Unruptured Intracranial Aneurysms
Contemporary Data and Management

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Saccular, unruptured intracranial aneurysms (UIAs) are weak dilations at major bifurcating brain arteries and have a prevalence of ≈3% in the middle-aged population, which means that ≈168 000 000 persons harbor a UIA worldwide.[1] UIAs are a noncongenital, thus degenerative disorder and a typical example of so-called complex diseases where idiopathic, genetic, and environmental risk factors, such as smoking and hypertension, play a role and may even reinforce each other during pathogenesis.[2] Aneurysms can remain clinically silent for long periods or rupture, which is often preceded by aneurysm growth. Aneurysm rupture results in subarachnoid hemorrhage (SAH)—a type of stroke with poor prognosis: 35% die, and most survivors have long-term disability or cognitive impairment.[3] The poor prognosis of SAH does not only have implications on the individual patient but also on a socioeconomic level because SAH affects predominantly young people (peak of age between 50 and 60 years) leading to an early loss of productive life years.[3] However, in view of the worldwide SAH incidence of ≈700 000 person-years and the UIA prevalence of 3%, it must be assumed that only ≈0.3% of all UIAs rupture per year. Thus, most UIAs are detected incidentally and increasingly because of improved quality and higher frequency of neuroimaging for nonspecific symptoms, such as headache and vertigo.[4] For these patients, 2 management options exist: preventive aneurysm repair or observation with follow-up imaging.

Preventive aneurysm repair is an effective option to eliminate the risk of aneurysm rupture but carries a risk of ≈6% to 10% for poor neurological outcome, which—for the majority of UIA—is distinctly higher than the risk of rupture (mean 5-year risk, 3.4%; 95% CI, 2.9–4.0).[5–7] A multidisciplinary group of clinicians counseling patients with UIA is required to estimate the short-term or long-term risk of rupture of an individual aneurysm and balance this against the presumed risk of preventive aneurysm repair. However, such an estimate is often challenging because there are numerous suggested patient- or aneurysm-related risk factors for rupture but only limited robust data on patient- or aneurysm-specific risk factors for complications after preventive repair.[8] This is further complicated by varying levels of evidence of these data or their limited validity because of geographical patient selection.

This review discusses the current clinical data on risk factors for aneurysm rupture and treatment complications, in relation to treatment modality, as well as current mechanisms for a systematic counseling of patients with UIA in clinical practice. Furthermore, we highlight novel management options and remaining uncertainties. For this purpose, we performed a systematic literature search up to March 2018 using the key words Unruptured intracranial aneurysms and cross-referenced this search with the personal database of the senior author (N.E.).

Risk of Aneurysm Rupture

A pooled analysis on the risk of rupture based on 6 prospective cohort studies on UIA included data of 8382 patients and 10 272 UIAs from Europe (including Finland), North America, and Japan. The mean observed 1-year risk of rupture in this meta-analysis was 1.4% (95% CI, 1.1–1.6), the 5-year risk of rupture 3.4% (95% CI, 2.9–4.0), and 6 independent predictors for rupture could be established: (1) population, (2) arterial hypertension, (3) patient age, (4) aneurysm size, (5) earlier SAH from another aneurysm and (6) aneurysm site (PHASES).[7] The PHASES study presently constitutes the largest and most comprehensive pooled data set on the risk of aneurysm rupture and thus the highest level of evidence in this respect. However, it should be noted that additional important risk factors for aneurysm rupture could not be included in the PHASES study, owing to lack of data or heterogeneous definitions of these data in the underlying studies. Furthermore, the selection of patients because of age, preventive UIA repair, or geographic location in cohort studies on the risk of rupture challenge the entire concept of the so-called natural history of UIA and underline that this remains incompletely understood.[9–12]

Here, population-based or case-control studies identified additional data, which can be used to further estimate the relative risk of rupture (Table; Figure). However, because these data are also often derived from selected populations (eg, Finnish or Japanese), they may not be applied to the general population of patients with aneurysm.[23] Nevertheless, these risk factors can be categorized into patient and aneurysm related.

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Table. Risk Factors for Rupture

Risk Factors	Change in Rupture Risk (95% CI)	Level of Evidence	Geographical Region
Patient related			
Modifiable			
Arterial hypertension	HR, 1.4 (1.1–1.8)	IIa	Europe (including Finland), Japan, North America[7]
	HR, 1.3 (0.9–1.9)	IIa	Japan[13]
	HR, 7.9 (1.3–47.4)	IIb	Japan (UIA size, <5 mm)[10]
Smoking (current)	RR, 2.2 (1.3–3.6)	IIa	Europe (including Finland), Asia (including Japan), North America[14]
	HR, 3.2 (1.3–7.6)	IIb	Finland[15]
Alcohol (>150 g/wk)	RR, 2.2 (1.5–2.8)	IIa	Europe (including Finland), Asia (including Japan), North America[14]
Nonmodifiable			
Age, y			
≥70	HR, 1.44 (1.05–1.97)	IIa	Europe (including Finland), Japan, North America[7]
<50	HR, 5.23 (1.03–26.52)	IIb	Japan (UIA size, <5 mm)[10]
per 10	HR, 0.62 (0.39–0.99)	IIb	Finland[15]
Geographical location			
Japan	HR, 2.8 (1.8–4.2)	IIa	Europe (including Finland), Japan, North America[7]
Finland	HR, 3.6 (2.0–6.3)	IIa	Europe (including Finland), Japan, North America[7]
History of SAH	HR, 1.4 (0.9–2.2)	IIa	Europe (including Finland), Japan, North America[7]
Women	RR, 1.6 (1.1–2.4)	IIa	Europe (including Finland), Japan, North America[16]
Multiplicity	HR, 4.9 (1.6–14.7)	IIb	Japan (UIA size, <5 mm)[10]
Family history (≥2 relatives with UIA or SAH)	17-fold	IIb	North America[17]
Aneurysm related			
Size, mm		IIa	Europe (including Finland), Japan, North America[7]
<5.0	Reference		
5.0–6.9	HR, 1.1 (0.7–1.7)		
7.0–9.9	HR, 2.4 (1.6–3.6)		
10.0–19.9	HR, 5.7 (3.9–8.3)		
≥20.0	HR, 21.3 (13.5–33.8)		
Location		IIa	Europe (including Finland), Japan, North America[7]
ICA	HR, 0.5 (0.3–0.9)		
MCA	Reference		
Anterior	HR, 1.7 (0.7–2.6)		
Posterior	HR, 1.9 (1.2–2.9)		
PCOM	HR, 2.1 (1.4–3.0)		
Irregularity	HR, 1.5 (1.0–2.2)	IIa	Japan[13]
	OR, 4.8 (2.7–8.7)	IIa	[18]
Growth	12-fold	IIIb	The United States[19]
Aneurysm wall enhancement	HR, 9.2 (2.9–29.0)*	IIIb	France[20]
Size ratio	OR, 5.1 (2.1–19.1)	IIb	Japan[21]
	OR, 9.1 (3.1–15.0)	IIb	Japan (aneurysm size, <5 mm)[21]
Aspect ratio	OR, 162.3 (24.8–1060.8)	IIIb	China[22]

HR indicates hazard ratio; ICA, internal carotid artery; MCA, middle cerebral artery; OR, odds ratio; PCOM, posterior communicating artery; RR, relative risk; SAH, subarachnoid hemorrhage; and UIA, unruptured intracranial aneurysm.

*HR of stable vs unstable (ruptured, symptomatic, grown).

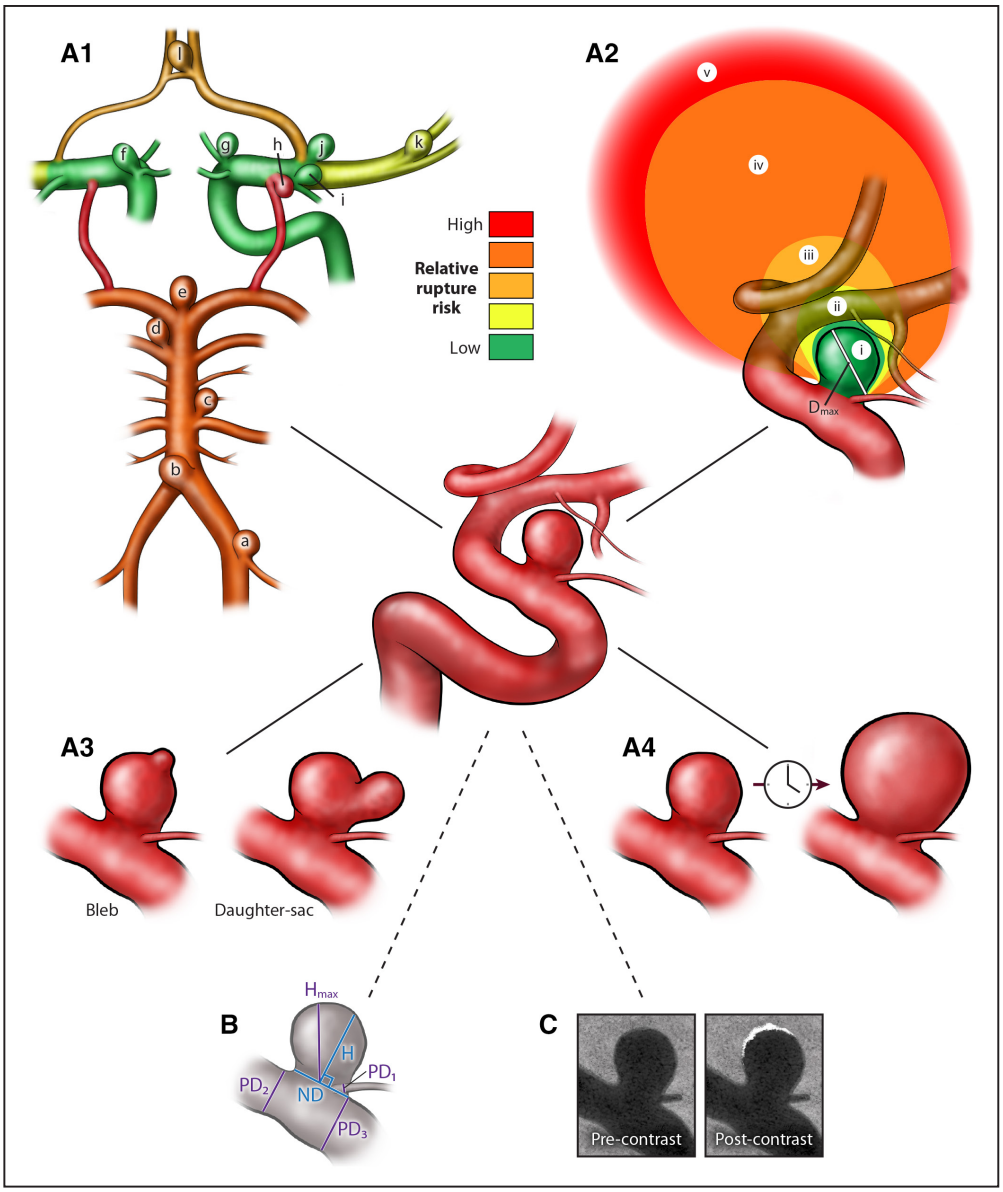

Figure. Established (**A1**–**A4**) and assumed aneurysm-related (**B** and **C**) risk factors. A paraophthalmic aneurysm of the internal carotid artery (ICA; center) with a maximum size of 4 mm is illustrated. **A1**, Unruptured intracranial aneurysm (UIA) location (according to PHASES [population, arterial hypertension, patient age, aneurysm size, earlier SAH from another aneurysm, and aneurysm site]). The risk of aneurysm rupture varies with the individual aneurysm location, ranging from the lowest risk (green) at the ICA and the highest risk (red) at the posterior communicating artery (PCOM).[7] Aneurysm locations are (a) posterior inferior cerebellar artery, (b) junction of vertebral arteries, (c) anterior inferior cerebellar artery, (d) superior cerebellar artery, (e) basilar artery, (f) superior hypophyseal artery, (g) ophthalmic artery, (h) PCOM, (i) anterior choroidal artery, (j) ICA terminus, (k) medial cerebral artery, and (l) anterior communicating artery. **A2**, UIA diameter (according to PHASES). The maximum diameter (D_{max}) is a significant predictor for rupture. Size categories are (i) <5 mm, (ii) 5.0 to 6.9 mm, (iii) 7.0 to 9.9 mm, (iv) 10.0 to 19.9 mm, and (v) ≥20 mm.[7] **A3**, UIA irregularity, that is, the presence of blebs or daughter sacs increases the risk of rupture by 1.5 fold.[13] **A4**, UIA growth, defined as growth by >1 mm in any diameter, increases the risk of rupture.[19] **B**, UIA morphology. A size ratio (SR) >3 or an aspect ratio (AR) >1.06 seems to be at a higher risk for rupture.[21,22] $SR=H_{max}/([PD_1+PD_2+PD_3]/3)$, AR=H/ND. where H indicates height perpendicular to neck diameter; H_{max}, height maximal; ND, neck diameter; and PD, parent vessel diameter. **C**, Aneurysm wall enhancement, as depicted on precontrast and postcontrast magnetic resonance imaging. Aneurysm wall enhancement seems to reflect aneurysm wall inflammation and thus subsequent aneurysm instability (growth or rupture).[20]

Patient-related, modifiable risk factors—in addition to arterial hypertension, established in PHASES—are current cigarette smoking and heavy alcohol consumption.[14,15] For cigarette smoking, a dose-dependent detrimental effect has been recently reported: a case-control study including 4701 patients with 6411 UIAs highlighted that smoking intensity and duration are associated with the incidence of SAH.[24] However, the detrimental effect of alcohol, including a specific dose threshold for such an effect, has not been replicated in several studies. Further, it remains unclear within which time the risk of aneurysm rupture decreases in patients with UIA after normalization of blood pressure, cessation of smoking, or heavy alcohol consumption.

It has been suggested that stimulants, for example, cocaine, are risk factors for rupture, but it also remains incompletely understood whether these risk factors are truly independent because stimulants result in episodes of increased blood pressure or are often concomitantly consumed in smokers.[25]

The most important nonmodifiable, patient-related risk factors for aneurysm rupture—in addition to those identified in the PHASES study (earlier SAH from another aneurysm, patient age, and geographical location)—are a familial history for SAH or UIA (defined as ≥2 first-degree relatives with SAH or UIA), as well as female sex and presence of multiple aneurysms. The FIA study (Familial Intracranial Aneurysm) screened and followed first-degree relatives of patients with intracranial aneurysms who had either a history of smoking or arterial hypertension. The risk of rupture in patients with FIA for a UIA <6 mm in diameter was 17-fold higher, compared with rupture rates for similar aneurysms within the International Study on Unruptured Intracranial Aneurysms.[17] Despite the increased risk of rupture in patients with FIA, no specific genes have yet been linked to this increased risk: a meta-analysis of studies on gene association or genome-wide association including data on 32 887 sporadic aneurysms and 83 683 controls identified 3 single-nucleotide polymorphisms associated with the presence of intracranial aneurysms. The single-nucleotide polymorphisms were located within the *CDKN2B-AS1* gene on chromosome 9, on chromosome 8 near the *SOX17* transcription regulator gene, and on chromosome 4 near the endothelin receptor gene31. These variants all resided in loci that code polymorphisms related to increased incidence of cardiovascular structural deficiencies and diseases, but it is uncertain whether these polymorphisms are also associated with an increased risk of rupture.[26] Female sex and aneurysm multiplicity are assumed but not established risk factors for rupture, and more data from non-Japanese populations are needed to further estimate their effect.[10,13,16] There are conflicting data on the implication of patient age. Two prospective cohort studies (from Finland and Japan) highlighted an inverse age regression for rupture risk, especially an increased long-term risk of rupture in patients <50 years of age, whereas PHASES indicated an increased risk of rupture in patients >70 years of age.[10,15] Thus, patient age has implications for 5-year risk but also long-term rupture risk, that is, the number of elapsed life years under the presence of aneurysm versus a high cumulative long-term risk because of long life expectancy. Further, geographical location in Japan or Finland has been attributed to an increased risk of rupture, and it remains unclear whether the increased risk is truly derived from ethnicity or rather exposure to environmental risk factors because of geographical location. The latter hypothesis is supported by recent data on a dramatic decline in SAH incidence, that is, an indirect measure for the risk of rupture, parallel to a decline of smoking prevalence in Finland.[27]

The most important aneurysm-related risk factors for rupture (in addition to UIA size and location identified in PHASES) are UIA irregularity/morphology, UIA growth, and inflammation of the aneurysm wall (Figure). An increasing number of studies, including 2 meta-analyses of high-quality prospective cohort studies, highlighted the relevance of aneurysm irregularity as an independent risk factor for aneurysm rupture.[13,18] Aneurysm morphology, for example, measured using size ratio (the largest aneurysm diameter divided by parent artery diameter) or aspect ratio (aneurysm height divided by neck width perpendicular to height), is associated with an increased risk of rupture in previous case-control studies, but these indicators remain to be validated in larger prospective UIA cohorts.[21,22] UIA growth occurs in ≈12% to 18% of patients with UIA during 2.2- to 2.7-year follow-up or ≈45% of UIAs during 19 years and is an established surrogate for UIA rupture.[19,28,29] A pooled analysis of data from 10 prospective cohorts and 1507 patients and 1909 UIAs followed during a total of 5782 patient-years (median, 2.5 years; range, 0.5–14.3 years) identified earlier SAH, aneurysm location, age >60 years, population, aneurysm size, and shape (ELAPSS) as independent predictors for UIA growth. The ELAPSS score is useful to estimate the risk of growth and thus has implications for scheduling of UIA follow-up imaging (see below).[30] Another pooled analysis demonstrated that higher PHASES scores (thus a higher risk of aneurysm rupture) are associated with an increased risk of aneurysm growth on serial imaging and established UIA growth as a surrogate for rupture.[28] Further, a retrospective study including 165 patients with 258 aneurysms highlighted the events of aneurysm rupture to incidences of UIA growth and found a 12-fold higher risk for rupture in growing aneurysms.[19]

Last, an increasing number of case-control studies indicate the importance of aneurysm wall inflammation or—its assumed radiological equivalent—aneurysm wall enhancement in contrast-enhanced magnetic resonance imaging on aneurysm instability defined as growth or rupture[20,31] (Figure). Importantly, aneurysm wall inflammation seems to be present irrespective of aneurysm size or location and may have implications for novel treatment strategies[32,33] (see below). It should be emphasized that aneurysm wall enhancement is presumed to correspond to aneurysm wall inflammation, but it is not known whether this is always the case or whether aneurysm wall enhancement could also correspond to other structures, for example, enhancement of the pia surrounding an aneurysm.

Risk of Preventive Aneurysm Repair

It should be emphasized that data from randomized controlled trials on outcomes after repair of ruptured aneurysms, such as the ISAT (International Subarachnoid Aneurysm Trial) or BRAT (Barrow Ruptured Intracranial Aneurysm Trial), cannot be applied to the population of UIA. This is predominantly derived from the generally less-favorable neurological outcomes in patients with SAH but also from the more challenging microsurgical treatment of ruptured intracranial aneurysms in the setting of SAH, for example, because of limited visualization of the cerebrovascular anatomy because of subarachnoid blood clot, brain swelling, higher aneurysm fragility, and, therefore, intraoperative rupture of aneurysms, etc. Despite numerous single-center or retrospective studies on specific endovascular devices, which are often sponsored by the industrial partners, to date, only 1 randomized controlled trial on outcomes after preventive surgical versus endovascular repair exists in the setting of UIA. The CURES trial (Canadian Unruptured Endovascular Versus Surgery) was designed as a pragmatic trial, investigating clinical and radiological outcomes of patients, randomized into surgical clipping or any endovascular treatment (simple, balloon-assisted, or stent-assisted coiling) based on the local practice of the treating center.[34] The interim results of this ongoing trial were

recently published. The primary outcome was a composite of initial failure of aneurysm treatment, intracranial hemorrhage, or residual aneurysm at 1-year follow-up evaluated by an independent but not blinded neuroradiologist. Main secondary outcomes included overall morbidity (modified Rankin Scale score, >2) and mortality at 1 year, new perioperative neurological deficits at 30 days after aneurysm repair and peritreatment hospitalization lasting for >5 days. The primary outcome was reached in 5 of 48 patients allocated to clipping versus 10 of 56 patients allocated to endovascular coiling (odds ratio, 0.54; 95% CI, 0.13–1.9). There were more frequent new neurological deficits (odds ratio, 3.12; 95% CI, 1.05–10.57) and hospitalizations >5 days (odds ratio, 8.85; 95% CI, 3.22–28.59) in patients undergoing clipping, but there was no difference in morbidity and mortality at any time point between the groups. Until the trial is completed and the final results become available, the safest and most effective treatment modality for preventive UIA repair remains uncertain.

Additionally, a meta-analysis including data (a total of 71 studies and only 4 of which were considered to report high-quality data) on 5044 patients and 5771 UIAs undergoing endovascular treatment repair reported an unfavorable outcome, including death of 4.8% (99% CI, 3.9–6.0) and a mortality of 2.0% (99% CI, 1.5–2.6).[6] In 38 studies reporting aneurysm obliteration rates (22 studies with follow-up results), complete obliteration was achieved in 86.1% initially with recanalization rates ranging between 24.4% and 34.6% with a retreatment rate of 9.1% (99% CI, 6.2–13.1).[6] The subgroup analyses demonstrated no significant difference in neurological outcome in patients treated with balloon-assisted or stent-assisted coiling compared with simple coiling, but the frequency for unfavorable outcome was 11.5% (99% CI, 4.9–24.6) in patients treated with flow-diverting stents.[35] Another meta-analysis showed significant higher risk of mortality and thrombosis because of stent-assisted coiling compared with simple coiling.[36]

The largest meta-analysis on surgical (clipping, bypass, and wrapping) UIA repair including data from 60 studies (of which 9 were high-quality studies) with 9845 patients and 10 845 UIA found an overall mortality of 1.7% (99% CI, 0.9–3.0) and unfavorable outcome, including death of 6.7% (99% CI, 4.9–9.0). Data on obliteration rates were available for 32% of studies in which complete UIA occlusion was reported for 91.8% (99% CI, 90.0–93.2) of cases.[5]

Based on the data of these 2 meta-analyses, assumed but not established risk factors for preventive UIA repair—irrespective of modality—are aneurysm size, posterior circulation UIA, and patient age. However, more data are needed to establish such factors and their relative complication risk. However, robust data on more individual aneurysm-related factors to permit an estimate of the treatment risk of aneurysms based on its complexity are needed.

Importantly, the use of intrasaccular devices for endovascular flow disruption is an emerging and promising alternative for stent-assisted coiling or flow-diversion for repair of wide-neck aneurysms, predominantly because these devices do not require any platelet inhibitor treatment as opposed to intraluminally applied stents. The currently largest multicenter registry including data from 168 patients and 169 UIAs on safety and efficacy of flow disruption using an intrasaccular device (Woven EndoBridge [WEB]) reported complete aneurysm occlusion of only 52.9% at 1-year follow-up and retreatment rates of 6.9% with adjunctive advices as coils, stents, or flow diverters.[37] However, preliminary data from the next-generation WEB devices indicate distinctly higher occlusion rates.

Management of UIAs

The decision on whether or not to consider preventive (endovascular or surgical) repair of an UIA should be made within a multidisciplinary and dedicated cerebrovascular team and should include all relevant aneurysm- and patient-related risk factors for aneurysm rupture and preventive repair.[8] Because of the large number of data derived from different levels of evidence in this respect, such decisions can often be challenging. Here, different studies, in addition to current guidelines of the American Heart Association/American Stroke Association on management of UIA can provide guidance.[38]

The aforementioned PHASES score enables the estimation of the absolute 5-year risk of aneurysm rupture based on 6 independent predictors.[7] A recent prospective population-based study showed that a threshold of an absolute PHASES score of 3 to 4 was able to distinguish between low and high rupture risk UIA in a cohort of 841 patients with unruptured and ruptured aneurysms. In this study, patients with PHASES scores <3 were mostly followed up with serial imaging, whereas patients with PHASES scores >4 were more likely to be treated.[39] The UIA treatment score, derived from consensus among a large interdisciplinary group of UIA specialists, can serve as a comprehensive mechanism to balance patient-related, aneurysm-related, and treatment-related risk factors in the decision making for or against preventive repair. Simplified, the UIATS system consists of 2 columns that contain all relevant factors for or against UIA repair. The sum of these individual scores of each column results in a proportion of scores on each side: if this difference constituted ≥3 points on either side, the column with the higher score would provide the recommendation for the individual management of the patient. If the score difference was ≤2 points, the recommendation would not be definitive, and other individual factors need to be considered.[40]

If the decision is made to observe a UIA, either because of the low risk of rupture or the high risk of treatment, it is important to follow the aneurysm using serial imaging, especially to detect UIA growth or de novo formation. The aforementioned ELAPSS score is useful to identify UIA at increased risk for growth and thus for the scheduling of follow-up intervals because it enables to estimate the 3- and 5-year risk of aneurysm growth.[30] Data from a comparative effectiveness study on management of UIA with a size <3 mm in diameter demonstrated that in these patients, no treatment and no follow-up imaging have the highest health benefit from a societal perspective.[41] Among follow-up strategies, magnetic resonance imaging every 5 years comprised the most effective management strategy.[41] However, individual follow-up intervals should probably be adapted according to the ELAPSS score, especially in UIA >3 mm in diameter.

If preventive repair is required, the least risky and most effective treatment modality should be discussed within a multidisciplinary team, especially in consideration of aneurysm

rupture risk, patient age, and comorbid diseases, as well as aneurysm-related risk factors for complications, such as size, location, and shape, including calcifications. According to the current literature, simple coiling is the preferred technique for endovascular UIA repair and clipping for surgical UIA repair. The higher perioperative morbidity in older patients or patients with comorbid diseases suggests endovascular coiling as the first-line strategy in such patients, whereas higher occlusion rates and durability of surgical clipping, especially in wide-neck aneurysms, could be an argument for surgical repair in younger patients. In general, UIA of the posterior circulation should preferably be repaired using endovascular coiling or stent-assisted coiling because of the disproportionally higher morbidity and mortality of surgical repair of these aneurysms.

Medical Management of UIA

The majority of UIAs <5 mm in diameter usually remain untreated because in these patients, the risk of preventive repair often does not outweigh the generally low risk of rupture (mean 5-year risk of rupture, <2%).[7] Nevertheless, sole follow-up imaging in these patients leaves them at a small but definite risk of rupture, if the modifiable risk factors in these patients are not treated. Hypertension, aneurysm wall inflammation, and smoking are important modifiable risk factors, and cessation or lowering of these risk factors could result in a reduction of risk for aneurysm rupture or growth.

The current American Heart Association guidelines for patients with UIA recommend a systolic blood pressure <140 mm Hg. However, it remains uncertain whether this blood pressure threshold is adequate: recent data on patients experiencing cardiovascular disease indicate that intensive blood pressure reduction (systolic blood pressure, <120 mm Hg) is associated with a lower incidence of cardiovascular events, such as myocardial infarction, stroke, or death.[42] Because hypertension also is a major risk factor for growth and rupture of intracranial aneurysms, there is a scientific rationale to investigate whether blood pressure reduction in patients with UIA could reduce the incidence of aneurysm growth or rupture (see below).[2,14] Different studies suggested that acetylsalicylic acid (ASA) decreases aneurysm wall inflammation by unselective inhibition of cyclooxygenase 2 and thereby exerts a protective effect on aneurysm rupture. In a nested case-control study of 1691 patients with UIA, patients treated with ASA for other indications had lower odds for UIA rupture in the multivariable analysis (odds ratio, 0.27; 95% CI, 0.11–0.67).[43] A small phase IIa proof-of-concept trial randomizing patients to 81 mg ASA daily or treatment as usual showed that patients randomized to ASA treatment had a reduction of radiological and histological signs of aneurysm wall inflammation as surrogates for rupture.[44] A recent population-based study, in which 199 079 low-dose ASA users were 1:1 matched with nonusers, further demonstrated that ASA use >1 year was associated with a decreased risk of SAH (relative risk, 0.69; 95% CI, 0.50–0.94).[45]

The recently initiated PROTECT-U (Prospective Randomized Open-Label Trial to Evaluate Risk Factor Management in Patients With Unruptured Intracranial Aneurysms; clinicaltrials.gov ID: NCT03063541) investigates whether an intervention with daily intake of 100 mg ASA in combination with intensive blood pressure treatment (targeted systolic blood pressure, <120 mm Hg) reduces the risk of aneurysm rupture or growth (primary outcome) compared with standard care (targeted systolic blood pressure, <140 mm Hg).[46] The trial is currently recruiting patients in Germany and the Netherlands. Other scientific groups from around the globe are also pursuing similar anti-inflammatory strategies in patients with UIA, either based on sole ASA treatment or using selective cyclooxygenase-2 (COX-2) inhibitors.

Although it is challenging to test the efficacy of smoking cessation as an intervention within a randomized, controlled trial, patients with UIA should be strongly recommended to stop smoking or—if this is unfeasible—at least substantially reduce the absolute number of cigarettes per day.[24] The same holds true for heavy alcohol use.

Open Scientific Questions

Despite abundant and novel preclinical and clinical data on the pathogenesis of formation, progression, and rupture of intracranial aneurysms, many uncertainties remain.

The true risk of aneurysm rupture will remain incompletely understood, especially because unselected UIA cohort studies will likely never be completed. Thus, the actual risk of rupture for an individual aneurysm may not be estimated precisely, and novel radiological surrogates for rupture are needed. Whereas existing imaging modalities can only illustrate the lumen of an aneurysm or its parent artery, the molecular components of the aneurysm or vessel wall are not visualized by present radiological means. Molecular imaging could potentially help to differentiate between stable or unstable UIA based on the degree of structural turnover or aneurysm wall inflammation. Further, high-quality data on patient- and aneurysm-related risk factors for outcome after preventive aneurysm repair in relation to treatment modality are lacking. There is a strong need for unbiased and investigator-initiated studies with blinded outcome assessment to compare long-term neurological and radiological outcomes after preventive repair and also assess consequential costs because of rehabilitation, follow-up imaging, and retreatment on a socioeconomic level. Last, the further development of low-risk strategies for stabilization of UIA, including pharmaceutical strategies, should be established to overcome the unbalance between the generally low risk of rupture of the majority of aneurysms and the usually higher risk of preventive aneurysm repair.

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