Guidelines for the Management of Patients With Unruptured Intracranial Aneurysms

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons, the Congress of Neurological Surgeons, and the Society of NeuroInterventional Surgery

B. Gregory Thompson, MD, Chair; Robert D. Brown, Jr, MD, MPH, FAHA, Co-Chair; Sepideh Amin-Hanjani, MD, FAHA; Joseph P. Broderick, MD, FAHA; Kevin M. Cockroft, MD, MSc, FAHA; E. Sander Connolly, Jr, MD, FAHA; Gary R. Duckwiler, MD, FAHA; Catherine C. Harris, PhD, RN, MBA, CRNP; Virginia J. Howard, PhD, MSPH, FAHA; S. Claiborne (Clay) Johnston, MD, PhD; Philip M. Meyers, MD, FAHA; Andrew Molyneux, MD; Christopher S. Ogilvy, MD; Andrew J. Ringer, MD; James Torner, PhD, MS, FAHA; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, and Council on Epidemiology and Prevention

Purpose—The aim of this updated statement is to provide comprehensive and evidence-based recommendations for management of patients with unruptured intracranial aneurysms.

Methods—Writing group members used systematic literature reviews from January 1977 up to June 2014. They also reviewed contemporary published evidence-based guidelines, personal files, and published expert opinion to summarize existing evidence, indicate gaps in current knowledge, and when appropriate, formulated recommendations using standard American Heart Association criteria. The guideline underwent extensive peer review, including review by the Stroke Council Leadership and Stroke Scientific Statement Oversight Committees, before consideration and approval by the American Heart Association Science Advisory and Coordinating Committee.

Results—Evidence-based guidelines are presented for the care of patients presenting with unruptured intracranial aneurysms. The guidelines address presentation, natural history, epidemiology, risk factors, screening, diagnosis, imaging and outcomes from surgical and endovascular treatment. (***Stroke*. 2015;46:000-000. DOI: 10.1161/STR.0000000000000070.)**

Key Words: AHA Scientific Statements ■ cerebral aneurysm ■ epidemiology ■ imaging ■ natural history ■ outcome ■ risk factors ■ treatment

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This guideline was approved by the American Heart Association Science Advisory and Coordinating Committee on January 28, 2015, and the American Heart Association Executive Committee on February 16, 2015. A copy of the document is available at http://my.americanheart.org/statements by selecting either the "By Topic" link or the "By Publication Date" link. To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

The American Heart Association requests that this document be cited as follows: Thompson BG, Brown RD Jr, Amin-Hanjani S, Broderick JP, Cockroft KM, Connolly ES Jr, Duckwiler GR, Harris CC, Howard VJ, Johnston SC, Meyers PM, Molyneux A, Ogilvy CS, Ringer AJ, Torner J; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, and Council on Epidemiology and Prevention. Guidelines for the management of patients with unruptured intracranial aneurysms: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2015;46:•••–•••.

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Unruptured intracranial aneurysms (UIAs) are relatively common in the general population, found in ≈3.2% (95% confidence interval [CI], 1.9%–5.2%) of the adult population (mean age 50 years) worldwide, and they are being discovered incidentally with an increasing frequency because of the widespread use of high-resolution magnetic resonance imaging (MRI) scanning. The large majority of UIAs will never rupture. For example, of the 1 million adults in the general population with a mean age of 50 years, ≈32 000 harbor a UIA, but only 0.25% of these, or 1 in 200 to 400, will rupture.[1–3] To put these numbers in perspective, in any given year, ≈80 of 32 000 of these UIAs would be expected to present with subarachnoid hemorrhage (SAH). Complicating matters further is the fact that aneurysms that rupture may not be the same as the ones found incidentally. Physicians are now often faced with the dilemma of whether to treat patients who present with an incidental finding of an unruptured aneurysm or to manage them conservatively. Patients and families may push for the surgical or endovascular management of an incidental UIA out of fear of the unknown and potentially catastrophic outcome that could occur. However, no treatment comes without risk, and the benefit of treating an incidental UIA must outweigh the potential risks of treating it.

Despite the relatively small number of rupture events that occur, many uncertainties remain. There are still concerns regarding the risk of rupture for particular aneurysm types such as multilobed aneurysms, those with irregularity of the aneurysm dome, those with selected morphological characteristics (such as size relative to the parent artery), those in selected locations, and those of larger diameter. Other concerns include presentations that may mimic sentinel headaches, patients who smoke or have hypertension, those who have a family history of aneurysmal rupture, and those with an enlarging aneurysm. How do these factors play a role in the natural history of incidental UIA, and should they alter management strategies? Should subsets of incidental UIAs be treated differently or more aggressively?

The purpose of this statement is to provide guidance for physicians, other healthcare professionals, and patients and to serve as a framework for decision making in determining the best course of action when a UIA is discovered. The committee chair nominated writing group members on the basis of their previous work in relevant topic areas. The American Heart Association (AHA) Stroke Council's Scientific Statement Oversight Committee and the AHA's Manuscript Oversight Committee approved all writing group members. All members of the writing group had the opportunity to comment on the recommendations and approved the final version of this document. Recommendations were formulated using standard AHA criteria (Tables 1 and 2).

Recent Data Regarding Natural History

Since the last US consensus statement was published in 2000, the International Study of Unruptured Intracranial Aneurysms (ISUIA)[4] has published prospective data regarding a large cohort of patients with UIAs, stratified by size. The ISUIA reported 49 aneurysmal ruptures during its mean observation period of 4.1 years of follow-up of the enrolled population of 1692 prospective unoperated patients. Similarly, with a mean observation period of 3.5 years and 11 660 patient-years of follow-up in a large Japanese study of unruptured aneurysms (the Unruptured Cerebral Aneurysm Study [UCAS]),[5] only 110 aneurysmal ruptures were reported. To date, there has been no completed randomized comparison of either clipping or coiling treatment with regard to natural history to evaluate its risk/benefit ratio. The Trial of Endovascular Aneurysm Management (TEAM) was initiated by Canadian researchers to examine this issue, but the study failed to recruit patients, and the trial grant was withdrawn on grounds of futility.[6] A new Canadian trial has since commenced recruiting in a pilot study to compare endovascular treatment with clip ligation.[7]

Changes in the Treatment of Unruptured Aneurysms

Since the last recommendation document in 2000, major changes have emerged in the treatment of UIA, largely in the widespread use of endovascular techniques. The use of coil embolization increased substantially after publication of the results of the International Subarachnoid Aneurysm Trial (ISAT) in 2002 and 2005.[8,9] ISAT was a randomized trial comparing clip ligation to coil occlusion in ruptured aneurysms; it showed improved clinical outcomes in the coiling arm at 1 year. Although trials of UIAs and ruptured aneurysms cannot be compared on the basis of outcomes or future risk, the relative safety and medium-term efficacy of both coiling and surgical clipping in preventing future hemorrhage from the treated aneurysm has been better established after ISAT. Furthermore, experience in treating aneurysms continues to increase, with an improved measure of safety and with better devices.

This guideline is the result of a collaborative effort of an expert committee researching the best available evidence in the English language on the prevalence, natural history, and management of UIA. The committee was composed of experts in the field with an interest in developing practice guidelines. This guideline is the continued review of existing literature that builds on the foundations of the recommendations made by the first consensus committee in 2000.[10]

Epidemiology

There are no data on incidence rates for UIAs, because these data require prospective, long-term follow-up studies of populations at risk with repeated assessments over time. The prevalence of UIAs depends on the population(s) studied, method of case ascertainment, reason for undergoing brain imaging, and whether the study was retrospective or prospective.

In a comprehensive systematic review and meta-analysis with strict inclusion criteria that included 68 studies reporting on 83 study populations, the prevalence of UIAs ranged from 0.0% to 41.8%, with an overall mean prevalence of 2.8% (95% CI, 2.0%–3.9%).[11] With these data, the estimated prevalence of UIA in a population without comorbidity and with a mean age of 50 years is calculated to be 3.2% (95% CI, 1.9%–5.2%).[1] The years included in these studies ranged from 1931 to 2008, including some with unknown years. When studies that used intra-arterial digital subtraction angiography (DSA)

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Table 1. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT: CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/Test / Treatment COR III: No benefit: Not Helpful / No Proven Benefit COR III: Harm: Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/administered/other; is not useful/beneficial/effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/administered/other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

were compared with those that used magnetic resonance angiography (MRA), there was no difference in prevalence, but prevalence was significantly lower in studies that used MRI and remained lower after adjustment for age and sex.[11] When the studies that primarily used MRI were excluded, the overall prevalence was 3.5% (95% CI, 2.7%–4.7%).[11] Although the crude prevalence of UIAs was higher in studies using imaging versus autopsy definitions, there was no difference in prevalence estimates after adjustment for sex, age, and comorbidities.[11] Women had a higher prevalence of UIAs than men, even after adjustment for age and comorbidities.[11] Prevalence overall was higher in people aged ≥30 years. In comparisons made between the United States and other countries, after adjustment for sex and age, a similar prevalence was noted, but no data by race/ethnicity have been reported.[11] Another report that summarized the literature before this systematic review suggested that the prevalence of UIAs in the population >30 years of age is ≈3.6% to 6.0%, with higher prevalence in women and an increased prevalence with age.[12] A recent cross-sectional study from China of 4813 adults aged 35 to 75 years found a prevalence of 7.0% based on MRA, also with a higher prevalence in women than men.[13]

In the population-based Rotterdam Study, in which 2000 patients (mean age 63 years; range, 45.7–96.7 years)

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Table 2. Definition of Classes and Levels of Evidence Used in AHA/ASA Recommendations

Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
Class IIa	The weight of evidence or opinion is in favor of the procedure or treatment
Class IIb	Usefulness/efficacy is less well established by evidence or opinion
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful
Therapeutic recommendations	
Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C	Consensus opinion of experts, case studies, or standard of care
Diagnostic recommendations	
Level of Evidence A	Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator
Level of Evidence B	Data derived from a single grade A study or one or more case-control studies, or studies using a reference standard applied by an unmasked evaluator
Level of Evidence C	Consensus opinion of experts

AHA/ASA indicates American Heart Association/American Stroke Association.

underwent protocol-driven high-resolution structural brain MRI, the prevalence of incidental intracranial aneurysms (IAs) was found to be 1.8%, with no change in prevalence by age[14]; however, in another systematic review and meta-analysis of other population-based observational studies of incidental findings on MRI (including the Rotterdam Study), the prevalence of IAs was only 0.35% (95% CI, 0.13%–0.67%), but age data were not complete, and only cross-sectional MRI was available.[15] In the large population-based Norwegian Nord-Trøndelag Health (HUNT) cohort study, based on MRA, the prevalence in the 1006 volunteers aged 50 to 65 years was 1.9%.[16] Data from the US National Hospital Discharge Survey indicate an increase in the number of patients admitted with UIAs from 1996 to 2001 compared with earlier years of 1986 to 1995.[17] This may be related to increased availability and use of brain imaging over the period. The mean age of patients included from 1986 to 1990 was lower than for patients included from 1990 to 1995.[17]

Mortality associated with UIAs may best be described in relation to natural history and the treatment studies discussed below. Mortality in patients with UIAs has not been well studied. In a Finnish study of 140 patients with 178 UIAs who were hospitalized between 1989 and 1999, during a mean follow-up of 13 years, patients had a 50% excess mortality compared with the general population.[18] Rates of in-hospital mortality in acute care hospitals in the United States for UIAs were 5.9% in 1986 to 1990, which increased to 6.3% (1991–1995), then decreased to 1.4% (1996–2001).[17]

Risk Factors

IA risk can be divided into factors associated with 3 phases: (1) risk for aneurysm development; (2) risk for growth or morphological change; and (3) risk for rupture.[19] Aneurysm risk can be assessed through image-based screening on a population basis, of high-risk populations, clinical populations, or registries of patients.

IAs are acquired lesions and are the cause of most cases (80%–85%) of nontraumatic SAH[2,20]; however, the proportion of IAs that rupture is unknown. There is also substantial discrepancy between unruptured aneurysm annual prevalence (2000–4000 per 100 000) and SAH annual incidence (10 per 100 000).[21] This ratio suggests that only ≈1 rupture occurs among 200 to 400 patients per year. There are no studies of SAH that delineate a documented history of a prior unruptured aneurysm diagnosis.

The frequency of identification of UIAs depends on the selection of patients for imaging.[12,14,22–29] In a meta-analysis of UIA prevalence studies, the detection rate was 0.4% (95% CI, 0.4%–0.5%) in retrospective autopsy studies, 3.6% (95% CI, 3.1%–4.1%) in prospective autopsy studies, 3.7% (95% CI, 3.0%–4.4%) in retrospective angiography studies, and 6.0% (95% CI, 5.3%–6.8%) in prospective angiography studies.[3] Larger UIAs may present with mass effect, cranial nerve deficits (most commonly a third nerve palsy), seizures, motor deficit, or sensory deficit, or they may be detected after imaging performed for headaches, ischemic disease, ill-defined transient spells, or other reasons.[30] Small aneurysms, <7 mm in diameter, uncommonly cause aneurysmal symptoms and are the most frequently detected. They are labeled as incidental or asymptomatic.[12,23]

Most risk factors for aneurysm occurrence that have been identified were from patients with SAH, clinical retrospective or prospective series, and screening of at-risk populations. Autopsy and imaging screening offer information on detection (prevalence) but little information on risk factors other than age and sex.[4,5,14,25–29,31–35] Few population-based studies or controlled comparative studies exist.[14] Only a few large registries of patients, obtained either retrospectively or prospectively, have been compiled.[3–5,32–35] Also, there is variation in these studies of clinical, inheritable, and modifiable risk factors.

Nonmodifiable Risk Factors

Most studies, regardless of design, show similar age and sex trends. Prevalence studies have demonstrated an increasing frequency by age, with a peak in the fifth and sixth decade of age (Table 3).[4,5,14,25–29,31–35] Cases reported in children usually are associated with other conditions or genetic risk.[36,37] There

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Table 3. Detection of Intracranial Saccular Aneurysm by Age and Sex in Olmsted County, Minnesota, 1965–1995[26]

	Counts			Rates*					
	Actual Number of Cases Detected			All Cases			All Cases Excluding Asymptomatic Cases Diagnosed at Autopsy		
Age Group, y	Male	Female	Total	Male	Female	Total	Male	Female	Total
≤34	11	10	21	1.3	1.1	1.2	1.3	1.1	1.2
35–44	20	14	34	10.5	7.1	8.8	9.9	7.1	8.5
45–54	20	35	55	14.4	24.5	19.5	13.0	24.5	18.8
55–64	21	23	44	21.0	21.0	21.0	17.0	20.1	18.6
65–74	21	45	66	33.4	52.6	44.5	15.9	44.4	32.3
75–84	11	26	37	35.3	44.7	41.4	16.0	31.0	25.8
≥85	1	12	13	12.0	49.0	39.6	0.0	16.3	12.2
Total	105	165	270	9.3†	12.2†	11.1‡	6.7†	10.7†	9.0‡

*Crude age- and sex-specific detection rate for Olmsted County, Minnesota population.
†Age-adjusted incidence rate per 100 000 per year adjusted to the 1980 US white population.
‡Age- and sex-adjusted incidence rate per 100 000 per year adjusted to the 1980 US white population.

is an increased frequency of IAs in women compared with men, with aneurysms occurring more frequently in women across the age spectrum.[4,5,22,24,31–35]

At-Risk Disorders

There is substantial evidence from autopsy clinical series and imaging studies of specific clinical groups that there is an increased risk of aneurysm formation in disorders such as polycystic kidney disease, type IV Ehlers-Danlos syndrome, Marfan syndrome, coarctation of the aorta, bicuspid aortic valve, pseudoxanthoma elasticum, hereditary hemorrhagic telangiectasia, neurofibromatosis type 1, α_1-antitrypsin deficiency, fibromuscular dysplasia, pheochromocytoma, Klinefelter syndrome, tuberous sclerosis, Noonan syndrome, α-glucosidase deficiency, microcephalic osteodysplastic primordial dwarfism, and intracranial arteriovenous malformations.[24,38–47] For autosomal dominant polycystic kidney disease, the increased risk may be 3- to 14-fold.[11] However, when examined in a large clinical cohort, all of these conditions constituted <10% of patients presenting with unruptured aneurysms, which left the majority attributable to other risk factors.[4]

Family History and Genetics

Estimates of the frequency of familial occurrence of IAs range from 7% to 20%.[48–56] This variation is largely a result of the various methods of family history ascertainment. The prevalence ratios (prevalence adjusted for comorbidity, age, and sex) indicate an increased risk between 1.9% and 5.9%.[11] There may be a slightly higher frequency of aneurysm detection in first-degree relatives of those with a history of SAH. In a study using MRA screening, 4% (95% CI, 2.6%–5.8%) of such first-degree relatives were found to have a UIA. Siblings had a higher likelihood of detection than children of those affected.[54,57] Factors that increased the likelihood of aneurysm detection in those with familial risk included other risk factors, such as older age, female sex, cigarette smoking, history of hypertension, higher lipid levels, higher fasting glucose, family history of polycystic kidney disease, and family history of SAH or aneurysm in ≥2 relatives.[57] There is also an increased risk of detection if ≥2 members of a family have a history of SAH or UIA. In 1 study of 438 people from 85 families, 38 first-degree relatives (8.7%) had a UIA on screening imaging.[52] In the Familial Intracranial Aneurysm (FIA) Study, first-degree relatives of those affected with brain aneurysm who were >30 years old and had a history of either smoking or hypertension were screened with MRA. Among the first 304 patients screened, 58 (19.1%) had at least 1 IA.[55] In long-term serial MRA or computerized tomographic angiography (CTA) screening of people with ≥2 first-degree relatives with a history of aneurysmal SAH (aSAH) or UIA, aneurysms were identified in 11% of 458 subjects at first screening, 8% of 261 at second screening, 5% of 128 at third screening, and 5% of 63 at fourth screening, which represents a substantial risk of UIA with up to 10 years of follow-up, even after 2 initial negative screenings.[58] In this study, significant risk factors for UIA at first screening were smoking, history of previous aneurysm, and family history of aneurysm. In the follow-up screening, the only significant risk factor was history of previous aneurysm.

The inheritance patterns of IAs are unclear, but autosomal dominance transmission is suspected to be the most common mode of inheritance. A variety of genes or chromosomal regions have been identified in both familial and sporadic cases of IAs.[59–73] In linkage studies, regions on chromosomes 1p34.3-p36.13, 7q11, 19q13.3, and Xp22 have been associated with IAs. Genome-wide association studies identified replicated associations on chromosome 4q31.23 (*EDNRA*), 8q12.1 (*SOX17*), 9p213 (*CDKN2A/CDKN2B/CDKN2BAS*), 10q24.32 (*CNNM2*), 12q22, 13q13.1 (*KL/STARD13*), 18q11.2 (*RBBP8*), and 20p12.1, with the strongest evidence for the *CDKN2BAS* and *SOX17* genes.[74] A meta-analysis of ruptured IAs (RIAs) and UIAs identified the gene IL 6 G572C to have an elevated risk; however, no predominant genetic risk factor has been identified.[60] In another meta-analysis, 19 single-nucleotide polymorphisms were associated with aneurysm occurrence.[75] Single-nucleotide polymorphisms with the strongest association to IA occurrence include chromosome 9 within the *CDKN2B* antisense inhibitor gene, chromosome 8 near the

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SOX17 transcription regulator gene, and on chromosome 4 near the *EDNRA* gene.

Modifiable Risk Factors

As with aSAH, an increased prevalence of smoking among patients with UIAs has been demonstrated in several controlled studies.[4,5,32–35,76–80] For UIAs, in the large, prospective clinical registry of the ISUIA of patients with UIA, 44% of patients in the prospective cohort were current smokers and 33% were former smokers.[4] The retrospective component of the ISUIA had a rate of 61% smokers and 19% former smokers.[34] In the Finland prospective series, 36% were current smokers and 24% were former smokers.[33] In the Japanese cohort, the prevalence of former and current smokers combined was only 17%.[5] Hence, the role of smoking as a risk factor appears differential. Smoking cessation studies have shown a modified risk of aSAH,[77,81] but no studies in patients with UIAs have been reported. In reference to hypertension, no prospective studies of blood pressure control have been performed that demonstrate prevention of aneurysm development. There was indirect evidence of the effectiveness of antihypertensive medication in prevention in a recent study from Kuopio, Finland; antihypertensive medication use was more frequent in the UIA incident group, and untreated hypertension was more frequent in the ruptured aneurysm group.[82] Excessive alcohol use may also be a risk factor for aneurysm development.[83] The role of oral contraceptives has been controversial in aSAH, with some data suggesting a potential association of high-dose estrogen oral contraceptives with SAH; there are few studies to demonstrate an association with aneurysm development.[84–86] In summary, the increased prevalence of cigarette smoking and hypertension in some UIA cohorts supports the concept that IAs may be subject to risk factor modification, but there are limited data available regarding the impact of risk factor modification and the occurrence of UIA.

Multiplicity

Two or more aneurysms are found in 15% to 30% of patients.[4,87–91] Risk factors for multiple aneurysms have been evaluated primarily in mixed UIA and SAH populations. Risk factors include female sex, cigarette smoking, hypertension, a family history of cerebrovascular disease, and postmenopausal hormone replacement therapy.[84–86]

Risk Factors for Aneurysmal Change

Growth

The incidence of growth has been widely variable depending on the definition of growth and the population studied.[92] Factors attributed to growth have been increased blood pressure, hemodynamic stress based on location and shape of the aneurysm, and inflammation. Most research has been limited to experimental settings. Most epidemiological studies have been retrospective, with only a few prospective studies with short follow-up periods. A variety of factors for growth that have been identified include female sex, cigarette smoking, younger age, excessive alcohol consumption, aneurysm location, multiplicity of aneurysms, history of stroke, and history of transient ischemic attack.[93–95] Recent findings indicate the propensity for growing aneurysms to rupture and indicate that risk factors for growth were initial aneurysm size, arterial branch–related aneurysms, hypertension, tobacco smoking, and female sex.[96–98] More prospective studies with either imaging or biomarkers are needed, and intervention studies with blood pressure or inflammation control would be of interest.

Ruptured Versus Unruptured

Few studies have simultaneously collected data on ruptured and unruptured aneurysms. Most of these have concentrated on size and location differences. Anterior communicating artery aneurysms and pericallosal artery aneurysms may be overrepresented in the rupture cohort.[99,100] Middle cerebral artery aneurysms are less likely to be in the ruptured cohort. The likelihood of detection after rupture is higher with larger size. In addition, sex differences in rupture status may vary by location. Several characteristics of aneurysm morphology, such as a bottleneck shape and the ratio of size of aneurysm to parent vessel, have been associated with rupture status, but how these might be applied to individual patients to predict future aneurysmal rupture is still unclear.[99–102] There is interest in the relationship of morphology (maximum diameter, complex spatial geometry, high aspect ratio [maximum aneurysm height/neck diameter]) and hemodynamics (complex flow pattern, low wall shear stress, high oscillatory shear index) to aneurysm rupture. Recent studies have demonstrated the combination is discriminatory between ruptured and unruptured aneurysms.[103–109]

In a prospective Finnish cohort of 118 UAI patients aged 22.6 to 60.7 years followed up from diagnosis (1956–1978) to SAH or death, 29% had SAH during their lifetime, and the annual rupture rate per patient was 1.6%. Risk factors for lifetime SAH were female sex, current smoking, and aneurysm diameter >7 mm.[110] In the HUNT longitudinal cohort study, with linkage to hospital and death records, the overall rupture risk in people with UIAs aged 50 to 65 years was 0.87% per year.[16]

Comparison of risk factors at the patient level was evaluated in the retrospective and prospective cohorts of patients of the ISUIA classified by prior SAH or no prior SAH. Those without an SAH history were older, had more hypertension, more cardiac disease, less alcohol use, less current smoking, and more oral contraceptive use.[34]

Predictors

Prospective studies of the risk of rupture in previously unruptured aneurysms have consistently recognized the role of aneurysm size and location.[4,5,31–35] Potential but not universally demonstrated risk factors for rupture include younger age, cigarette smoking, hypertension, aneurysmal growth, morphology, female sex, prior SAH, and family history of SAH.[111,112] In annual follow-up of 384 UIAs, significant independent predictors of rupture were hypertension and age <50 years.[113] Inflammation may play an important role in the pathogenesis and growth of IAs.[114,115] The role of anti-inflammatory medications in prevention of growth and rupture has been hypothesized but needs controlled, prospective confirmation.[114] Comparative and prospective cohort studies

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of aspirin use have shown fewer SAH events in patients with routine aspirin use.[116] Other interventions, such as the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) and calcium channel blockers, may retard aneurysm formation through the inhibition of nuclear factor-κB and other pathways, but observational findings are not supportive of the use of statins for prevention.[115]

Similarities With aSAH Risk Factors

Demographic risk factors associated with aSAH include age, sex, and race. A familial history of aSAH and evidence of familial aneurysms (at least 1 first-degree family member with an IA) increase the risk of aSAH in an individual.[117] Certain genetic syndromes, such as autosomal dominant polycystic kidney disease, type IV Ehlers-Danlos syndrome, and microcephalic osteodysplastic primordial dwarfism (autosomal recessive inheritance), have an association with aSAH. Modifiable risk factors for aSAH include hypertension, smoking, and alcohol abuse. Elevated aSAH risk associated with the use of sympathomimetic drugs (eg, cocaine) and decreased risk among those with diabetes mellitus and those with elevated body weight have not been shown in subjects with unruptured aneurysms.[2,12,20]

Summary

The prevalence of UIAs increases with age. Aneurysms are thought to be acquired, although there is evidence of genetic and familial risk in some patients. There is increased risk in patients with selected other vascular abnormalities. There are several heritable conditions associated with an increased occurrence of a UIA, including autosomal dominant polycystic kidney disease, but UIAs associated with these conditions are very uncommon in clinical practice. Women appear to be at increased risk, but the role of oral contraceptives and estrogen loss or prevention of estrogen loss after menopause is inconclusive. The substantial increase in prevalence among smokers and people with hypertension indicates that both are likely modifiable factors for aneurysm development. Factors related to hemodynamic stress and inflammation may accelerate the rate of rapid aneurysm development and rupture and need to be elucidated. A combination of risk factor prevention and management may be necessary to reduce the prevalence of unruptured aneurysms and the precursor for SAH in the majority of cases.

Risk Factors for Aneurysm Development, Growth, and Rupture: Recommendations

1. **Given that smoking appears to increase the risk of UIA formation, patients with UIA should be counseled regarding the importance of smoking cessation *(Class I; Level of Evidence B)*.**
2. **Given that hypertension may play a role in growth and rupture of IAs, patients with UIA should monitor blood pressure and undergo treatment for hypertension *(Class I; Level of Evidence B)*.**
3. **Aneurysmal growth may increase the risk of rupture, and intermittent imaging studies to follow those UIAs managed conservatively should be considered *(Class I; Level of Evidence B)*.**

Clinical Presentation

UIAs are most commonly identified after hemorrhage from another aneurysm, or incidentally during evaluation of neurological symptoms other than from a hemorrhage, or a sudden severe or "different" headache. In the ISUIA, the diagnosis of the target unruptured aneurysm was made during evaluation of hemorrhage from another aneurysm (30.4%), headache (23.7%), ischemic cerebrovascular disease or transient ischemic attack (10.6% and 10.5%, respectively), cranial nerve palsy (8.0%), seizures (2.9%), symptoms of mass effect (2.7%), subdural or intracerebral hemorrhage (1.2%), brain tumor (0.8%), central nervous system degenerative disorders (0.4%), and undefined "spells" (7.1%).[4] In another prospective observational study that excluded patients presenting with SAH from another source, the combination of cerebrovascular disease, transient ischemic attack, and nonspecific spells was the most common indication for evaluation leading to aneurysm discovery (43.4%), whereas headache accounted for 16%.[118] The results of ISUIA support the use of aneurysm size and location in the consideration of optimal management after UIA detection. The manner of presentation may also influence the natural history of the aneurysm or the decision to treat. Wermer et al[99] found a 4-fold increased risk of rupture with symptomatic unruptured aneurysms.

ISUIA assessed the prospective risk of spontaneous hemorrhage from UIAs identified in patients after presentation with a ruptured aneurysm. The ruptured aneurysm was treated, and the UIA was then followed up. In these patients, during a 5-year period, the risk of hemorrhage for aneurysms <7 mm in diameter was significantly greater than for patients with similarly sized unruptured aneurysms and no prior history of hemorrhage.[4] The rate of rupture was not significantly different between these groups for aneurysms >7 mm.

In the absence of hemorrhage, the most common indication for diagnostic evaluation leading to the discovery of an unruptured aneurysm is headache.[4,118] In the ISUIA, patients presenting with headache were more likely to undergo treatment of their unruptured aneurysm, but no data were provided regarding the risk of spontaneous hemorrhage. Several small observational studies have reported improvement in headache frequency or severity after aneurysm treatment in those patients presenting with headache attributed to the aneurysm.[119–122] No studies, however, have sufficiently correlated presentation with headache with a change in the risk of spontaneous hemorrhage, and it remains likely that most headaches in patients with UIA are not directly related to the aneurysm.

UIAs may be discovered in the evaluation of cranial nerve palsy. Patients whose aneurysm was identified in the presence of cranial nerve palsy were more likely to undergo treatment than observation in ISUIA, and no data were provided regarding the risk of subsequent rupture.[4] Several small observational studies have reported improvement in cranial nerve function after aneurysm treatment in those patients presenting with cranial nerve palsy, but no randomized trials have evaluated this practice.[123–127] For patients presenting with oculomotor palsy secondary to posterior communicating aneurysms, several retrospective studies have indicated better resolution with surgery than endovascular therapy[128–130] or conservative

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management.[128] Sudden onset of third nerve palsy in this setting is generally considered an indication of expansion and concern for imminent rupture, necessitating rapid workup and intervention.

Evaluation after presentation with ischemic cerebrovascular disease may lead to the discovery of a UIA.[4,118] A small minority of these aneurysms are found proximal to the ischemic territory, and particularly when a given aneurysm has an intra-aneurysmal thrombus, it may be considered a potential source of the ischemic event.[131] No prospective randomized trial has compared the risk of subsequent ischemic events, rupture, death, or disability after treatment or medical management. Although the practice of leaving a symptomatic aneurysm unsecured or treating the patient with antiplatelet or anticoagulation therapy remains controversial, there are insufficient data to evaluate and support the treatment of UIAs for the prevention of ischemic cerebrovascular disease. Aneurysms found after presentation with stroke or transient ischemic attack and that have clearly defined intrasaccular thrombus proximal to the ischemic territory on imaging may warrant consideration for treatment, but a lack of prospective data makes it uncertain as to whether such treatment will reduce the risk of subsequent ischemia.

Clinical Presentation: Recommendations

1. **Patients with an aSAH should undergo careful assessment for a coexistent UIA *(Class I; Level of Evidence B)*.**
2. **Early treatment is generally indicated for patients presenting with cranial nerve palsy caused by a UIA *(Class I; Level of Evidence C)*.**
3. **The effectiveness of the routine treatment of UIAs for the prevention of ischemic cerebrovascular disease is uncertain *(Class IIb; Level of Evidence C)*.**

Diagnosis/Imaging

The methods of imaging of aneurysms have expanded greatly, with advanced MRA, CTA, and DSA techniques. Each has advantages and disadvantages, and each is used variably by individual practitioners at various stages in the evaluation of cerebral aneurysms. Initial imaging diagnosis, full evaluation of the anatomy of the aneurysm and the relationship to the parent vessel(s), and follow-up imaging evaluation for UIAs are covered in this section.

After the diagnosis of an aneurysm, the specific anatomic (and perhaps in the future, dynamic) details of the aneurysm(s) both initially and in follow-up are necessary to adequately categorize the lesion to select appropriate management and assess the outcomes of that management.[132–134]

Digital Subtraction Angiography

DSA continues to be the "gold standard" of aneurysm diagnosis; however, with the advent of 3-dimensional (3D) rotational angiography, even more detailed imaging can be performed than with 2-dimensional planar imaging. Studies have shown greater sensitivity of DSA, especially in aneurysms smaller than 3 mm.[135–138] In addition, the resolution provided by DSA is greater for the smallest of vessels, such as perforators.[139–144]

Although DSA remains the gold standard, it should be recognized that catheter arteriography does have risks, albeit small. Possible complications include contrast-related events, cerebral infarction, aneurysmal rupture, arterial injury, and others.[145,146] In patients with renal insufficiency or Ehlers-Danlos syndrome, in whom the risk of catheter angiography is higher, clinicians may favor noninvasive imaging; however, in general, the risks are low, with most contemporary data indicating permanent neurological complications in patients with cerebral aneurysms, SAH, and arteriovenous malformation occurring at a rate of 0.07%.[147] There is also the potential for radiation risks, but in the setting of diagnostic angiography, these risks are small. The invasiveness and the cumulative radiation make it less frequently used for follow-up[148]; however, selective DSA follow-up for treated aneurysms carries a low risk.[149,150]

Computed Tomography

With the development of multidetector scanners, CTA is frequently added to the noncontrast computed tomography (CT) to assist diagnosis. There are multiple generations of scanners, but in general, the sensitivity, specificity, and accuracy of aneurysm detection with modern-generation scanners is very high compared with DSA with 3D rotational acquisition, with 1 report indicating values of 96.3%, 100%, and 94.6%, respectively. However, in that same report, there was lesser sensitivity for smaller aneurysms (typically characterized as those <3 mm), of 81.8%, 100%, and 93.3%, respectively.[151]

In 2003, a meta-analysis of 21 studies that included 1251 patients resulted in a sensitivity of 93.3% and specificity of 87.8% for CTA compared with DSA.[152] In addition, CT is very useful in identifying mural calcification and thrombus, which can have a significant impact on treatment decisions.[153] However, the reconstruction methods may not accurately depict the true neck/dome/adjacent small vessel anatomy, which can be important determinates of the type of treatment rendered.[139] Despite this shortcoming, with its high sensitivity and specificity, even in smaller aneurysms, CTA can be considered as an initial diagnostic test for aneurysm detection and screening.

CTA may be limited by artifact from bone and metal (coils, stents, and clips), thereby reducing its usefulness as an alternative to DSA as a follow-up technique for noninvasive imaging in treated aneurysms. The associated exposure to radiation is another issue in its use in long-term follow-up.[154–157]

Magnetic Resonance Imaging

Imaging of aneurysms with MRA typically uses time-of-flight (TOF) or contrast methods. It is unclear which method is most useful, but generally, MRA has been reported to have a detection sensitivity ranging from 74% to 98%.[158] However, 1 study showed that overall, sensitivity was 79% with the most experienced readers, and aneurysm size greatly affected the results. Aneurysms >3 mm were detected with a sensitivity of 89% by the most experienced readers.[159–161] These data suggest that as a primary method of screening for UIAs, magnetic resonance can be very useful for aneurysms larger than 3 mm. A recent analysis of small aneurysms (≤5 mm) with 3T TOF

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MRA with volume rendering versus DSA showed very high accuracy (96.4%–97.3% for the readers), with the continued caveats regarding small-vessel detection (infundibula versus aneurysm) and contrast merging because of vessel tortuosity yielding false-positive and false-negative results. However, with this level of accuracy, using appropriate protocols, even small aneurysms should be detected.[162]

For follow-up after interventional treatment, although susceptibility artifacts occur at the skull base and surrounding metallic implants such as stents, coils, and clips, MRA remains an effective alternative for noninvasive follow-up of both treated and untreated aneurysms.[163–168] A meta-analysis of contrast-enhanced MRA in postcoiled aneurysms showed that contrast-enhanced MRA had an overall sensitivity of 92% and a specificity of 96% in detecting residual aneurysm compared with DSA.[169] However, with treated aneurysms, the resulting susceptibility artifacts on MRA can cause an underestimation of the size of the residual or recurrent aneurysm, and formal DSA may be necessary to determine the need for retreatment.[166,167] As is always the case for MRI, care should be taken to ensure that the metallic implants are compatible with the magnetic environment of the MRI scanner.[170–172]

In the follow-up of treated UIAs, magnetic resonance is a reasonable option given the high sensitivity for a residual aneurysm, lack of beam-hardening artifacts seen with CT, and invasiveness of DSA. For untreated UIAs already diagnosed, the lack of ionizing radiation or contrast (for TOF MRA) would make it the option of choice in those patients with renal compromise or in whom radiation exposure risks are relevant.

Analysis and Reporting

Whatever aneurysm imaging method is chosen, certain aspects of the anatomy require appropriate analysis and documentation to be useful for management and follow-up of UIAs. For determination of the method of treatment, including conservative management, endovascular, surgical, or combined therapy, accurate measurement of the neck size, a neck-to-dome ratio descriptor, measures of the aneurysm in 3 dimensions, and the relationship of the aneurysm to the surrounding vessels are essential.[132] For treated aneurysms, the presence, measurements, and descriptors of residuals and any parent vessel changes are necessary, along with identification of any new aneurysm development.[132]

The follow-up requirements for treated aneurysms remain uncertain. Long-term follow-up in treated UIAs has not been studied in randomized trials, so much of the general practices have been extrapolated from ruptured aneurysm trials. In general practice with adequate clipping, often no follow-up imaging is performed, or it may be limited to immediate perioperative angiography.[156] In ISAT, there was a slightly higher risk of recurrent hemorrhage from a coiled aneurysm than from those treated with surgical clipping, but the risks in both groups were very small.

For endovascularly treated aneurysms, because a residual or recurrent aneurysm is more common, imaging is often performed at 6 months to 1 year after treatment.[161,163–168,173] Timing of the later follow-ups is variable and depends on the occlusion status of the initial and early follow-up, as well as the condition of the patient. However, with residual aneurysms after coiling, long-term follow-up is indicated because there are late hemorrhages and aneurysm recurrences. For example, annual rates of hemorrhage in large and giant aneurysms (the most difficult group to treat with coiling) are up to 1.9%.[174] There is evidence that certain characteristics, such as wider neck diameters, larger aneurysms, and partial treatment, have a greater association with recurrence.[175,176]

With unruptured aneurysms, follow-up is indicated. This is discussed further in the section regarding follow-up of untreated aneurysms.

Diagnosing/Imaging: Recommendations

1. **DSA can be useful compared with noninvasive imaging for identification and evaluation of cerebral aneurysms if surgical or endovascular treatment is being considered *(Class IIa; Level of Evidence B)*.**
2. **DSA is reasonable as the most sensitive imaging for follow-up of treated aneurysms *(Class IIa; Level of Evidence C)*.**
3. **CTA and MRA are useful for detection and follow-up of UIA *(Class I; Level of Evidence B)*.**
4. **It is reasonable to perform MRA as an alternative for follow-up for treated aneurysms, with DSA used as necessary when deciding on therapy *(Class IIa; Level of Evidence C)*.**
5. **Coiled aneurysms, especially those with wider neck or dome diameters or those that have residual filling, should have follow-up evaluation *(Class I; Level of Evidence B)*. The timing and duration of follow-up is uncertain, and additional investigation is necessary.**
6. **The importance of surveillance imaging after endovascular treatment of UIAs lacking high-risk features for recurrence remains unclear, but surveillance imaging is probably indicated *(Class IIa; Level of Evidence C)*.**

Screening

The decision to screen for unruptured aneurysms by noninvasive CTA or MRA depends on the patient under consideration. Clinicians should consider aneurysmal prevalence associated with a given trait (such as prevalence in selected inherited disorders), projected disease morbidity, accessibility of a cost-effective screening test, the likely availability of an acceptably low-risk and effective treatment, and the patients' understanding of the potential implications of detecting an intracranial finding on imaging (such as future obtainment of life insurance), as well as the stress and anxiety that can be associated with UIA detection. Screening for unruptured aneurysms is appropriate in families with >1 affected person with an IA; in patients with a family history of IA and evidence of autosomal dominant polycystic kidney disease, type IV Ehlers-Danlos (vascular subtype), or the extremely rare microcephalic osteodysplastic primordial dwarfism[177] ; and in those with selected conditions associated with an increased occurrence of IAs, such as coarctation of the aorta or bicuspid aortic valve.[178–181] The likelihood of aneurysm detection among first-degree relatives of those with sporadic SAH is

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≈4% (95% CI, 2.6%–5.8%),[54] with somewhat higher risk among siblings than among children of those affected.[57] An AHA guideline regarding management of SAH suggested that it might be reasonable to offer noninvasive screening to first-degree relatives of those with SAH, but the risks and benefits of this approach are uncertain.[20]

Populations at Increased Risk of Harboring an IA

Certain genetic syndromes have been associated with an increased risk of aSAH, such as autosomal dominant polycystic kidney disease, type IV Ehlers-Danlos syndrome, and microcephalic osteodysplastic primordial dwarfism.[177] These syndromes also support the theory of an inherited susceptibility to aneurysm formation. Patients who have clinical evidence of polycystic kidney disease and are without a family history of IA/hemorrhagic stroke have a reported 6% to 11% risk of harboring a UIA compared with 16% to 23% of those who also have a family history of IA/hemorrhagic stroke.[179,181] In the latter group, noninvasive screening should be strongly considered, although the aneurysms are often small, and the risk of rupture is generally low in the small series reported previously.[179,181] In addition, first-degree family members of patients who have type IV Ehlers-Danlos syndrome (including a family history of IA) should also be strongly considered for screening.[178] In a neurovascular screening program of patients with microcephalic osteodysplastic primordial dwarfism,[177] 13 of the patients (52%) were found to have cerebral neurovascular abnormalities, including moyamoya angiopathy and IAs. Finally, of 117 consecutive patients with coarctation who were >16 years of age who underwent screening with brain MRA, 10.3% had a UIA.[182] Screening for UIA in these latter 2 groups of patients is also appropriate.

In addition to rare but well-defined genetic causes of IAs, such as polycystic kidney disease, population studies of aSAH have demonstrated that 9% to 14% of patients with an SAH have a family history of SAH in a first-degree relative.[80,117,183,184] It is in these families that screening for UIA should be most strongly considered.

The National Institute of Neurological Disorders and Stroke–funded FIA Study was designed to find genetic risk factors for IA and, as part of its design, included screening by MRA for UIA.[74,185,186] Eligible families included those with at least 2 affected siblings or ≥3 affected family members. The first-degree relatives of those affected with IA were offered screening if they were previously unaffected, were >30 years of age, and had a history of smoking or hypertension. The MRA screening was performed in 303 patients, and of these, 58 (19.1%) had at least 1 aneurysm. In a multivariate analysis, independent predictors of detection of IA included female sex (odds ratio [OR], 2.46), pack-years of cigarette smoking (OR 3.24 for 20 pack-years of cigarette smoking compared with never having smoked), and duration of hypertension (OR 1.26 when comparing those with 10 years of hypertension to those with no hypertension).[55,187] Most of the detected aneurysms were small: 2 IAs were ≥7 mm in maximal diameter; 19 were 4 to 6 mm; and 50 were 2 to 3 mm. Both of the aneurysms that were ≥7 mm in maximal diameter were treated.[187]

In another earlier screening study for IAs but with less aggregation of familial aneurysms, first-degree family members of patients with an IA were screened if they were at least 30 years of age and if there was no history of polycystic kidney disease. Among 438 individuals from 85 families, 38 (8.7%) had an IA.[52] As was the case in the FIA Study, most of the aneurysms detected were small. Large screening studies have also been performed in patients with sporadic SAH (those without any family history of IA). Among 626 first-degree relatives of 160 patients with sporadic SAH, 4% had aneurysms (25 of 626).[57] Thus, screening for IAs among unaffected family members in FIA families with multiple members with IA, particularly in smokers and those with hypertension, has strong justification, whereas screening among family members of patients with sporadic IA is not justified at present.

Cost-Effectiveness of Screening

In evaluation of the cost-effectiveness of screening for asymptomatic IAs, the monetary costs of screening should be weighed against the risks, consequences, and costs of an untreated ruptured aneurysm. Several assumptions must be made to estimate cost-effectiveness: likelihood of aneurysm detection by noninvasive imaging in the population studied, the sensitivity and specificity of noninvasive imaging, risk of intra-arterial angiography, risk of rupture in patients with detected aneurysms who are managed medically, the aggressiveness of medical management (example, smoking cessation), the morbidity and mortality associated with clipping or coiling of an unruptured aneurysm in cases in which the aneurysm is deemed treatable by either method, and the risk of subsequent rupture after intervention.

Although none of the models of cost-effectiveness include data for all of these variables, recent studies provide reasonable estimates of the utility of screening. One study provided evidence for recommendations to screen individuals with ≥2 first-degree relatives with SAH. The optimal screening strategy according to the authors' model is screening every 7 years from age 20 years until 80 years given a cost-effectiveness threshold of $20 000 per quality-adjusted life-year (QALY) ($29 200/QALY).[188] In another reported model of families with ≥2 affected first-degree relatives, screening compared with no screening had an incremental cost-effectiveness ratio of $37 400 per QALY. With screening, life expectancy increased from 39.44 to 39.55 years. The incremental cost-effectiveness ratio of screening was >$50 000 per QALY if age at screening was ≥50 years. In family members with 1 affected first-degree relative, screening compared with no screening had an incremental cost-effectiveness ratio of $56 500 per QALY.[189] Finally, Li and colleagues[190] examined various screening models of the asymptomatic general population. Overall, screening resulted in a QALY loss, which equated to a negative clinical impact. The threshold for 5-year risk of rupture at which screening resulted in a gain in QALYs was 13%. This held true for any prevalence of IA between 1% and 25%. Risk of rupture had a greater impact on outcome than prevalence. Halving the risk of intervention (either surgery or coiling) reduced the threshold 5-year risk of rupture at which screening resulted in gain of QALYs to 6%. Thus, noninvasive screening for IA is beneficial only in populations with a higher expected prevalence and higher risk of rupture.[190]

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Table 4. Five-Year Cumulative Rupture Rates (%) According to Size and Location of Unruptured Aneurysm*

	<7 mm				
	Group 1	Group 2	7–12 mm	13–24 mm	≥25 mm
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 indicates anterior communicating or anterior cerebral artery; IC, internal carotid artery (not cavernous carotid artery); MC, middle cerebral artery; and Post-P comm, vertebrobasilar, posterior cerebral arterial system, or the posterior communicating artery.

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Screening: Recommendations

1. **Patients with ≥2 family members with IA or SAH should be offered aneurysmal screening by CTA or MRA. Risk factors that predict a particularly high risk of aneurysm occurrence in such families include history of hypertension, smoking, and female sex *(Class I; Level of Evidence B)*.**
2. **Patients with a history of autosomal dominant polycystic kidney disease, particularly those with a family history of IA, should be offered screening by CTA or MRA *(Class I; Level of Evidence B)*, and it is reasonable to offer CTA or MRA to patients with coarctation of the aorta and patients with microcephalic osteodysplastic primordial dwarfism *(Class IIa; Level of Evidence B)*.**

Natural History of UIAs

A large number of studies of varying quality have evaluated rupture risk of UIAs. The ISUIA and the Unruptured Cerebral Aneurysm Study Japan (UCAS Japan) study are the most carefully designed large studies.[4,5,34] In its first phase, ISUIA obtained retrospective natural history data on 1449 patients with 1937 unruptured aneurysms seen at 63 centers in North America and Europe.[34] Among patients with no history of SAH, the rupture risk was 0.05% per year for aneurysms <10 mm in diameter and ≈1% per year for larger aneurysms; aneurysm size (relative risk, [RR] 11.6 for 10–24 mm and 59 for >25 mm compared with <10 mm) and location in the posterior circulation (RR 13.8 for basilar tip and RR 13.6 for vertebrobasilar or posterior cerebral versus anterior circulation) or posterior communicating artery (RR, 8.0) were predictors of rupture risk in this group. Among those with a history of SAH from a different aneurysm, the rupture risk was 0.5% per year for those <10 mm and ≈0.7% per year for larger aneurysms; basilar tip aneurysms (RR, 5.1) and older age were predictors of rupture risk in this group.

Phase 2 of the ISUIA included a prospective natural history study of 1692 patients with 2686 unruptured aneurysms followed up for a mean of 4.1 years at 61 centers in North America and Europe.[4] After the results were analyzed, aneurysm rupture rates were stratified by size (with a new cut point of <7 mm to define the smallest group of aneurysms), history of SAH from a different aneurysm, and location (cavernous carotid, anterior circulation except posterior communicating artery, or posterior circulation plus posterior communicating artery). For patients with no history of SAH and aneurysms <7 mm in diameter, there were no ruptures among aneurysms in the anterior circulation, and the risk was 2.5% per year in those with aneurysms in the posterior circulation or posterior communicating artery (Table 4). Among those with a history of SAH and an aneurysm <7 mm, the risk of rupture was 1.5% per year in the anterior circulation and 3.4% per year in the posterior circulation. History of SAH was not a predictor of rupture for aneurysms >7 mm, and rupture risks were higher with larger aneurysms.[4]

The natural history data from the ISUIA have been criticized for several reasons. First, the number of patients in certain categories is small, so some of the estimates of rupture risk in the strata shown in Table 4 are imprecise. Second, although some predictors of rupture were confirmed in the second phase of the study, some were not. For example, a smaller cut point for size (<7 versus <10 mm) was defined in the second phase of ISUIA, identifying a group at extremely low risk of rupture. When cut points are optimized, findings are less likely to be validated in independent studies. Third, although the proportion of patients undergoing an interventional procedure varied tremendously from center to center in this nonrandomized study, in general, the surgeon or radiologist evaluating the patient would only have conservatively managed those patients who were deemed to be at low risk of rupture, and therefore, selection biases could change the risk profile of included participants. Fourth, differential follow-up and detection biases could alter apparent rates, and some outcome events may have been missed. In spite of these and other limitations, ISUIA remains one of the most rigorous and largest studies of the natural history of UIAs that includes patients of European descent.

Many other studies of the natural history of unruptured aneurysms have been published. The most recent meta-analysis of these included 19 studies with 6556 unruptured aneurysms and 4705 patients[99]; >70% of the patient-years of observation in the meta-analysis were contributed by the ISUIA. Together, these 19 studies published between 1966 and 2005 varied dramatically in size and duration of follow-up, and they included both prospective and retrospective designs. Overall, the annual rupture rates were 1.2% for studies with mean follow-up <5 years, 0.6% for those with mean follow-up of 5 to 10 years, and 1.3% for those with mean follow-up >10 years. Several risk factors for rupture were identified, including age >60 years (RR, 2.0; 95% CI, 1.1–3.7), female sex (RR, 1.6; 95% CI, 1.1–2.4), Japanese or Finish descent (RR, 3.4;

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95% CI, 2.6–4.4), symptomatic aneurysm (RR, 4.4; 95% CI, 2.8–6.8), diameter >5 mm (RR, 2.3; 95% CI, 1.0–5.2), and posterior circulation aneurysm (RR, 2.5; 95% CI, 1.6–4.1). The overall annual rupture rate for aneurysms <7 mm was 0.4%. Published data were limited, so the meta-analysis could not evaluate more than 1 risk factor at a time.

Several studies of natural history have been published since this meta-analysis. The large, prospective UCAS Japan study included 6697 patients followed up for a mean of 1.7 years and found an annual rupture rate of 0.95%.[5] The annual risk of rupture varied dramatically by size, ranging from 0.36% for 3- to 4-mm aneurysms, 0.50% for 5- to 6-mm aneurysms, 1.69% for 7- to 9-mm aneurysms, 4.37% for 10- to 24-mm aneurysms, and 33.4% for aneurysms ≥25 mm. Location in the anterior or posterior communicating arteries (hazard ratio 1.90 and 2.02, respectively, versus location in the middle cerebral artery) and aneurysms with daughter sacs (hazard ratio, 1.63) were also at greater risk of rupture. A daughter sac was defined as an irregular protrusion from the aneurysmal wall. Family history and history of SAH from a different aneurysm were not identified as risk factors for rupture. The authors noted that rates of rupture in Japan were higher, and results might not be generalizable to other populations.

Another recent small prospective study from Japan followed 374 patients with 448 unruptured aneurysms <5 mm in diameter for a mean of 41 months.[191] The overall risk of rupture was 0.5% per year, with younger age, larger aneurysm size, hypertension, and aneurysm multiplicity being predictors of rupture. All ruptures occurred in those with anterior circulation aneurysms, and most occurred in those without a history of SAH or family history, thus failing to confirm the extremely low risk of rupture in these groups in ISUIA. However, the patients were of Japanese descent, and it is unclear whether the data can be validly compared with studies evaluating patients of principally European descent. A second small study from Japan included 419 patients with 529 unruptured aneurysms followed up for a mean of 2.5 years and found a rupture rate of 1.4% per year.[192] Larger aneurysm size, posterior circulation location, and a history of SAH were all independent risk factors for rupture. The rupture rate of those with no history of SAH and an aneurysm <5 mm in diameter was 0.6% per year. However, 5 of the 19 ruptures occurred in patients with <7-mm diameter anterior circulation aneurysms and no history of SAH; the annualized rupture risk in this group was not reported but was higher than the comparable group in ISUIA. It is unclear whether the failure to confirm the extremely low risk of rupture in this subgroup in these 3 Japanese studies reflects differences in aneurysm characteristics and risk of SAH in people of Japanese descent or whether it represents a failure of validation of ISUIA more broadly. A limitation of the Japanese cohort studies and ISUIA is the relatively short mean follow-up; all 3 studies have a mean follow-up of ≤4.1 years.

A prospective study of 319 aneurysms <7 mm in diameter in US patients with no history of SAH followed patients for a mean of 2.4 years with serial CTA and MRA of intracranial vessels.[111] They did not report any aneurysm ruptures during follow-up, confirming the low risk in this subgroup of unruptured aneurysms identified from ISUIA. However, aneurysm growth of at least 0.75 mm was observed at an annual rate of 5.4%. Given that the threshold for growth was the resolution of imaging, the authors acknowledged that some assessments of growth may have been false-positive results.

A prospective study of patients enrolled in the large FIA study followed 113 patients with 148 unruptured aneurysms, nearly all <7 mm and none with a history of SAH, for a mean of 1.5 years.[187] Among these patients, there were 2 SAHs in patients with 3- and 5-mm anterior communicating artery aneurysms, respectively, for a rupture rate of 1.2% per year (95% CI, 0.14%–4.3%), 17-fold higher than that seen in patients with comparably sized and positioned aneurysms in ISUIA. The small number of ruptures and large CI lead to ongoing uncertainty regarding the relative rupture risks in patients with familial aneurysm.

Although ISUIA provides evidence for stratifying that risk by aneurysm size and location at the time of discovery, it cannot address the risk of aneurysms that may change in size over time, because repeat imaging was not required. Multiple studies have reported an increased risk of spontaneous hemorrhage from aneurysms with documented growth over time.[25,95] A recently published prospective observational study reported a dramatically increased risk of spontaneous hemorrhage from aneurysms with documented growth on serial magnetic resonance angiography.[193] The authors of this study evaluated 1002 patients with 1325 aneurysms followed up by routine serial MRA, which identified 18 patients with interval aneurysm growth. They reported an annual hemorrhage rate of 18.5% for those patients with documented growth and estimated that 90.3% of growing aneurysms would be detected before hemorrhage with screening performed at 6-month intervals. A second, smaller study of 258 aneurysms showed 18% of aneurysms grew. When compared with the nongrowing group, the per year rate of hemorrhage was 2.4% in the growing aneurysm group versus 0.2% in the nongrowing group. As with the other study, some growing aneurysms were treated before rupture, so the rate could be higher.[98] Therefore, routine screening by noninvasive vascular imaging techniques to detect aneurysm growth is probably indicated, and treatment of aneurysms with documented growth may be reasonable.

Patients with aneurysms in the setting of autosomal dominant polycystic kidney disease do not appear to be at increased risk of aneurysm rupture, but experience is limited.[194] Several other recent studies have reported rupture rates and their risk factors but have had methodological limitations that reduced the reliability of their conclusions.

Natural History: Recommendations

1. **Prior history of aSAH may be considered to be an independent risk factor for future hemorrhage secondary to a different small unruptured aneurysm *(Class IIb; Level of Evidence B)*.**
2. **Patients with aneurysms with documented enlargement during follow-up should be offered treatment in the absence of prohibitive comorbidities *(Class I; Level of Evidence B)*.**

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3. **Treatment of UIAs in patients with a family history of IA is reasonable even in aneurysms at smaller sizes than spontaneously occurring IAs *(Class IIa; Level of Evidence B)*.**

Surgical Clipping

Outcomes

Surgical treatment for UIAs comprises primarily direct surgical clipping, although other options such as occlusion with bypass and wrapping have also been used in treatment of more complex aneurysms. The majority of studies examining treatment outcomes related to UIA surgery have been single-center retrospective case series. These reports frequently lack features of high-quality studies, such as independent assessment of outcome, adequate specification of patient and lesion characteristics, reporting of occlusion rates and methods of determination, periprocedural complication data, and standardized time frame of follow-up.

Despite these shortcomings, several meta-analyses have analyzed data regarding outcome of surgery for UIAs. The first[195] included patients with only asymptomatic UIAs, totaling 733 patients from 28 studies published between 1966 and 1993 and reported a 1% mortality and 4.1% morbidity rate. Morbidity was defined as permanent significant deficit or was based on individual study authors' assessment without defined criteria and at variable follow-up time points. Subsequently, Raaymakers et al[196] analyzed 2460 patients from 61 studies published between 1966 and 1996 and reported 2.6% mortality and 10.9% morbidity (defined as all permanent deficit not present before operation and all outcomes other than the best category). Of note, the generally poor quality of studies was reflected by the fact that only half of the studies used clearly defined outcome measures, and fewer than half specified the time point of outcome determination, which itself varied from evaluation at discharge to a median of 24 weeks. More recently, Kotowski et al[197] reported on 9845 patients from 60 studies published in a more contemporary time frame spanning 1990 to 2011. They found an overall mortality rate of 1.7% and morbidity rate of 5%, for a total unfavorable outcome estimate of 6.7% up to 1 year after surgery. Morbidity was defined as nonindependence (modified Rankin Scale [mRS] score >2, Glasgow Outcome Scale score <4) or "fair"/"poor" on qualitative scores. It is notable that the majority of included studies (85%) were rated as poor quality based on STROBE (Strengthening the Reporting of Observational Studies in Epidemiology)[198] reporting criteria.

The combined estimates of morbidity show the most variability among these meta-analyses, potentially reflecting the definition of morbidity used and the case mix of aneurysms and patients represented in the studies included. For example, the analysis by King et al[195] included only asymptomatic UIA and a predominance of small and anterior circulation lesions, whereas these lower-risk features represented a smaller proportion in the other reviews.[196,197] The highest morbidity, exceeding 10%, was reported in the meta-analysis by Raaymakers et al[196]; however, 112 of 268 patients categorized as experiencing morbidity were independent in daily life despite signs or symptoms and likely would not have met the definition of unfavorable outcome used in the other meta-analyses. With variability in reporting and a lack of high quality of the studies, these meta-analyses serve best to help identify potential risk factors rather than to definitively set the benchmark for surgical outcomes or conclusively identify predictors.

Regional or population-based data extracted from administrative data sets, such as the National (Nationwide) Inpatient Sample (NIS), have also been used as an estimation of "real-world" UIA treatment outcomes. These retrospective database studies have reported mortality from surgical treatment ranging from 0.7% to 3.5% and morbidity ranging from 13.5% to 27.6%.[199–208] Because of the lack of specific outcome information available in such databases, morbidity has generally been defined as discharge status to a facility other than home (including rehabilitation facilities). No longer-term outcome data past the time of discharge can be assessed, and assumptions that discharge status is a reliable surrogate for longer-term outcome are not well validated. Furthermore, because of a lack of information within these databases related to specific aneurysm features such as location and size, a robust determination or adjustment of risk factors for poor outcomes cannot generally be performed. Thus, despite large sample sizes, the inherent limitations to hospital-based administrative data sets, including their retrospective nature and potential for miscoding of complications, limit interpretation of outcomes. A review by Lee et al[209] performed an aggregate analysis of 30 studies, combining case series and database studies to arrive at an overall unfavorable outcome of 17.8% with surgical clipping of UIAs; however, the heterogeneity of the study designs and the lack of uniformity in the definition of morbidity limit the utility of this analysis.

Prospective registries that include patient- and aneurysm-specific parameters, as well as specified outcome determinations at predefined intervals after discharge, are likely to offer more reliable data. The prospective arm of the ISUIA followed 1917 patients after clipping for UIA and reported an overall mortality of 2.3%.[4] One-year morbidity, defined as mRS score>2 or impaired cognition (measured by Mini-Mental State Examination or telephone survey of cognitive status) was present in 12.1% at 1 year after treatment. Importantly, several risk factors strongly predictive of outcome were evident, as outlined in the sections below.

Beyond morbidity related to functional outcomes, the potential cognitive impact of surgical treatment for UIA has also been a topic of interest. As noted, ISUIA included cognition in its determination of postoperative morbidity and found that impaired cognition alone accounted for 55% of the overall reported morbidity. Subsequent small, prospective, single-center series examining cognitive function before and after clipping have not borne out the same conclusion, demonstrating no cognitive dysfunction on Mini-Mental State Examination at 1 month after surgery.[210,211] There have been contradictory results in series that used more comprehensive neuropsychological batteries.[210,212,213] Nonetheless, it appears that standard outcomes instruments such as the mRS and the Glasgow Outcome Scale do not correlate with results of the Mini-Mental State Examination after aneurysm surgery,[214] and

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thus, the incorporation of cognitive assessment of patients can provide additional useful outcomes information.

A number of small series have also examined quality of life using health outcome scales such as the Short Form-36 and the Hospital Anxiety and Depression Scale (HADS). These have generally indicated that there may be a short-term negative impact on quality of life but largely with full recovery to baseline or to reference population values by 1 to 3 years after treatment.[215,216]

In terms of specific complications after UIA surgery, the rate of seizure after craniotomy for UIA is poorly defined. Analyses of administrative data sets have reported a very low incidence of 0.1% for status epilepticus[199] and as high as 9.2% when reporting any seizures,[217] although these studies do not account for preexisting seizures or use of anticonvulsant drugs. For example, in the ISUIA cohort, 4.4% of patients with surgically treated UIAs had a preexisting convulsive disorder.[4] For postoperative stroke, administrative database studies have reported ischemic complications in 6.7% to -10%[199,207] and hemorrhagic complications in 2.4% to 4.1%[199,207] of patients undergoing UIA clipping. In ISUIA, the incidence of cerebral infarction was reported to be 11%, with a 4% incidence of intracranial hemorrhage. One small prospective series of 51 aneurysms (UIAs and RIAs) using diffusion-weighted imaging MRI before and after clipping found silent ischemia in 9.8% but only an 2% incidence of symptomatic stroke despite complex aneurysms by size and location.[218]

Efficacy and Durability

Although surgical clipping is believed to provide definitive and long-term treatment of aneurysms, data on efficacy of treatment in terms of complete obliteration have not been reported consistently. In addition, the mode of imaging and timing of postoperative examination may not be clear. In the meta-analysis by Raaymakers et al,[196] only 10 of 61 studies reported postoperative angiography to verify the clipping, and results were only available in 5 studies that demonstrated 11 incomplete clippings among 158 patients, for a 93% complete obliteration rate. Kotowski et al[197] similarly found that information on occlusion rates was missing for the majority of studies examined, but based on 1969 postoperative examinations, 91.8% were completely occluded, 3.9% had neck remnants, and 4.3% were incompletely occluded.

There are limited data available regarding the long-term risk of intracranial hemorrhage after UIA clipping. Kotowksi et al[197] found data available in only 9 of 60 publications, representing 773 patients; 3 hemorrhages (0.38%) were reported during an average 1.2-year follow-up. The retrospective studies that used large-scale administrative databases provided no data on the success of the intervention in regard to aneurysm obliteration or risk of subsequent hemorrhage. Single-center long-term follow-up studies have typically included both UIA and RIAs. In a study that evaluated the long-term efficacy of clip ligation in 147 ruptured and unruptured aneurysms,[219] immediate postoperative angiography confirmed complete occlusion in 135 aneurysms (91.8%) and a residual neck in 12 (8.2%). The residual necks were defined as "dog ear" versus "broad-based." Of the completely occluded aneurysms, angiography at 3 years demonstrated 2 recurrent aneurysms (1.5%) without new SAH. Of the 12 aneurysms with a known residual neck, 2 of the 8 dog-ear residua enlarged, compared with 3 of the 4 broad-based. These data confirm both the immediate and long-term efficacy of clip obliteration and also highlight the need for continued follow-up in patients with known residua.

Another study of 140 aneurysms followed up for a mean of 9.3 years reported a regrowth rate of 0.26% per year for completely clipped aneurysms and a 0.89% per year risk of de novo aneurysm formation.[220] Similarly, the incidence of regrowth was higher in incompletely clipped lesions (7.1% versus 2.4%). In a previous study, the same authors noted a cumulative risk of SAH from de novo and recurrent aneurysms of 1.4% in 10 years and 12.4% in 20 years.[221] A recent study reported a lower incidence of hemorrhage, with only 2 patients (0.2%) having SAH and a total of 9 patients (0.9%) having recurrent aneurysms among 1016 aneurysms clipped over a 15-year period; however, follow-up was not routinely performed in this series, and thus, the true incidence of recurrence is unclear.[222]

Given the inclusion of both UIA and RIA, these results may not be generalizable to UIA alone. Although overall reported rates of recurrence appear to be very low, the limited available data suggest that recurrence rates may increase with incompletely clipped aneurysms and longer lengths of follow-up. Along with the reported risk of de novo aneurysms, these findings warrant consideration for repeat imaging within a 5- to 10-year time frame, and even up to 20 years in younger patients.

Risk Factors: Lesion Specific

The size and location of aneurysms have been most consistently associated with surgical risk.[196,197] In the prospective ISUIA cohort, aneurysm size >12 mm was a significant predictor of poor outcome, with an RR of 2.6.[4] In the recent meta-analysis by Kotowski et al,[197] unfavorable outcome (including death) was noted in 4.0%, 12.1%, and 26.5% of patients with small (<10 mm), large (10–24 mm), and giant (≥25 mm) aneurysms respectively, with an RR of 3.5 for aneurysms >10 mm. Increasing aneurysm size conferred an OR of 1.13 per 1-mm increase in a prospective cohort of 603 UIAs.[223] The same cohort study also noted an OR of 2.9 for anterior versus posterior circulation aneurysms. Location (anterior versus posterior) was associated with an RR of 4.1 in the meta-analysis by Kotowski et al,[197] and in the ISUIA cohort, posterior circulation location was an independent predictor of poor outcome, with an RR of 1.6.

The interaction of size and location appears to be particularly pertinent. In the meta-analysis by Raaymakers et al,[196] non-giant (<25 mm) anterior circulation aneurysms carried the lowest mortality estimate of 0.8% (1.9% morbidity) compared with non-giant posterior circulation aneurysms at 3% (12.9% morbidity), giant anterior circulation aneurysms at 7.4% (26.9% morbidity), and giant posterior circulation aneurysms at 9.6% (37.9% morbidity). Giant aneurysms can pose a dilemma, given their higher surgical risk yet poor natural history. Overall favorable results can be achieved in younger

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patients[224] and for all patients with regard to mortality, but at a cost in terms of morbidity: In a series of 39 patients with giant UIAs, Nakase et al[225] noted that mortality was markedly reduced by surgical intervention (4% versus 31%), but morbidity affected 19% compared with 8% of untreated patients.

Other aneurysm features, such as atheroma/calcification, thrombus, nonsaccular morphology, and multiplicity, pose additional challenges and have been reported to adversely affect surgical outcome in small case series. Atherosclerosis and calcifications have typically been noted in single-center retrospective series to be associated with worse outcomes,[226–228] although 1 study of 51 aneurysms did not identify extent of aneurysmal atherosclerotic plaques to be a risk for postoperative stroke.[218] Calcifications appear to be correlated with aneurysm size,[226] and atherosclerotic burden is typically higher in elderly patients. Although it is generally presumed that worse outcomes with age reflect increased medical comorbidities, an increased incidence of atherosclerosis may also be a factor. Presence of intra-aneurysmal thrombus has also been a factor associated with increased risk of stroke.[218] Multiple UIAs have been reported to be associated with worse outcomes in some[227,229] but not all[230] studies.

Risk Factors: Patient Specific

Age has emerged as an important risk factor influencing outcomes after surgical clipping. In ISUIA, multivariate analysis demonstrated age as a powerful predictor of poor surgical outcome, with an RR of 2.4 for age ≥50 years.[4] In 1 large prospective series of >600 UIAs, age was associated with an OR of 1.03 for morbidity and mortality per year of increased age.[223] Administrative database studies have also identified age as a factor that affects outcome,[199,200,231] with mortality ranging from as low as 0.6% to 0.9% in patients <50 years old and averaging ≈2% thereafter, and as high as 21.4% in those ≥80 years old.[199,231] The published meta-analyses of case series have not been able to identify an age effect, but this likely reflects insufficient power given that information regarding outcome with respect to age was reported in the minority of patients in the included studies.[195–197] Presentation of patients with symptoms other than rupture, as opposed to those with incidentally found UIAs, appears to carry a higher surgical risk,[4] particularly for those presenting with ischemic symptoms (whether directly attributable to the aneurysm or otherwise).[232,233] In the ISUIA cohort, a history of prior ischemic cerebrovascular disease was associated with a significantly higher risk for adverse events after clipping, at an RR of 1.9.[4] This could relate to ischemia serving as a marker for atheroma or intraluminal thrombus, features that can increase surgical risk as noted above. Patients presenting with symptoms of mass effect from compression of cranial nerves or surrounding brain structures can be treated effectively with surgical clipping/decompression for relief of symptoms.[123] Higher overall surgical risks in this setting may be primarily a reflection of aneurysm size, given the tendency of lesions presenting in this manner to be large.[230,231] A new deficit related to the finding of an aneurysm, such as new-onset oculomotor nerve palsy, is considered an urgent indication for treatment, because it implies growth of the aneurysm with attendant risk of hemorrhage; prognosis for recovery of deficit in this setting is high with early surgical management.[128]

Direct evidence for the presumed negative impact of general medical comorbidities in surgical outcome is difficult to document. Published studies have the selection bias of including patients already chosen for intervention, with the likelihood that the status of medical comorbidities contributed to that decision making. However, it is reasonable to presume that medical comorbidities negatively influence outcomes in UIA clipping, as in any other surgery.

Surgical Experience and Hospital Volume

A number of studies have demonstrated a strong volume-outcome relationship related to outcomes after aneurysm surgery for both UIA and RIA in the United States.[202,234,235] For UIAs specifically, 3498 patients with UIA treated at 463 hospitals by 585 surgeons in the NIS were assessed.[201] Hospitals with >20 cases compared with those with <4 cases per year had better discharge disposition (84.4% versus 76.2% discharged to home) and lower mortality (1.6% versus 2.2%).[201] In a study of 2200 admissions for UIA from the New York State database and for clipped aneurysms found lower morbidity (OR, 0.85) and mortality (OR, 0.94) for each additional 10 cases per year in total procedural volume.[202] Surgeon experience, in addition to overall hospital volume, may also be pertinent; individual surgeon volume was also a strong predictor of better functional outcome in a review of 449 aneurysms treated by 10 different surgeons at the same institution.[236]

Other Considerations: Intraoperative Factors/ Technical Advances

Surgical technique in aneurysm surgery continues to evolve, in addition to advances in intraoperative tools to maximize the safety of surgical clipping. The use of intraoperative angiography to verify complete aneurysm obliteration at the time of surgery and verify the patency of branch vessels has become more widespread, especially at tertiary centers.[237–241] Case series have demonstrated unexpected findings (such as vessel occlusions or residual aneurysms) in ≈7% to 12% of cases,[237,239,242] leading to alterations in clipping and thus providing an indirect validation of its value. Because of the time, expertise, and expense associated with intraoperative angiography, other tools have also emerged that can provide more immediate feedback related particularly to vessel compromise. Both intraoperative Doppler sonography[243] and ultrasonic flowmetry[244] have demonstrated utility in assessing the patency of vessel branches associated with the aneurysm after clipping. The introduction of intravenous indocyanine green video angiography has been a further advance, providing the ability to quickly visualize the patency of perforators and larger branch vessels associated with the aneurysm. This technique uses a rapid intravenous injection of dye, which is then visualized through the operating microscope.[245,246] Each modality has strengths and limitations, and although there are no prospective controlled studies examining the benefits of these intraoperative adjuncts, the prevailing belief is that the use of these tools, alone or in combination, is beneficial in reducing surgical risk and optimizing successful aneurysm

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obliteration. Physiological brain monitoring with intraoperative somatosensory or motor evoked potentials to predict adverse ischemic sequelae during surgery has also demonstrated some value.[247,248] The use of judicious temporary clipping of vessels to facilitate aneurysm dissection and clipping, or of adenosine for temporary cardiac arrest, especially in large aneurysms, offers additional techniques to enhance surgical safety.[249,250]

Neuroprotection with intraoperative hypothermia has been assessed as a strategy to reduce the risk of surgical clipping. A pilot randomized study of intraoperative hypothermia demonstrated no outcome advantage in patients with UIAs.[251] Subsequent randomized trials have also failed to demonstrate an overall benefit for RIAs.[252] However, both hypothermia and intraoperative burst suppression to reduce metabolic demand are still used selectively by neurosurgeons and neuroanesthesiologists for cerebral protection during aneurysm surgery, especially in the setting of anticipated temporary vessel occlusion.[253]

Surgical technique has also evolved, with increased emphasis on avoiding the use of fixed brain retractors during surgery.[254,255] Additionally, smaller, less invasive surgical exposures are becoming more commonplace, including "key-hole" approaches, through small calvarial openings and incisions that minimize soft tissue disruption and brain manipulation/retraction.[256] Interestingly, in the larger reported meta-analyses, unfavorable outcomes were found to decrease in more recent publication years.[196,197] Even in the large-scale database studies, unfavorable outcomes, particularly mortality, are generally lower in the more contemporary studies,[207] which could be construed as reflecting improvements in surgical paradigms, although other factors such as centralization of care or changes in patient selection may also be invoked.

Surgical Clipping: Recommendations

1. **Several factors, including patient age and aneurysm location and size, should be taken into account when considering surgical clipping as the mode of treatment for a UIA *(Class I; Level of Evidence B)*.**
2. **Imaging after surgical intervention, to document aneurysm obliteration, is recommended given the differential risk of growth and hemorrhage for completely versus incompletely obliterated aneurysms *(Class I; Level of Evidence B)*.**
3. **Long-term follow-up imaging may be considered after surgical clipping given the combined risk of aneurysm recurrence and de novo aneurysm formation. Long-term follow-up may be particularly important for those aneurysms that are incompletely obliterated during initial treatment *(Class IIb; Level of Evidence B)*.**
4. **Surgical treatment of UIA is recommended to be performed at higher-volume centers (eg, performing >20 cases annually) *(Class I; Level of Evidence B)*.**
5. **The use of specialized intraoperative tools and techniques for avoiding vessel compromise or residual aneurysms may be considered to reduce the adverse outcomes seen with operative management of UIAs *(Class IIb; Level of Evidence C)*.**

Endovascular Treatment

In 1995, the US Food and Drug Administration approved the Guglielmi detachable coil for the treatment of nonsurgical cerebral aneurysms based on a study of 150 patients, 67 of whom had unruptured aneurysms.[257] Over the next 20 years, various permutations of this seminal adaptation of the endoluminal aneurysm occlusion coil have been applied to increasing numbers of ruptured and unruptured cerebral aneurysms worldwide, making endovascular aneurysm repair the preferred treatment in many medical centers.

During the 1990s, some authors noted improving endovascular results while surgical complications were increasing despite the practice of reserving endovascular treatment for higher-risk surgical patients.[4,206,258] Event rates declined in endovascular coil series from 1990 to 2000, but differences in study design made direct comparison difficult.[209] This occurred despite the fact that most aneurysm patients were prescreened for surgical clipping during the 1990s before referral for endovascular treatment.[4]

Since the publication of ISAT, which showed better outcomes for endovascular coil occlusion of ruptured aneurysms than for surgical clipping in selected cases,[8] there has been a steady increase in the relative proportion of patients with ruptured and unruptured aneurysms undergoing endovascular procedures. From 1998 to 2003, the proportion of unruptured aneurysms alone undergoing endovascular treatment increased from 11% to 43%.[259] Increased use of endovascular techniques, increased awareness of high-risk surgical indications, and the sensitivity of modern brain imaging, including CT and MRI, to identify unruptured aneurysms resulted in more endovascular procedures.[48,52,55,260] Increasing proportions of patients undergoing endovascular procedures have been identified in developed countries.[199,208,231,261] Still, most reports on the endovascular treatment of unruptured aneurysms remain small, single-center series.[262–267] Technical failure rates range between 0% and 10%.[268–270] Complications occur in 5% to 10% of cases.[265,271–274] Meanwhile, researchers identified significant potential for bias in the literature on unruptured aneurysm.[209,275]

The prospective ISUIA aimed not only to evaluate the natural history of unruptured aneurysms but also to measure the risk of treatment.[4] Among treated patients, 1917 patients underwent craniotomy and surgical clipping, and 451 underwent coil occlusion of their aneurysms. The combined surgical morbidity and mortality at 1 year was 10.1% for patients without prior SAH and 12.6% for patients with prior SAH versus 7.1% and 9.8%, respectively, for the endovascular group. Endovascular treatment in patients older than 50 years appeared safer than surgical clipping, but the difference was not statistically significant. Because the endovascular group was relatively small, wide CIs and variance limited comparability.[4] Nevertheless, until recently, ISUIA remained among the best data available on the natural history of untreated aneurysms in relation to treatment outcomes.

Two publications analyzed endovascular aneurysm series in aggregate or through meta-analysis. Lanterna et al[276] performed a systematic review of English, French, and Italian literature from 1990 to 2002 and identified 1379 patients,

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including a case fatality rate of 0.6%, permanent morbidity rate of 7%, and hemorrhage rate of 0.9%. Procedural morbidity decreased from 8.6% to 4.5% in studies after 1995, which suggests improvement in operator skills and experience, as well as improved devices and technology. Naggara et al[277] performed a systematic review of the medical literature on endovascular treatment of unruptured aneurysms from 2003 to 2008. Seventy-one publications were included in this review, which identified procedural complications in 4.8% of cases, satisfactory aneurysm occlusion in 86.1%, and aneurysm regrowth or recurrence in 24.4% over 0.4 to 3.2 years of surveillance, as well as retreatment in these cases in 9.1%. The annual risk of bleeding in treated patients was 0.2%, although clinical follow-up was often brief, only 6 months in 76.7% of reported cases. The authors concluded that endovascular aneurysm coil occlusion appears to be relatively safe, although the efficacy of these procedures had not been rigorously documented.[277]

Because of perceived limitations in the available data on unruptured aneurysm occlusion, Pierot et al[278] performed the Analysis of Treatment by Endovascular Approach of Nonruptured Aneurysms (ATENA) to determine risk and clinical outcomes of endovascular treatment. In this study sponsored by the French Society of Neuroradiology, 649 patients with 1100 unruptured aneurysms ≤15 mm were prospectively and consecutively treated by a multidisciplinary team of physicians at 27 French and Canadian neurointerventional centers. Aneurysms were discovered incidentally in 65% of patients, after rupture from another aneurysm in 20%, because of neurological symptoms in 13%, and during screening for familial disease in 2.5%. A balloon-remodeling technique was used in 37%, stent-assisted coil occlusion was used in 7.8%, and 98.4% of aneurysms were treated with coils. Aneurysm occlusion was deemed complete by the treating physician in 59%, with neck remnant in 21.7% and an aneurysm remnant in 19.3%. Systemic anticoagulation was used in all cases during treatment, and antithrombotic medications were used during or after treatment in up to 57% of patients. Inability to treat the aneurysm occurred in 4.3%, most commonly at the middle cerebral bifurcation, and failure was more common in smaller (1–6 mm) than larger (7–15 mm) aneurysms. Treatment-related adverse events occurred in 15.4%, including thromboembolic events. Aneurysm rupture during the procedure occurred in 2.6%, which was asymptomatic in 50% of such cases but fatal in 3 patients (16.7% of occurrences.). Neurological complications predominantly caused by thromboembolic complications occurred in 5.4%, were permanent in 2.6%, and led to death in 0.9%. For patients who were neurologically normal before treatment (mRS=0), 96% continued to have an mRS score of 0, 3.4% had an mRS of 1, 0.4% had an mRS of 2, and 0.2% had an mRS of 3. Complications were higher in patients >60 years of age. The authors concluded that there was a high rate of procedural success and a low rate of permanent complications, seemingly better than reported outcomes of surgical clipping.[278]

The durability of aneurysm occlusion when endovascular coils are used remains problematic, and a number of measures have been applied in an effort to improve this issue. In ISAT, the risk of aneurysm recanalization after endovascular occlusion was associated with recurrent hemorrhage, although that risk was small, with 10 episodes after 1 year in 1073 patients (8447 person-years).[279] The likelihood of aneurysm recanalization appears greater in previously ruptured aneurysms than in unruptured aneurysms[280]; however, if recanalization of an unruptured aneurysm occurs, then the benefit of endovascular coil occlusion may be called into question, which has led some authors to suggest preferential clipping of anterior circulation aneurysms, especially in patients <40 years old, when possible.[279,281,282] For unruptured aneurysms, recanalization of bifurcation aneurysms after endovascular coil occlusion remains a problem, especially at the middle cerebral bifurcation and at the carotid and basilar artery termini, although recanalization can also occur with clipped aneurysms at lower rates.[99,220,283] Attempts to improve the durability of occlusion by adding coatings such as polyglycolic acid, polyglycolic-lactic acid, and hydrogel (acrylamide:sodium acrylate gel) to platinum coils in an effort to augment aneurysm healing and fibrosis have not proved beneficial despite increased cost.[284–291] Other studies have also suggested that the risk of permanent disability or death attributable to treatment of aneurysm recurrence after prior endovascular coiling is quite low, which supports the practice of regular surveillance and prophylactic treatment of recurrences.[292]

Adjunctive methods such as balloon remodeling and stent-assisted occlusion are commonly reported, although the potential added value to accomplish superior aneurysm occlusion is not clearly defined. It is generally recognized that these techniques allow for the treatment of more aneurysms and with higher packing density than was possible with endosaccular coil occlusion alone.[293] In the ATENA study, balloon remodeling was commonly used and resulted in no excess morbidity.[278] However, other authors have identified increased rates of cerebral ischemia when using a balloon-remodeling technique, especially when assessed with advanced imaging techniques such as MRI with diffusion.[264,294] Endovascular stents represent a departure from the endosaccular occlusion paradigm, because prosthetic material now lies in the normal vessel adjacent to the aneurysm. A number of single-center retrospective studies have reported increased rates of progressive aneurysm occlusion with the use of stents.[295–298] However, stents were allowed in the Matrix and Platinum Science (MAPS)[299] and Hydrocoil Endovascular Aneurysm Occlusion and Packing (HELPS)[285] trials, but not in the Cerecyte Coil Trial,[284] and no greater rates of aneurysm occlusion were observed in the studies in which stents were used. The morbidity and mortality associated with the adjunctive use of balloon remodeling or endovascular stents have not been systematically assessed.

Some single-center studies are available regarding the use of stent-assisted endovascular therapy for aneurysm morphology and locations that are otherwise highly risky or impossible to treat, and in these cases, chronic double-antiplatelet therapy is advocated. However, to date, the efficacy of such treatment remains unproven.

From a cost-effectiveness perspective, early analysis suggested that coil embolization of cerebral aneurysm was efficacious. Kallmes et al[300] found that the cost-effectiveness of

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endovascular aneurysm occlusion depended primarily on the natural history of untreated cerebral aneurysms, and less so the morbidity of treatment and patient life expectancy at the time of Guglielmi detachable coil treatment. Johnston et al,[205] using empirical data, showed that treatment of large (≥10 mm) or symptomatic aneurysms or of a patient with prior SAH was cost-effective, possibly more effective and more cost-effective than surgical clipping.[301] Similarly, a retrospective analysis of 2484 aneurysm cases in a 12-state database revealed more adverse outcomes, more in-hospital deaths, longer hospital stays, and greater total charges in the surgical group than in the endovascular group.[302]

Outside of any trial or registry, recent administrative database studies show increased rates of use of endovascular coils for treatment of unruptured aneurysms, with increasing cost of treatment procedures, but no definite outcome benefit through use of endovascular techniques.[303] Huang et al[303] reviewed >100 000 records from the US NIS from 1997 through 2006, which showed a 75% increase in the number of hospital admissions for the treatment of unruptured cerebral aneurysms. Inflation-adjusted charges increased 60% during this time period, but the total national bill increased by 200%. Length of hospital stay decreased by 37%, and in-hospital mortality was reduced by 54%, but endovascular aneurysm intervention had become the major driving force behind increasing overall national charges.[303] In Europe, the cost of the procedure and associated hospitalization for endovascular coil occlusion for ruptured cerebral aneurysms remained similar to the cost of surgical clipping, whereas the cost of endovascular treatment in the United States was generally higher than in Europe but less than the cost of surgical clipping in the United States.[304]

Some studies suggest that treatment of cerebral artery aneurysms should be performed at centers of excellence with both surgical and endovascular capabilities.[305,306] This dilution of experience has led some to argue for a moratorium on the training of neurointerventionalists to prevent further dilution of operator experience, training, and competence.[307]

Emerging technologies may lead to further evolutions in the endovascular treatment of unruptured cerebral aneurysms, even before the existing coil-based technology is completely understood. Low-porosity stent devices have the capability to channel or divert blood flow away from the aneurysm and provide a scaffold on which neointima can grow across the orifice of the aneurysm. In the Pipeline for Uncoilable or Failed Aneurysms (PUFS) trial, 106 of 107 patients underwent successful implantation of the Pipeline (Covidien) device with promising results, which led to approval by the US Food and Drug Administration for very limited (proximal intradural carotid circulation–cavernous, paraclinoid-ophthalmic segment) aneurysms.[308] High rates of use suggest application beyond the confines of its indication for use in the United States. In other countries, Pipeline has been applied successfully to a variety of aneurysms at different locations.[309] A liquid embolic agent (Onyx HD-500, Covidien) has been adapted to the treatment of cerebral aneurysms. During balloon occlusion of the parent artery, high density ethylene vinyl copolymer is injected into the aneurysm through a microcatheter. Molyneux et al[310] reported results of the Cerebral Aneurysm Multicenter Onyx (CAMEO) trial, in which 97 patients with 100 aneurysms, mostly large or giant, underwent treatment. A majority of the aneurysms treated were large or giant. Serious adverse events occurred in 26.8% of patients. Permanent morbidity and mortality occurred in 8.2% and 2.0%, respectively. Complete aneurysm occlusion was achieved in 79%.

Endovascular treatment of cerebral aneurysms requires the use of x-ray fluoroscopy, and this type of radiation is carcinogenic. It is assumed that the radiation exposure to the patient and medical staff is justified by the disease state for which the patient is undergoing treatment, so long as it is kept "as low as reasonably achievable."[311,312] Neurointerventional procedures commonly fall into the category of high-exposure fluoroscopic procedures. It is possible that the radiation exposure would become so significant that alternative surgical procedures should be considered, especially for patients with unruptured aneurysms who have a long potential life expectancy with appropriate treatment. Although radiation exposure has not commonly been accounted for during neurointerventional procedures, some authors have considered radiation dose and exposure.[311,313–315] Significant radiation exposure may occur from 30 minutes of fluoroscopy or a series of DSA acquisitions.[316] When a kerma area product, or dose-area product, of at least 500 Gy cm^2 has been reached, follow-up evaluation for signs of radiation injury may be necessary.[316] According to National Council on Radiation Protection guidelines, each procedure should be justified according to the medical goal accomplished, and specific patient follow-up for radiation injury is necessary.[317] In the future, trials and registries used to assess cerebral aneurysm treatment should include measures of patient radiation exposure. Finally, the procedural risks of radiation exposure encountered in endovascular aneurysm treatment should be included and specifically reviewed in any procedural consent.[311]

Endovascular Treatment: Recommendations

An AHA scientific statement published in 2009, "Indications for the Performance of Intracranial Endovascular Neurointerventional Procedures," provided a summary of indications and recommendations for the endovascular treatment of unruptured cerebral aneurysms.[318] Moreover, a set of imaging reporting standards for the endovascular treatment of cerebral aneurysms were published in the AHA journal *Stroke*.[132] On the basis of the available evidence, the existing recommendations have not changed and are summarized below in "Comparative Efficacy of Clipping Versus Coiling"; there is 1 new recommendation to address emerging technologies.

1. **Endoluminal flow diversion represents a new treatment strategy that may be considered in carefully selected cases *(Class IIb; Level of Evidence B)*. Other emerging technologies to treat unruptured cerebral aneurysms, such as liquid embolic agents, represent new treatment strategies that may be considered in carefully selected cases *(Class IIb; Level of Evidence C)*. The long-term effects of these newer approaches remain largely unknown. Strict adherence to the US Food and Drug Administration's indications for use is probably indicated until additional trial data**

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demonstrate an incremental improvement in safety and efficacy over existing technologies *(Class IIa; Level of Evidence C)*.

2. **Use of coated coils is not beneficial compared with bare-metal coils *(Class III; Level of Evidence A)*.**
3. **Endovascular treatment of UIAs is recommended to be performed at high-volume centers *(Class I; Level of Evidence B)*.**
4. **The procedural risk of radiation exposure should be explicitly reviewed in the consent process for endovascular procedures *(Class I; Level of Evidence C)*.**

Comparative Efficacy of Clipping Versus Coiling

Treatment paradigms for UIAs have shifted dramatically over the past 2 decades, in large part as a result of the increasing role of endovascular therapy. Historically, the primary indication for endovascular coiling of a UIA was in patients for whom surgery was deemed high risk. Over the past decade, however, advances in endovascular technology have revolutionized UIA treatment methods, and in fact, the number of patients with UIAs treated with endovascular coiling surpassed the number treated with surgical clipping (34 054 versus 29 866, respectively) between 2001 and 2008, according to the NIS.[231] Given the growth in popularity of endovascular coiling for the treatment of UIAs, several large-scale prospective and retrospective clinical studies have been conducted to compare the long-term efficacy of surgical clipping to endovascular coiling.

The ISUIA provided important natural history data on UIAs and information related to the risk of surgical repair.[34] A follow-up analysis in 2003 further reviewed outcomes after surgical clipping or endovascular coiling.[4] Of the 4060 eligible patients, 1917 were treated surgically and 451 were treated endovascularly. Overall morbidity and mortality (defined as death and mRS 3–5 or impaired cognitive status) at 1 year was 12.6% (if no prior history of SAH) and 10.1% (if prior history of SAH) for surgical clipping and 9.8% (if no prior history of SAH) and 7.1% (if prior history of SAH) for endovascular coiling. In the endovascular group, periprocedural hemorrhage was found in 2% and cerebral infarction in 5%. Within this cohort, complete obliteration was accomplished in 55% of patients, incomplete obliteration in 24%, and no obliteration in 3%. In the surgical cohort, intraprocedural rupture was noted in 6% of patients, intracranial hemorrhage in 4%, and cerebral infarction in 11%. The degree of aneurysmal obliteration is not routinely assessed after surgical clipping, whereas this analysis is readily available after endovascular coiling. Finally, as opposed to the surgical arm, rates of morbidity and mortality in the endovascular group were less dependent on patient age, which perhaps indicates that this treatment modality may be better suited for older patients. These endovascular data represent an early epoch in the use of endovascular coiling for UIAs.

Over the past decade, analyses of several large-scale national databases have provided important outcome data related to surgical clipping and endovascular coiling of UIAs. Table 5 summarizes these data, which indicate that patients

Table 5. Outcome Data From Large-Scale Analyses of Surgical Clipping and Coil Embolization of UIAs

First Author, Year	Database	No. of Patients	Adverse Outcomes/ Morbidity, %		Ischemic or Hemorrhagic Complications, %		Mortality, %		Mean Length of Stay, d		Discharge to Long-Term Care Facility, %	
			Clipping	Coiling	Clipping	Coiling	Clipping	Coiling	Clipping	Coiling	Clipping	Coiling
Barker, 2004[200]	NIS	3919	OR 1.9/4.1*		OR 2.0		2.1	1.7	5	2	3.3	2.4
Higashida, 2007[204]	Publicly available, nonfederal hospital records (18 states)	2535	13.2	6.6	…	…	2.5	0.9	7.4	4.5	…	…
Hoh, 2010[319]	NIS	9174 (hospitalizations)	…	…	…	…	…	…	9	4.5	…	…
Alshekhlee, 2010[199]	NIS	3738	8.4	3.7	6.7 (ischemic), 2.4 (hemorrhagic)	2.9 (ischemic), 1.4 (hemorrhagic)	1.6	0.5	4 (median)	1 (median)	…	…
Brinjikji, 2011[231]†	NIS	63 940	13.7	4.0	…	…	1.1	0.5	6.6	3.0	13.7	4.0
Brinjikji, 2011[203]	NIS	64 043	14.8	7.6	…	…	1.2	0.6	…	…	14	4.9
McDonald, 2013[207]	Perspective	4899	…	…	OR 2.2		0.7	0.5	…	…	OR 4.8	

NIS indicates National (Nationwide) Inpatient Sample; OR, odds ratio; and UIAs, unruptured intracranial aneurysms.

*Age ≤65 years, OR 1.9; age >65 years, OR 4.1.

†Data represent ages 50 to 64 years; additional data for age <50 years, ages 65 to 79 years, and age ≥80 years demonstrate decreased morbidity, mortality (except equal mortality for age <50 years), length of stay, and discharge to a long-term care facility for endovascular coiling compared with surgical clipping.

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with endovascularly coiled UIAs have fewer adverse outcomes and ischemic and hemorrhagic events, a lower overall mortality rate, shorter lengths of hospital stay, and fewer discharges to a long-term care facility. However, retrospective comparative data based on administrative data sets must be viewed with caution. Outcome assessment is often limited to discharge status to facilities other than home, including rehabilitation facilities, and is not an indication of longer-term outcome. Furthermore, adjustment for confounding factors is limited because of the lack of information within such data sets, including specific aneurysm features such as location and size.

Despite the focus on RIAs, important information can be learned from the ISAT[8] and Cerebral Aneurysm Rerupture After Treatment (CARAT)[320] studies. Long-term follow-up data (mean, 9 years) on 2004 treated patients from the initial ISAT report reveal 24 rehemorrhages, 13 of which were from the treated aneurysm (10 treated by coiling and 3 by clipping).[279] Long-term data from the CARAT study concluded that the degree of aneurysm occlusion after initial treatment is a strong predictor of the risk of rehemorrhage.[321] Overall, treated aneurysms with complete occlusion had a 1.1% risk of rehemorrhage compared with a 2.9% risk for 91% to 99% occlusion (small residual neck), a 5.9% risk for 70% to 90% occlusion (residual neck), and a 17.6% risk for <70% occlusion (partial). This trend was reflected in both the coil embolization and surgical clipping arms. For the 1001 patients in the study, there were 19 reruptures during 4 years of follow-up, with a 3.4% risk of rerupture for coil embolization and 1.3% for surgical clipping.

Higashida et al[204] performed a retrospective cohort study of 2535 patients with UIAs based on information in a publicly available database in 18 American states. Of these patients, 1881 were treated with surgical clipping and 654 with endovascular coiling. Overall, endovascular therapy was associated with fewer adverse outcomes at discharge (6.6% versus 13.2%) and decreased mortality (0.9% versus 2.5%) compared with surgical clipping. In addition, patients treated with endovascular coiling had an average hospital length of stay of 4.5 days compared with 7.4 days in the surgical cohort. This finding was echoed by Hoh et al,[319] who identified in an analysis of the NIS that surgically managed patients had an average length of stay 1.8 times that of patients treated with endovascular coiling. Similar conclusions were drawn from a review of the NIS by Alshekhlee et al,[199] in which clipped patients experienced increased hospital length of stay, higher hospital charges, and greater morbidity and mortality compared with the coiled population.

Brinjikji et al[203,231] have published several reports based on information gathered from 2001 to 2008 from the NIS. In 1 report, patients were stratified by age: <50 years of age, 50 to 64 years of age, 65 to 79 years of age, and ≥80 years of age.[231] In patients <50 years of age, endovascular coiling was associated with lower morbidity rates (3.5% versus 8.1%) than surgical clipping, but there was no difference in mortality (0.6% versus 0.6%). For the remaining age groups, endovascular coiling had decreased morbidity and mortality compared with surgical clipping. These data differ slightly from an analysis of the NIS by Barker et al[200] from 1996 to 2000, in which there was no difference in overall mortality rates after clipping or coiling of UIAs. In this same study, for patients ≥65 years of age, there was a trend toward worse outcomes for surgical patients with respect to death and discharge to a long-term facility, although this trend was not observed in patients <65 years of age. In another study by Brinjikji et al,[203] surgical clipping was associated with a 14% incidence of discharge to a long-term care facility and a 1.2% mortality rate, whereas endovascular coiling was associated with a 4.9% discharge rate to a long-term facility and a 0.6% mortality rate.

The Perspective database (Premier Inc, Charlotte, NC) is represented by >600 American hospitals and accounts for ≈15% of the hospitalizations nationwide. An examination of this database by McDonald et al[207] identified 4899 patients with UIAs between 2006 and 2011. In-hospital mortality was similar between the 1388 patients who underwent surgical clipping and the 3551 patients who underwent endovascular coiling; however, endovascular coiling was associated with a lower likelihood of discharges to long-term care facilities, ischemic complications, and hemorrhagic complications.

Since the emergence of coil embolization for the treatment of UIAs in 1990, this treatment modality has progressively become the dominant treatment method, as evidenced by analyses from the NIS. Prospective and retrospective data from national and international studies indicate that coil embolization may be superior to surgical clipping with respect to procedural morbidity and mortality, length of hospital stay, and associated hospital costs. On the basis of these prospective and retrospective data, it is reasonable to favor endovascular coiling over surgical clipping in the treatment of select UIAs, especially in cases in which surgical clipping is predicted to carry excess morbidity (ie, posterior circulation, elderly population) and aneurysm anatomy is likely to result in near-complete coil obliteration. Despite these observations, however, other data indicate that coil embolization may carry a higher risk of aneurysmal rerupture after treatment, likely as a result of incomplete aneurysm obliteration. Moving forward, large-scale prospective studies that incorporate not simply treatment modality but also aneurysm size and location as important predictors of outcome will be instrumental in guiding treatment paradigms for UIAs in the coming years.

Comparative Efficacy of Clipping Versus Coiling: Recommendations

1. **Surgical clipping is an effective treatment for UIAs that are considered for treatment *(Class I; Level of Evidence B)*.**
2. **Endovascular coiling is an effective treatment for select UIAs that are considered for treatment *(Class IIa; Level of Evidence B)*.**
3. **Patients with UIAs who are considered for treatment should be fully informed about the risks and benefits of both endovascular and microsurgical aneurysm clipping *(Class I; Level of Evidence B)*.**
4. **Endovascular coiling is associated with a reduction in procedural morbidity and mortality over surgical**

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clipping in selected cases but has an overall higher risk of recurrence *(Class IIb; Level of Evidence B)*.

Aneurysm Follow-Up (Patients Treated Without Surgery or Coiling)

For patients with UIAs that are managed noninvasively without either surgical or endovascular intervention, some form of radiographic follow-up is usually recommended. Various studies have documented aneurysm growth over time,[95,194,322–327] and interval growth has been believed to be a risk factor for hemorrhage. Unfortunately, there are no studies specifically addressing the appropriate imaging modality or interval for follow-up. Most published work indicates a preference for first follow-up imaging 6 to 12 months after initial discovery.[24,118,192,328,329] Continued follow-up is then generally recommended yearly or every 2 years once stability is documented.[329] Certainly, at some point a patient's age or medical comorbidities may become such that invasive intervention will become inordinately high risk or of no significant benefit, whereby it may be reasonable to discontinue further scheduled follow-up. Both CTA and MRA have been used for follow-up.[95,195,322–327] However, various CT and magnetic resonance protocols are available, and the question as to which modality is most appropriate is unresolved. In general, because a TOF MRA does not require intravenous contrast and does not involve x-ray radiation, this may be the most appropriate first-line method for repeated imaging follow-up. For patients with contraindications to MRA or whose aneurysm(s) cannot be suitably visualized with this technique, CTA remains a viable alternative.

Aneurysm Follow-Up (Patients Treated Without Surgery or Endovascular Coiling): Recommendations

1. **For patients with UIAs that are managed noninvasively without either surgical or endovascular intervention, radiographic follow-up with MRA or CTA at regular intervals is indicated. The optimal interval and duration of recommended follow-up are uncertain *(Class I; Level of Evidence B)*.**
2. **For patients with UIAs that are managed noninvasively without either surgical or endovascular intervention, a first follow-up study at 6 to 12 months after initial discovery, followed by subsequent yearly or every other year follow-up, may be reasonable *(Class IIb; Level of Evidence C)*.**
3. **For patients with UIAs that are managed noninvasively and in whom there are no contraindications to MRI, it may be reasonable to consider TOF MRA rather than CTA for repeated long-term follow-up *(Class IIb; Level of Evidence C)*.**

Conclusions

The overall prevalence of UIAs remains somewhat variable depending on the population studied and the analytical methods used. Nonetheless, it appears that older individuals and females tend to be more affected. Other nonmodifiable risk factors include a variety of inherited syndromes, such as polycystic kidney disease. Nonsyndromic familial cases are also well documented and account for roughly 10% of cases. Recent genome-wide association studies have indicated areas of intense genomic interest for further study in both familial and nonfamilial cases. The most important modifiable risk factors are cigarette smoking and hypertension, with excessive alcohol intake and oral contraceptive use being far less important. No studies have prospectively evaluated the impact of successful risk factor modification on either the development of UIA or the rupture of a previously asymptomatic UIA.

In any given year, only a minority of UIA patients will present with SAH, and many of the aneurysms that rupture may not be the same as those found incidentally. Although recent studies confirm that larger UIA size portends a worse prognosis in terms of bleeding, newer data suggest that strict size cutoffs may be less helpful than previously thought. The available data also continue to suggest that UIAs in certain locations, with certain morphological characteristics, are more likely to rupture. It also appears that growth of a UIA is associated with rupture, and several factors associated with growth on serial imaging have been identified. Unfortunately, no prospective data exist on whether modification of these factors will alter the risk of growth or rupture. Finally, we still lack high-quality data on whether any of the treatments available—surgical, endovascular, or medical (ie, anti-inflammatory medications, statins, antihypertensive medications, smoking cessation)—afford even a subset of UIA patients a better outcome than the natural history without such treatment.

Given these issues, it is reasonable to more strongly consider a patient for repair (1) when the UIA is discovered as a result of a prior SAH from a different lesion, (2) if the aneurysm is symptomatic, causing compressive symptoms, or a likely source of otherwise unexplained embolic stroke, or (3) if the patient has a family history of IA. Nonetheless, the risks, benefits, and alternatives to repair must be considered carefully in each individual case.

Although UIAs that are clearly growing or are causing a neurological deficit typically require an endovascular or surgical treatment, in a small minority of those cases, these lesions might reasonably be managed conservatively for several reasons, including very short or low-quality life expectancy. Routine serial imaging of aneurysms treated conservatively is reasonable, but the optimal interval between imaging studies and the mode of that imaging remain uncertain. When treatment is elected, it appears that in most instances, DSA is the best method to plan repair, and immediately after treatment, it is typically used to define whether the aneurysm has been excluded definitively and whether there is a need for repeat treatment. By contrast, routine delayed follow-up imaging of a treated lesion is usually performed noninvasively by either CTA or MRA, and the timing and frequency of that follow-up are dictated by the completeness and method of the original repair, as well as the documented duration of imaging stability and a host of other patient- and aneurysm-specific factors.

In part because decisions regarding UIA treatment remain so individualized, there is significant uncertainty as to which populations should undergo noninvasive MRA or CTA screening for these lesions. If screening is undertaken, it is critical

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to screen populations at higher risk of aneurysm formation than the general population and those in whom treatment would likely be elected if an aneurysm were identified. Two populations that might be considered to meet these criteria are patients with autosomal dominant polycystic kidney disease (especially those with a family history of IA) and individuals with a strong family history of aneurysms or SAH. Although others may benefit, neither the cost-effectiveness nor the clinical utility of any screening program has been evaluated prospectively.

When a patient is considered for repair of an aneurysm, patient age, presence of medical comorbidities, and aneurysm location and size should be taken into careful consideration, because these are strong predictors of perioperative morbidity and rupture risk. The treating physicians should consider the risk of treatment not only on the basis of published reports and trial results but also on the basis of their own personal results. This is of particular importance in low-volume (<20 cases annually) centers, where the results of UIA treatment appear to be inferior. At such centers, referral to a high-volume center makes intuitive sense and is more than reasonable. Although not true for all aneurysms, microsurgical repair is generally associated with higher perioperative morbidity than endovascular repair but is also associated with higher rates of aneurysm obliteration and lower rates of recurrence. In older patients (more than ≈60 years of age), the benefit of coiling compared with that of surgery appears to be greater for most lesions, because the risk of recurrence is less of a concern and the rates of perioperative microsurgical complications are higher. At least with current technology, there also appears to be an advantage to microsurgery in the treatment of most middle cerebral artery aneurysms and for endovascular repair in the treatment of most basilar apex and vertebrobasilar confluence aneurysms. Emerging technologies to treat unruptured cerebral aneurysms, particularly flow-diverting low-porosity stents, and the use of stent-assisted coiling procedures represent compelling new treatment strategies that may be considered in carefully selected cases. Because their long-term effects remain largely unknown, strict adherence to the US Food and Drug Administration's indications for use is recommended until additional trial data demonstrate an incremental improvement in safety and efficacy over existing technologies. After clipping, coiling, or stenting, assessment of cognitive outcome, in addition to standard measures of outcome, is reasonable. Early documentation of the degree of aneurysm obliteration after any repair technique is necessary to guide the frequency of further follow-up for the detection of recurrence and de novo aneurysm formation. Although the frequency of long-term imaging is uncertain, it is reasonable to increase the frequency for those with aneurysms that are incompletely obliterated during initial treatment.

Conclusions: Recommendations

1. **Several factors should be considered in selection of the optimal management of a UIA, including the size, location, and other morphological characteristics of the aneurysm; documented growth on serial imaging; the age of the patient; a history of prior aSAH; family history of cerebral aneurysm; the presence of multiple aneurysms; or the presence of concurrent pathology such as an arteriovenous malformation or other cerebrovascular or inherited pathology that may predispose to a higher risk of hemorrhage *(Class I; Level of Evidence C)*.**
2. **Patients with unruptured cerebral aneurysms who are considered for treatment should be fully informed about the risks and benefits of both endovascular and microsurgical treatment as alternatives to secure the UIAs and prevent bleeding *(Class I; Level of Evidence B)*.**
3. **The results of UIA treatment are inferior at low-volume centers, and hence treatment is recommended to be performed at higher-volume centers *(Class I; Level of Evidence B)*.**
4. **Data from prospective and retrospective studies from multiple national and international investigations indicate that microsurgical clip ligation may confer more durable protection against aneurysm regrowth, but coil embolization may be superior to surgical clipping with respect to procedural morbidity and mortality, length of stay, and hospital costs, so it may be reasonable to choose endovascular therapy over surgical clipping in the treatment of select UIAs, particularly in cases for which surgical morbidity is high, such as at the basilar apex and in the elderly *(Class IIb; Level of Evidence B)*.**
5. **The treatment risk of patients with UIAs is related to advancing age, medical comorbidities, and aneurysm location and size, so in older patients *(*>65 years of age*)* and those with associated medical comorbidities with small asymptomatic UIAs and low hemorrhage risk by location, size, morphology, family history, and other relevant factors, observation is a reasonable alternative *(Class IIa; Level of Evidence B)*.**

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B. Gregory Thompson	University of Michigan	None	None	None	None	None	None	None
Robert D. Brown, Jr	Mayo Clinic	NIH†	None	None	None	None	None	None
Sepideh Amin-Hanjani	University of Illinois at Chicago	None	None	None	None	None	None	None
Joseph P. Broderick	University of Cincinnati	NINDS†	None	None	None	None	None	None
Kevin M. Cockroft	Penn State Hershey Medical Center	None	None	None	None	None	Covidien†	None
E. Sander Connolly, Jr	Columbia University	None	None	None	None	None	None	None
Gary R. Duckwiler	University of California at Los Angeles	None	None	None	None	Sequent Medical (personally purchased stock)*	Sequent Medical*; EV3/Covidien Medical*; Concentric Medical (Stryker)*	UC Regents (employer) receives patent royalties from Guglielmi and Matrix; author receives no direct payments†
Catherine C. Harris	Jefferson University	None	None	None	None	None	None	None
Virginia J. Howard	University of Alabama at Birmingham	NIH†	None	None	None	None	None	None
S. Claiborne (Clay) Johnston	University of Texas, Dell Medical School	None	Stryker† (payment issued to employer/UCSF in October 2012; no direct payment to author)	None	None	None	None	None
Philip M. Meyers	Columbia University	None	None	None	None	None	Stryker (co-PI, SCENT trial, no financial interest)*	None
Andrew Molyneux	Oxford University	None	None	None	Medical expert witness in aneurysm cases†	None	Sequent Medical Inc: Case adjudication and study design advice†	
Christopher S. Ogilvy	Beth Israel Deaconess Medical Center	None	None	None	None	None	None	None
Andrew J. Ringer	University of Cincinnati, Mayfield Clinic	None	None	None	None	None	EV3/Covidien Medical*; Stryker*; MicroVention*	None
James Torner	University of Iowa	CDC†; NIH/ NINDS†; NIH/NIA†; VA†	None	None	None	None	None	None

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*Modest.

†Significant.

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Thomas Bleck	Rush University Medical Center	None	None	None	None	None	None	None
Ketan Bulsara	Yale University	None	None	None	None	None	None	None
J. Mocco	Mount Sinai Hospital	FEAT: randomized trial (PI for a prospective randomized trial of 2 different methods of aneurysm treatment)†; POSITIVE: randomized trial of flow diversion vs coil embolization (co-PI for a prospective randomized trial of 2 different methods of aneurysm treatment)*	None	None	None	Blockade Medical†	Codman Neurovascular*	None
Alejandro Rabinstein	Mayo Clinic	None	None	None	None	None	None	None

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*Modest.

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SUPPLEMENTAL MATERIAL

Supplemental Table I: Number and percentage of stroke centers by state and region in the United States in 2013. (PSC=Primary Stroke Center)

States	Census Region	Stroke Legislation	PSC	PSC by Joint Commission	Other PSC	Total General Hospitals	PSC as % of General Hospitals
Wyoming	West	No	1	1	0	25	4%
Hawaii	West	No	1	1	0	21	5%
Arkansas	South	No	4	4	0	74	5%
Mississippi	South	No	6	5	1	93	6%
South Dakota	Midwest	No	3	3	0	49	6%
Vermont	Northeast	No	1	1	0	14	7%
West Virginia	South	No	4	4	0	51	8%
Louisiana	South	No	10	10	0	119	8%
Montana	West	No	4	4	0	49	8%
Alabama	South	No	9	9	0	99	9%
Kansas	Midwest	No	11	11	0	127	9%
Idaho	West	No	4	3	1	39	10%
Alaska	West	No	2	2	0	21	10%
Maine	Northeast	No	4	4	0	36	11%
New Mexico	West	No	4	2	2	35	11%
New Hampshire	Northeast	No	3	2	1	26	12%
Nebraska	Midwest	No	11	11	0	82	13%
North Dakota	Midwest	Yes	5	5	0	38	13%
Minnesota	Midwest	No	17	17	0	124	14%
Iowa	Midwest	No	18	14	4	116	16%
Tennessee	South	No	19	19	0	114	17%
Utah	West	No	7	6	1	39	18%
Kentucky	South	Yes	21	20	1	99	19%
Wisconsin	Midwest	No	30	30	0	127	24%
Oregon	West	No	14	13	1	58	24%
Missouri	Midwest	Yes	29	28	1	114	25%
South Carolina	South	No	17	14	3	58	28%
Indiana	Midwest	No	33	24	9	117	28%
Georgia	South	Yes	41	38	3	140	29%
Oklahoma	South	Yes	32	8	24 by state	110	29%
Ohio	Midwest	No	49	43	6	159	31%
North Carolina	South	No	35	35	0	111	32%
Colorado	West	No	23	23	0	70	33%
Michigan	Midwest	No	46	37	9	133	34%
Texas	South	Yes	130	104	16 by state	382	34%
Maryland	South	Yes	17	17	0	46	37%
Arizona	West	No	25	20	5	64	39%

Illinois	Midwest	Yes	72	64	8	183	39%
Pennsylvania	Northeast	Yes	69	63	6	163	41%
California	West	No	148	145	3	346	43%
Nevada	West	No	14	14	0	32	44%
Washington	West	Yes	39	20	18 by state	87	45%
Virginia	South	Yes	40	34	6	81	49%
New York	Northeast	Yes	121	17	102 by state	189	64%
Connecticut	Northeast	Yes	22	15	7 by state	30	73%
Florida	South	Yes	144	100	39 by state	195	74%
District of Columbia	South	No	6	6	0	8	75%
Rhode Island	Northeast	Yes	9	9	0	10	90%
New Jersey	Northeast	Yes	65	29	34 by state	69	96%
Massachusetts	Northeast	Yes	61	5	56 by state	63	97%
Delaware	South	Yes	5	5	0	5	100%
Total		**18**	**1505**	**1118**	**387**	**4640**	**32.4%**

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Journal of the American Heart Association

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Stroke. published online June 18, 2015;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2015/06/18/STR.0000000000000070

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