible.

Prospective patients with presumed aneurysms defined only by MR imaging or means other than cerebral arteriography are not eligible. Also, patients with arteriograms performed more than 6 months before consultation by the study investigator are excluded unless a repeat angiogram is performed. Any patients who are not independent or able to care for themselves (Rankin grade 3, 4, or 5) at baseline are not eligible.

Patients are excluded from the study if there is lack of consent to follow-up, if they have a malignant brain tumor, or if they are bedridden or unable to communicate.

5. Radiology

Every eligible patient must have a hard copy cerebral arteriogram, copies of which are sent to the Mayo Clinic for central review. Centers were asked to send a maximum of three to six films that are relevant to the study, including at least anteroposterior and lateral views that include the aneurysm and the entire head.

Radiologic parameters are identified by central review of cerebral arteriogram hard copies. These parameters include: 1) aneurysmal size measured in the greatest diameter and corrected for magnification; 2) intraluminal aneurysmal volume calculated by the maximal longitudinal and coronal diameters corrected for magnification; 3) aneurysm dimensions along the medial-lateral, cephalic-caudal, and anterior-posterior planes; 4) number of aneurysmal lobes; 5) presence of daughter sacs; 6) aneurysmal location according to the parent artery; 7) total number of aneurysms; 8) size of the neck, if apparent; 9) presence or absence of calcification; 10) presence or absence of vasospasm; 11) presence or

absence of atherosclerotic stenosis; and 12) presence or absence of arteriovenous malformation.

Aneurysmal size is measured and corrected for magnification by using a specially constructed magnification ruler (Fig. 1). Starting with the lateral view of the aneurysm, the correction factor is determined from the magnification or minification of a United States dime placed on the patient's vertex in the midline during the angiogram. If a dime was not placed, then the front-to-back distance magnification scale along the bottom of the ruler is used to determine magnification or minification for the lateral view. The zero mark is placed over the frontal portion of the skull and aligned with the external cortex. The maximal distance to the occipital region is determined, which yields the correction factor. With the appropriate magnification or minification factor, the maximal anterior-to-posterior and superior-to-inferior distances are determined such that the measurements are perpendicular to each other. Next, the magnification factor for the anteroposterior image is determined by using a similar technique with a United States dime or the superior margin of the magnification ruler aligned with the maximum biparietal diameter. Once the magnification factor is determined, the maximal right-left diameter of the aneurysm is measured.

6. Follow-up

Follow-up is done principally by using a questionnaire mailed to the patient. Repeat assessments are made of the patient's employment status, medical and smoking history, medications, and blood pressure. Any neurologic symptoms, intracranial surgery, or repeat angiogram since the previous assessment is recorded.

1) Retrospective patient follow-up is accomplished by using the standardized, mailed

patient questionnaire sent at least 5 years after the UIA diagnosis, and annually thereafter. Unoperated patients and patients who have had operative intervention greater than 30 days after diagnosis undergo continued follow-up to assess the frequency of rehemorrhage and survival.

2) All prospective unoperated and operated patients, regardless of the timing of operation, are included in the study. For operated patients, the NIH Stroke Scale is administered 7 days postoperatively and a hospital discharge form is completed within 1 day of dismissal. At 30 days postoperatively, the Mini-Mental Status for patients returning in person or the Telephone Interview for Cognitive Status is administered and the patient questionnaire is completed. For unoperated patients, the study coordinator mails the follow-up questionnaire to the patient and conducts the Telephone Interview for Cognitive Status. At 1 year and annually thereafter, a follow-up questionnaire is mailed to operated and unoperated patients, a functional status assessment is completed and the Telephone Interview for Cognitive Status is administered.

7. Determination of Events

Detailed information was obtained on all definite or questionable endpoints (SAH, intracerebral hemorrhage, or death) that occurred during the study. Stroke severity was graded by the NIH-NINDS stroke scale. In deceased patients, the cause of death was determined by contacting the local physician or by obtaining medical records, including death certificate and autopsy information. If an intracranial hemorrhage or a stroke of any kind occurred during the course of the study, arteriography and aneurysmal surgery were performed as clinically indicated. Every effort was made to document all procedures performed in these

patients including serial CT or MR scans, digital subtraction or conventional arteriography, and repair of a ruptured or unruptured aneurysm. Hemorrhagic events were classified by diagnostic certainty and location of aneurysmal rupture. Classification of confirmed SAH/ICH was based upon uniform criteria:

1) Definite

----symptoms of SAH/ICH and CT or MRI or surgery or autopsy confirmation

2) Highly probable

---two or more symptoms of SAH/ICH and positive lumbar puncture

3) Probable

---symptoms of SAH/ICH only.

For the primary analysis, all definite, highly probable, and probable aneurysmal hemorrhages were included.

Etiology of the endpoint was also clarified using pre-specified criteria, based on clinical, radiologic, surgical and/or autopsy findings.

Adjudication for the prospective operated cohort was performed as to the evidence for procedure-related cerebral infarction, hemorrhage, or death. Also deficits that were present at 30 days or 1 year were evaluated for their relationship to treatment or comorbidity.

Morbidity from aneurysm treatment was based on Rankin Scale status 3, 4, or 5 at 30 days and 1 year and Mini-Mental Status Exam score of less than 24 or Telephone Interview Cognitive Status score less than 27 at the same time points.^{6,7,8} Mortality was considered separately.

8. Statistical Design

The study is divided into two study designs: retrospective and prospective. Within the retrospective, there are two groups. Group I patients have no history of SAH and have an unruptured

aneurysm. Group II patients have had an SAH with at least one other unruptured aneurysm. The ruptured aneurysm was surgically obliterated. Hence, the retrospective portion of the study provides follow-up of patients with one or more unruptured aneurysms for natural history determinations. In the prospective cases, there are two groups of patients (Groups I and II, as defined above) with unruptured aneurysms that are not surgically treated and two groups of patients that are surgically treated. All prospective cases are followed at 1 month and annually until the end of the study for determination of postoperative morbidity and mortality in operated patients and natural history in unoperated patients.

The advantage of the dual design is the opportunity to obtain longer follow-up in the retrospective follow-up study and to verify these observations with the prospective cohort study. The prospective cohort will allow for comparison of the initial and short-term risk of rupture with the retrospective cohort to validate its findings. Factors related to case ascertainment in the retrospective and prospective cohorts need to be compared to determine whether any biases exist that might be considered in analysis.

Discussion

In recent years it has become clear that data regarding patients with previously ruptured aneurysms cannot be applied to patients with UIAs.^{3,5} A further, more subtle distinction between two subgroups of patients with UIAs may also be important in facilitating optimal management of UIA patients. The first subgroup involves patients with UIAs and no history of SAH from a separate aneurysm. Available natural history data for this group of patients, though limited, suggest a strong relationship between size of the aneurysm at the time

of discovery and future rupture ($P < 0.0001$).^{4,5}

Although most neurologists and neurosurgeons agree that larger aneurysms are more likely to rupture than smaller ones in this group, there is little or no agreement on what if any size range portends a low enough future rupture rate to warrant conservative management.

The second subset of patients with unruptured aneurysms involves individuals who have a history of SAH from a separate aneurysm. Available natural history data for this group of patients are limited and do not allow determination about whether future rupture rate has any relationship to aneurysmal size. Although the largest study involving such patients⁹ reported that size was a significant predictor of future rupture for UIAs ($P < 0.04$), the relationship between size and future rupture was not statistically significant when the analysis was confined to patients with a history of SAH from a different aneurysm (131 of the 142 patients).

Another major difficulty in making management decisions concerning patients with UIA relates to scant and conflicting data about morbidity and mortality associated with aneurysmal repair and virtually no data about subgroups according to aneurysmal location and size.¹⁰⁻²⁰ Among four case series involving over 40 cases in the modern era,^{11,12,17,20} operative mortalities of 0 to 2.3% and operative morbidities of 0 to 6.5% were reported. A meta-analysis including case series from 1970 to 1993 reported an operative mortality of 1% and morbidity of 4.1%.¹⁰ However, the largest series addressing operative complications among 217 patients with unruptured aneurysms was reported as a part of a national survey among medical centers in Japan,¹⁶ and this study reported an operative mortality of 7%. Operative morbidity was not

assessed in this study. In another recent report²¹ involving 302 patients with subarachnoid hemorrhage and one or more unruptured aneurysms, the authors concluded that in many cases attempted repair of unruptured aneurysms was associated with increased morbidity and mortality.

The study design will utilize long follow-up of the retrospective cohort and prospective ascertainment of risk and prognostic factors in the prospective cohorts. There may be important differences between the retrospective cohort and the prospective cohort. The retrospective cohort is established through clinic records, radiologic records and hospital medical records. The prospective cohort is based on prospective surveillance of neurological and radiological patients. Differences in use of cross-sectional imaging (CT and MRI) have occurred over time. However symptoms and pre-existing conditions leading to diagnosis of the unruptured aneurysm are similar between the cohorts. The largest difference is that predictors of hemorrhage can be assessed more satisfactorily in the prospective cohort, (e.g. alcohol use, smoking, stimulant use, oral contraceptive history, anticoagulant use, aspirin use and presence of associated pathology).

With regard to the operative groups, the ISUIA has the ability to determine the aneurysmal obliteration rates as well as the rates of short and long-term morbidity and mortality in procedure subgroups (clipping, balloon occlusion, coils) and to determine the variability across patient subgroups and within important risk factors such as size and aneurysm location. This will allow confidence intervals to indicate the precision of the estimates of risk.

The current study represents the first attempt at standardizing radiologic measurements and characterization of intracranial aneurysms. In

order to achieve uniformity in these measurements, specific definitions and procedures were developed for size and magnification, including the use of a standardized ruler (Fig. 1). Uniformity of radiologic measurement and characterization will be important not only for allowing internal consistency of the data from this multicenter study but also for applying these data to settings outside of the study.

Although there is no consensus about how to manage patients with UIAs, opinions about management have been strongly held for the various approaches, precluding a randomized controlled trial. The current study could be utilized to facilitate sample size calculations and precise definitions of optimal entry and exclusion criteria and methodology for such a trial, if one appears to be appropriate for the aggregate group or some subgroups thereof, based on the detailed analysis of the first phase of the ISUIA.

References

1. Wiebers DO, Torner JC, Meissner I: Impact of unruptured intracranial aneurysms on public health in the United States. **Stroke** **23**:1416-1419, 1992
2. Brown RD Jr, Wiebers DO, Forbes GS: Unruptured intracranial aneurysms and arteriovenous malformations: frequency of intracranial hemorrhage and relationship of lesions. **J Neurosurg** **73**:859-863, 1990
3. Wiebers DO, Torres VE: Screening for unruptured intracranial aneurysms in autosomal dominant polycystic kidney disease (editorial). **N Engl J Med** **327**:953-955, 1992
4. Wiebers DO, Whisnant JP, O'Fallon WM: The natural history of unruptured intracranial aneurysms. **N Engl J Med** **304**:696-698, 1981
5. Wiebers DO, Whisnant JP, Sundt TM Jr, O'Fallon WM: The significance of unruptured intracranial saccular aneurysms. **J Neurosurg** **66**:23-29, 1987
6. Folstein MF, Folstein SE, McHugh PR: "Mini-Mental State": a practical method for grading cognitive state of patients for the clinician. **J Psychiatr Res** **12**:189-198, 1975
7. Brandt J, Spencer M, Folstein M: The telephone interview for cognitive status. **Neuropsychiatr Neuropsychol Behav Neurol** **1**:111-117, 1988
8. Rankin J. Cerebral vascular accidents in patients over 60. II. Prognosis. **Scott Med J** **2**:200-215, 1957
9. Juvela S, Porras M, Heiskanen O: Natural history of unruptured intracranial aneurysms: a long-term follow-up study. **J Neurosurg** **79**:174-182, 1993
10. Drake CG, Girvin JP: The surgical treatment of subarachnoid hemorrhage with multiple aneurysms, in Morley TP (ed): **Current Controversies in Neurosurgery**. Philadelphia: WB Saunders Company, 1976, pp 274-278
11. Heiskanen O: Risks of surgery for unruptured intracranial aneurysms. **J Neurosurg** **65**:451-453, 1986
12. Jomin M, Lesoin F, Lozes G, Fawaz A, Villette L: Surgical prognosis of unruptured intracranial arterial aneurysms. Report of 50 cases. **Acta Neurochir** **84**:85-88, 1987
13. King JT Jr, Berlin JA, Flamm ES: Morbidity and mortality from elective surgery for asymptomatic, unruptured, intracranial aneurysms: a meta-analysis. **J Neurosurg** **81**:837-842, 1994
14. Mount LA, Brisman R: Treatment of multiple aneurysms--symptomatic and asymptomatic. **Clin Neurosurg** **21**:166-170, 1974
15. Moyes PD: Surgical treatment of multiple aneurysms and of incidentally-discovered unruptured aneurysms. **J Neurosurg** **35**:291-295, 1971
16. Nishimoto A, Ueta K, Onbe H, Kitamura K, Omae T, Goto F, Ohneda G, Chigasaki H, Tsuru M, Suzuki J, Wada T, Sano K, Mannen T, Yoshioka M, Nakai O, Kageyama N, Nomura T, Handa H, Tanaka K: Nationwide co-operative study of intracranial aneurysm surgery in Japan. **Stroke** **16**:48-52, 1985
17. Rice BJ, Peerless SJ, Drake CG: Surgical treatment of unruptured aneurysms of the posterior circulation. **J Neurosurg** **73**:165-173, 1990
18. Salazar JL: Surgical treatment of asymptomatic and incidental intracranial aneurysms. **J Neurosurg** **53**:20-21, 1980

19. Samson DS, Hodosh RM, Clark WK: Surgical management of unruptured asymptomatic aneurysms. **J Neurosurg** **46**:731-734, 1977
20. Wirth FP, Laws ER Jr, Piepgras D, Scott RM: Surgical treatment of incidental intracranial aneurysms. **Neurosurgery** **12**:507-511, 1983
21. Rinne J, Hernesniemi J, Niskanen M, Vapalahti M: Management outcome for multiple intracranial aneurysms. **Neurosurgery** **36**:31-38, 1995

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