REVIEW

Management of unruptured incidentally found intracranial saccular aneurysms

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Abstract

Unruptured intracranial saccular aneurysms occur in 3–5% of the general population. As the use of diagnostic medical imaging has steadily increased over the past few decades with the increased availability of computed tomography (CT) and magnetic resonance imaging (MRI), so has the detection of incidental aneurysms. The management of an unruptured intracranial saccular aneurysm is challenging for both patients and physicians, as the decision to intervene must weigh the risk of rupture and resultant subarachnoid hemorrhage against the risk inherent to the surgical or endovascular procedure. The purpose of this paper is to provide an overview of factors to be considered in the decision to offer treatment for unruptured intracranial aneurysms in adults. In addition, we review aneurysm and patient characteristics that favor surgical clipping over endovascular intervention and vice versa. Finally, the authors propose a novel, simple, and clinically relevant algorithm for observation versus intervention in unruptured intracranial aneurysms based on the PHASES scoring system.

Keywords Intracranial aneurysms · Incidental intracranial aneurysms · Unruptured intracranial aneurysms · Open vascular · Endovascular intervention

Introduction

Intracranial aneurysms were first reported in the literature in 1761 when Morgagni of Padua described a case of an unruptured carotid aneurysm. [1] Our understanding of intracerebral aneurysms has advanced tremendously since that time, especially with the introduction and advancement of endovascular techniques. While intracranial saccular aneurysms may present with neurological deficits or other symptoms, an estimated 59% of unruptured aneurysms are asymptomatic. [2] However, with increased utilization of noninvasive imaging, patients are increasingly likely to have an aneurysm be incidentally discovered.

The management of unruptured incidental intracranial saccular aneurysms is challenging for both patients and physicians, as the decision to intervene involves balancing the risks of rupture and subarachnoid hemorrhage against the periprocedural risks inherent to surgical or endovascular intervention. Other factors, including the patient's potential anxiety regarding living with an unruptured aneurysm, play an unquantifiable role in decision-making. [3] This paper aims to provide an overview of select factors to be considered in the decision to offer intervention for this challenging pathology and to propose a simple treatment algorithm for observation versus intervention. As aneurysmal morphology can be infinitely complex, with various treatment options and protocols for each type, herein, the authors will focus on unruptured, non-enlarging saccular aneurysms. This aneurysm type accounts for approximately 90% of intracranial aneurysms and is thus most likely to be encountered by a treating physician. Aneurysms with new-onset neurological deficit are considered symptomatic and may warrant more urgent treatment and are therefore not included in this review.

Formation of intracranial aneurysms

Unruptured intracranial saccular aneurysms occur in 3–5% of the general population. [4] Histopathologically, their hallmark

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trait is a lack of intimal elastic lamina and disruption of the intima media. [5, 6] While the exact mechanisms that lead to aneurysm formation are incompletely understood, they are thought to result from a complex interplay of genetic and environmental factors. A family history of intracranial aneurysm or autosomal dominant polycystic kidney disease increases the risk of intracranial aneurysm, [7] and the prevalence of intracranial aneurysms is higher in females [8] and persons over 40 years old. [9] Hypertension and smoking, particularly if concurrent, also increase the risk of aneurysm formation. [3] Of note, when a single aneurysm is found, 20–30% of patients have additional aneurysms elsewhere, [10] which speaks to the role of both "nature" and "nurture" in the model of aneurysm formation.

Aneurysms occur most frequently at junctional or transitional points of the intracranial vasculature, such as bifurcations and termini. These locations involve a sudden change in blood flow directionality that disrupts normal laminar flow, resulting in turbulence and elevated pressures along the luminal wall. The majority of intracranial aneurysms are found in the anterior circulation, most frequently at the junction between the anterior communicating artery (Acom) and the anterior cerebral artery (ACA). Other common sites are the junction between the internal carotid artery (ICA) and the posterior communicating artery (Pcom) and the middle cerebral artery (MCA) bifurcation. In the posterior circulation, the most common site is the tip of the basilar artery. [11]

Intracranial aneurysm growth and rupture risk

Intracranial aneurysms often remain stable for long periods of time, and the majority will never rupture. However, when aneurysms do grow, they likely do so at an inconstant rate, with periods of rapid growth at irregular intervals. [12] During these periods of growth, rupture and resultant subarachnoid hemorrhage (SAH) are more likely. [3, 13] Several risk factors for both aneurysm growth and rupture have been identified, which include hypertension, smoking, female sex, and aneurysm-specific characteristics such as size, location, and morphology. [14]

Spontaneous SAH occurs at a rate of 6 to 10 events per 100,000 individuals per year, with the vast majority of cases resulting from aneurysm rupture. [15] It is estimated that 10–15% of affected individuals die before reaching the hospital. [16] Prevention of aneurysmal SAH is, therefore, a key goal of intracranial aneurysm management. Management of unruptured intracranial aneurysms has many nuances. Appropriate management ultimately requires an understanding of the patient's risk of rupture once an aneurysm is discovered and is often a joint decision made by both the provider and patient. It is thus essential for the surgeon to have a mastery of the known risk factors for rupture so that both parties can agree upon the best treatment option for the patient's aneurysm.

Contributions of size and location to rupture risk

Two large, prospective studies have been performed regarding the natural history of unruptured aneurysms: the International Study of Unruptured Intracranial Aneurysms (ISUIA) and the Unruptured Cerebral Aneurysms Study (UCAS). ISUIA was a 2003 prospective trial of 1692 patients with 2686 unruptured and untreated aneurysms in the USA, Canada, and Europe. [17] This study built upon a controversial retrospective study performed in 1998, [18] which was widely agreed to underestimate the rate of rupture at 0.05% rupture rate per year for aneurysms less than 10 mm in diameter and 1.0% rupture rate for aneurysms 10 to 25 mm in diameter. UCAS was a Japanese study published in 2012 of 5720 patients with 6697 aneurysms that were followed prospectively for 11,660 aneurysm years. [19]

Table 1 summarizes the 5-year cumulative rupture rate reported in ISUIA and the annual rupture rate per aneurysm reported in UCAS. Rupture rates were calculated according to aneurysm size and location, and the data from both studies showed that the risk of rupture was greater with increasing aneurysm size. Based on these data, there is a very low rupture risk for aneurysms less than 7 mm in diameter (0.00–2.50% for ISUIA and 0.36–0.50% for UCAS). However, there was a discrepancy in results reported by location. ISUIA showed that the anterior circulation had a lower risk of rupture compared with posterior circulation, whereas UCAS showed Acom and Pcom aneurysms had a higher risk of rupture when compared with MCA aneurysms. Differences in the patient population and circulation definition may account for this discrepancy. The ISUIA was multicentered in Europe, Canada, and America, whereas UCAS was conducted solely in Japan. In addition, the Pcom was considered posterior circulation in ISUIA, but aneurysm location was not dichotomized in UCAS. Additional single-population studies have found even lower rupture rates; however, these studies did not have sufficient data regarding aneurysm location. [20, 21] A 2013 long-term follow-up study based in Finland showed a cumulative rupture rate of 9% at 10 years, 18% at 20 years, and 26% at 30 years for aneurysms less than 7 mm in diameter; location in the Acom was associated with an increased risk of rupture during the study period (adjusted hazard ratio 3.73, 95% CI [1.23–11.36]). [22]

Other contributors to rupture risk

The PHASES (Population, Hypertension, Age, Size, Earlier subarachnoid hemorrhage, and Site) scoring system was developed from a meta-analysis of data from ISUIA, UCAS, and other studies and provides a useful framework to determine the risk of rupture within five years of presentation (see Table 2 for a summary of the PHASES scoring system).

Table 1 Aneurysm rupture rates reported by the International Study of Unruptured Intracranial Aneurysms and the Unruptured Cerebral Aneurysm Study according to size and location

Aneurysm location	Aneurysm size			
International Study of Unruptured Intracranial Aneurysms (ISUIA), 5-year cumulative rupture rate[a]				
	< 7 mm	7–12 mm	13–24 mm	≥ 25 mm
Anterior circulation	0.00%	2.60%	14.50%	40.00%
Posterior circulation	2.50%	14.50%	18.40%	50.00%
Cavernous ICA	0.00%	0.00%	3.00%	6.40%
Unruptured Cerebral Aneurysm Study (UCAS), annual rupture rate per aneurysm[b]				
	3–4 mm	5–6 mm	7–9 mm	10–24 mm	≥ 25 mm
ACA	0.90%	0.75%	1.97%	5.24%	39.77%
MCA	0.23%	0.31%	1.56%	4.11%	16.87%
ICA	0.14%	0.00%	1.19%	1.07%	10.61%
ICA-Pcom	0.41%	1.00%	3.19%	6.12%	126.97%
Basilar tip/SCA	0.23%	0.46%	0.97%	6.94%	117.82%
Vertebral artery-proximal basilar artery	0.00%	0.0%	0.00%	3.49%	0.00%
Other	0.78%	1.37%	0.00%	2.81%	0.00%
Total	0.36%	0.5%	1.69%	4.37%	33.40%

Rupture risk based on aneurysm size and location reported by the International Study of Unruptured Intracranial Aneurysms (ISUIA) and the Unruptured Cerebral Aneurysm Study (UCAS). Note: ISUIA reports the 5-year cumulative rupture rate, while UCAS reports annual rupture rate per aneurysm

[a] From Wiebers DO, Whisnant JP, Huston J et al. (2003) Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet Lond Engl 362:103–110

[b] From The UCAS Japan Investigators (2012) The natural course of unruptured cerebral aneurysms in a Japanese Cohort. N. Engl. J. Med. 366:2474–2482

ACA, anterior cerebral artery; *ICA*, internal carotid artery; *MCA*, middle cerebral artery; *Pcom*, posterior communicating artery; *SCA*, superior cerebellar artery

[23] The PHASES score has been validated as a predictor for aneurysm growth and rupture. [24] The components of the PHASES score highlight six independent risk factors for aneurysm rupture identified in the meta-analysis. Other risk factors for aneurysm rupture that are not captured by the PHASES scoring system include family history of SAH, [25, 26] smoking, [27] blood flow directly into the aneurysm, [28] and irregular morphology, especially the presence of daughter aneurysms (i.e., non-smooth domes). [19]

Recent studies have evaluated vessel wall enhancement on magnetic resonance imaging as a potential risk factor for rupture. Increased wall enhancement has been associated with increased rupture risk as determined by PHASES score. [29, 30] One study suggested a "thick (> 1 mm), circumferential pattern of wall enhancement" as a marker of aneurysm instability, [31] and increased circumferential enhancement has been demonstrated in evolving aneurysms compared with stable unruptured and ruptured aneurysms. [32]

The decision to intervene

The decision to intervene on incidentally found unruptured intracranial aneurysms can vary based on presentation. There are no randomized controlled trials on which to base recommendations. In addition to the prevention of aneurysmal SAH, treatment decisions should aim to maximize the number of quality-adjusted life years. [3] Likewise, the decision to treat should be based on the comfort level of the surgeon and patient, as well as the predicted morbidity and mortality of an intervention, weighed against the risk of rupture. [33] The Unruptured Intracranial Aneurysm Treatment Score (UIATS) has been developed to aid physicians in balancing a patient's risk of aneurysm rupture against the risks of morbidity and mortality resulting from preventive treatment. [34] If the aneurysm bleeds or is enlarging with mass effect, urgent or emergent intervention may be warranted.

Generally speaking, the complication rate of intervention for unruptured intracranial aneurysms is reported as high as 5% for endovascular treatment and 8% for surgical treatment. [35] Thus small (less than 5–7 mm in diameter), asymptomatic, anterior circulation aneurysms are generally medically managed and observed with serial imaging unless they are found to be enlarging or progressively symptomatic or the patient has several risk factors for rupture because the risk of intervention outweighs the risk of rupture. [36, 37] Observation with serial imaging is especially recommended for older patients with few additional risk factors. In these patients, the increased risk of rupture conferred by older age (e.g., > 70 years) [23, 38] should be balanced against the

Table 2 PHASES scoring system for unruptured aneurysm risk

Risk Factor	Points
(P)opulation	
North American, European (other than Finnish)	0
Japanese	3
Finnish	5
(H)ypertension	
No	0
Yes	1
(A)ge	
< 70 years	0
≥ 70 years	1
(S)ize of aneurysm	
< 7.0 mm	0
7.0–9.9 mm	3
10.0–19.9 mm	6
≥ 20 mm	10
(E)arlier SAH from another aneurysm	
No	0
Yes	1
(S)ite of aneurysm	
ICA	0
MCA	2
ACA/Pcom/posterior circulation	4

ACA, anterior cerebral artery; *ICA*, internal carotid artery; *MCA*, middle cerebral artery; *Pcom*, posterior communicating artery

From Greving JP, Wermer MJH, Brown RD et al. (2014) Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. Lancet Neurol 13:59–66

presumably lower cumulative probability of rupture given their lower remaining life expectancy (although this may differ depending on the population). However, more aggressive treatment can be considered in younger patients (≤ 50 years old) with asymptomatic aneurysms given their presumed higher cumulative lifetime rupture risk. [36, 39] Note that the lifetime rupture risk may be roughly estimated by multiplying the annual aneurysm rupture risk by the patient's life expectancy, with the caveat that the rupture risk is not constant over time. [40] One might also consider intervention in the case of small aneurysms with daughter sacs or other irregular morphology, given the increased rupture risk of such aneurysms [19] or in patients with a history of SAH in two or more first-degree relatives, as the risk of rupture may outweigh the treatment risk. [36]

Treatment is generally recommended for aneurysms larger than 12 mm, given the increased risk of rupture. The decision to intervene on aneurysms between 7 and 12 mm is often made on a case-by-case basis, [39] with the patient's comfort level with having an unruptured aneurysm weighing even

more heavily in the final recommendation. [3] Table 4 lists selected factors favoring observation versus intervention in unruptured intracranial aneurysms.

An aneurysm with a PHASES score of less than 3 is considered a relatively lower risk for rupture, whereas a score of greater than 4 is considered a higher risk for rupture (see Table 3 for hazard ratios for aneurysm growth by PHASES score). [24, 41] As such, aneurysms with PHASES scores less than 3 are often observed, and those with scores greater than 4 are treated; PHASES scores of 3 and 4 are indeterminate. [24, 41] In Fig. 1, we propose a simple algorithm for the treatment of unruptured intracranial aneurysms based on the PHASES score. It should be noted that an individualized approach may lead to different variations of the algorithm.

Surgical versus endovascular treatment

While there are no data definitively demonstrating that either endovascular (e.g., coiling) or open vascular surgery (e.g., clipping) is superior, many consider surgical intervention to be definitive but endovascular treatment to be less invasive. A meta-analysis of 60 studies containing 9845 total patients and 10,845 total aneurysms found that surgical intervention on unruptured aneurysms had a 1.7% mortality rate and a 6.7% rate of unfavorable outcomes. [42, 43] Morbidity rates were higher with posterior circulation aneurysms and large aneurysms. Endovascular mortality varies from 1.4 to 4.2%, and morbidity rates vary from 4.2 to 8.8%. [17, 20] However, the decision for endovascular versus surgical intervention in an individual patient depends on several factors in addition to morbidity and mortality associated with treatment, including—but not limited to— patient factors such as age, comorbidities, and risks of antiplatelet therapy after intervention; aneurysm factors such as aneurysm location, morphology, and type; and surgeon factors such as experience and comfort level, and personal outcomes (see Table 4 for a summary of factors favoring surgical versus endovascular intervention).

Table 3 Hazard of aneurysm growth by PHASES score

PHASES score	Aneurysm growth hazard ratio (95% CI)
1	Reference
2, 3	1.07 (0.49–2.32)
4	2.29 (1.05–4.95)
5–14	2.85 (1.43–5.67)

CI, confidence interval

From Backes D, Vergouwen MDI, Groenestege ATT et al. (2015) PHASES score for prediction of intracranial aneurysm growth. Stroke 46:1221–1226

Fig. 1 Algorithm for the
treatment of unruptured
intracranial aneurysms. Proposed
algorithm for observation versus
intervention in unruptured
intracranial aneurysms
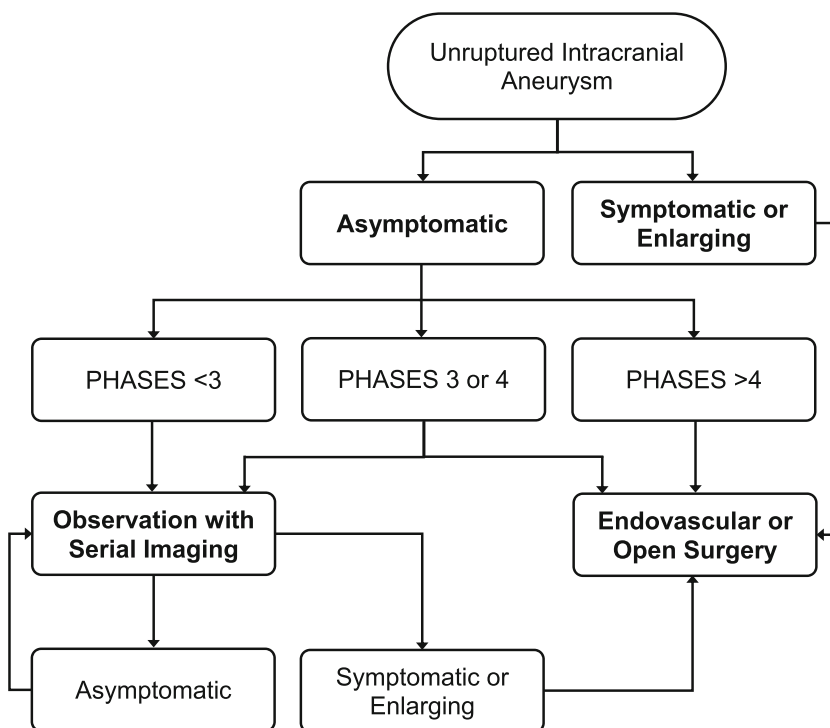
Age

Given the increased risk of poor outcome with open
vascular surgery in patients over 50 years old, [17]
endovascular treatment is often preferred for patients
in this age group when treatment is to be pursued.
[44] It is has been recommended that a younger patient
have their aneurysm clipped for definitive treatment
since the long-term natural history of clipping is known
to be safe, effective, and economical. [37, 45] However,
as endovascular treatment has progressed, rates of treat-
ment failure at 1 year and case morbidity between
endovascular and open treatments have equalized, [46]
making the decision to intervene via one approach or
another dependent on a surgeon's skill set, personal
preferences, and available resources.

Table 4 Factors favoring observation, surgical intervention, and endovascular intervention in unruptured intracranial aneurysms

Factor	Factors favoring observation	Factors favoring surgical intervention	Factors favoring endovascular intervention
Age[a]	Older age with relatively low remaining life expectancy, asymptomatic with low risk of aneurysm rupture		> 50 years old
		≤ 50 years old	
Aneurysm size and morphology	< 7 mm in diameter	> 12 mm in diameter	
		Complex/irregular morphology (e.g., daughter aneurysms, the incorporation of branches into the aneurysm neck)	Neck size < 4 mm or dome-to-neck ratio > 1.5
Aneurysm location	Cavernous ICA	MCA, tortuous or occluded vessels leading to aneurysm	Posterior circulation, cavernous or paraclinoidal ICA
Vessel wall enhancement on MRI		Circumferential enhancement, especially if > 1 mm	
Antiplatelet therapy		Contraindications to antiplatelet therapy	

Summary of factors favoring observation, surgical intervention, and endovascular intervention presented in this review

[a] For older patients with a relatively low remaining life expectancy and an asymptomatic aneurysm with a low risk of rupture, observation is recom-
mended. If intervention is pursued, endovascular intervention is recommended for patients > 50 years old. For patients ≤ 50 years old, more aggressive
treatment can be considered at the onset, and there is no clear preference for surgical or endovascular intervention. *ICA*, internal carotid artery; *MCA*,
middle cerebral artery; *MRI*, magnetic resonance imaging

Aneurysm morphology

Aneurysms with complex morphology (e.g., the incorporation of branches into the aneurysm neck) may be more amenable to clipping than to endovascular treatment. The aneurysm neck size and dome-to-neck ratio form are important factors to consider when determining whether an aneurysm may be safely coiled. A neck size of greater than 4 mm or dome-to-neck ratio less than 1.5 (i.e., a wide neck) indicates that the aneurysm may not be a good candidate for coiling alone. [47] Recent developments have allowed these aneurysms to be treated endovascularly using balloon or stent-assisted coiling as well as with parent vessel and intrasaccular flow diverters. [48]

Aneurysm location and accessibility

The accessibility of the aneurysm should be considered in the decision to offer surgical or endovascular intervention. MCA, Acom, and Pcom aneurysms are typically easily accessible through surgical corridors, mostly via a pterional or orbitozygomatic craniotomy, and are therefore amenable to surgery. [49] Notably, MCA aneurysms often have a wide neck and complex morphology, making endovascular treatment more complicated. [47] The posterior inferior cerebellar artery (PICA), anterior inferior cerebellar artery (AICA), and superior cerebellar artery (SCA) blood vessels are also considered accessible by surgical corridors and can be treated with surgery. As posterior circulation aneurysms are notoriously difficult in terms of surgical corridor access, there is now a preference for endovascular treatment, [50] especially for basilar aneurysms. Endovascular treatment may also be preferred for cavernous or paraclinoid ICA aneurysms, which are both difficult to access surgically and associated with poorer surgical outcomes. [51] Vessel tortuosity and vessel occlusion are also important factors to consider when evaluating a patient's candidacy for endovascular intervention, regardless of aneurysm location. [52]

Antiplatelet therapy

If a neck-bridging or flow-diverting stent is used to treat the aneurysm, the patient will often require dual antiplatelet therapy for at least three months following stent placement to prevent thrombosis of the device and subsequent stroke. [53, 54] Therefore, if a patient has a contraindication for antiplatelet therapy through adverse medication side effects, poor adherence, or poor response, endovascular treatment may not be a viable option. Clinicians may consider platelet function testing in these patients to identify those who are nonresponders to antiplatelet therapy, which would result in an increased risk of thrombotic complications. However, the routine use of platelet function testing is controversial, and no high quality, randomized controlled data exist. [55] If a patient is a nonresponder to antiplatelet therapy, anticoagulation may be considered, which brings additional hemorrhage risk. In elderly patients, the risk of a fall resulting in intracranial hemorrhage may also be considered, although there is evidence that direct oral anticoagulation may not increase traumatic brain injury-associated morbidity and mortality in this population. [56]

Observation and medical management

When the decision for medical management is made (i.e., a small, stable, asymptomatic aneurysm), annual imaging via digital subtraction angiogram, computed tomography angiography, or magnetic resonance angiography is recommended to observe the aneurysm for enlargement. [36, 57] As stated previously, enlarging or symptomatic aneurysms are at increased risk of rupture and should be considered for surgical or endovascular intervention. In addition to serial imaging, modifiable risk factors for aneurysm formation and growth, such as hypertension and smoking, and risk factors for vascular disease, such as type 2 diabetes mellitus and hyperlipidemia should be addressed and treated to optimize conservative treatment. [36]

Conclusion

The decision to treat an unruptured intracerebral aneurysm should be a joint decision made between patient and provider based on a desire to balance the risk of rupture against that of observation, as well as potential morbidity and mortality associated with intervention. The most significant risk of observation is aneurysm rupture and possible SAH. An enlarging aneurysm may therefore require urgent treatment, especially if there is neurological deficit. In this review, we provide a novel, simple, and clinically relevant algorithm for helping determine when to treat versus observe in the management of intracranial aneurysms using the PHASES scoring system. Medical management should be strongly considered for aneurysms with a PHASES score of less than 3, while surgical management is often preferred when the PHASES score is greater than 4. The recommendations for scores of 3 and 4 remain indeterminate. Several patient-specific factors must be considered when deciding whether an unruptured, non-enlarging aneurysm should be treated surgically/endovascularly or observed, including (1) age, with younger age favoring intervention; (2) aneurysm location, with posterior circulation favoring intervention; (3) aneurysm size, where larger aneurysms favor intervention; (4) aneurysm morphology, with the presence of daughter aneurysms or other irregular morphology favoring intervention; and (5) patient preference. Ultimately, this list is not comprehensive, and treatment decisions may vary depending on the interplay

between patient-specific factors and preference as well as surgeon training and management preferences.

Data availability Not applicable.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval As this work was a review of existing literature, it was not subject to approval by an institutional review board or ethical committee.

Informed consent As this work did not involve human participants, informed consent was not required.

Code availability Not applicable.

References

1. Smith RR, Zubkov YN, Tarassoli Y (1994) The history of aneurysm surgery. In: Smith RR, Zubkov YN, Tarassoli Y (eds) Cerebral aneurysms: microvascular and endovascular management. Springer US, New York, NY, pp 1–9
2. Raps EC, Rogers JD, Galetta SL, Solomon RA, Lennihan L, Klebanoff LM, Fink ME (1993) The clinical spectrum of unruptured intracranial aneurysms. Arch Neurol 50:265–268. https://doi.org/10.1001/archneur.1993.00540030031010
3. Etminan N, Rinkel GJ (2016) Unruptured intracranial aneurysms: development, rupture and preventive management. Nat Rev Neurol 12:699–713. https://doi.org/10.1038/nrneurol.2016.150
4. Brisman JL, Song JK, Newell DW (2006) Cerebral aneurysms. N Engl J Med 355:928–939. https://doi.org/10.1056/NEJMra052760
5. Hassler O (1961) Morphological studies on the large cerebral arteries, with reference to the aetiology of subarachnoid haemorrhage. Acta Psychiatr Scand Suppl 154:1–145
6. Scanarini M, Mingrino S, Giordano R, Baroni A (1978) Histological and ultrastructural study of intracranial saccular aneurysmal wall. Acta Neurochir 43:171–182
7. Ronkainen A, Hernesniemi J, Puranen M, Niemitukia L, Vanninen R, Ryynänen M, Kuivaniemi H, Tromp G (1997) Familial intracranial aneurysms. Lancet 349:380–384. https://doi.org/10.1016/S0140-6736(97)80009-8
8. Vlak MH, Rinkel GJ, Greebe P, Algra A (2013) Risk of rupture of an intracranial aneurysm based on patient characteristics: a case–control study. Stroke 44:1256–1259
9. Stehbens WE (1963) Aneurysms and anatomical variation of cerebral arteries. Arch Pathol 75:45–64
10. Weir B (2002) Unruptured intracranial aneurysms: a review. J Neurosurg 96:3–42
11. Schievink WI (1997) Intracranial aneurysms. N Engl J Med 336: 28–40. https://doi.org/10.1056/NEJM199701023360106
12. Koffijberg H, Buskens E, Algra A, Wermer MJH, Rinkel GJE (2008) Growth rates of intracranial aneurysms: exploring constancy. J Neurosurg 109:176–185. https://doi.org/10.3171/JNS/2008/109/8/0176
13. Chien A, Callender RA, Yokota H, Salamon N, Colby GP, Wang AC, Szeder V, Jahan R, Tateshima S, Villablanca J, Duckwiler G, Vinuela F, Ye Y, Hildebrandt MAT (2019) Unruptured intracranial aneurysm growth trajectory: occurrence and rate of enlargement in 520 longitudinally followed cases. J Neurosurg 1–11. doi: https://doi.org/10.3171/2018.11.JNS181814
14. Backes D, Rinkel GJE, Laban KG, Algra A, Vergouwen MDI (2016) Patient- and aneurysm-specific risk factors for intracranial aneurysm growth. Stroke 47:951–957
15. van Gijn J, Kerr RS, Rinkel GJE (2007) Subarachnoid haemorrhage. Lancet Lond Engl 369:306–318. https://doi.org/10.1016/S0140-6736(07)60153-6
16. Huang J, Van Gelder JM (2002) The probability of sudden death from rupture of intracranial aneurysms: a meta-analysis. Neurosurgery 51:1101–1107
17. Wiebers DO, Whisnant JP, Huston J, Meissner I, Brown RD, Piepgras DG, Forbes GS, Thielen K, Nichols D, O'Fallon WM, Peacock J, Jaeger L, Kassell NF, Kongable-Beckman GL, Torner JC, International Study of Unruptured Intracranial Aneurysms Investigators (2003) Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet Lond Engl 362:103–110
18. The International Study of Unruptured Intracranial Aneurysms Investigators (1998) Unruptured intracranial aneurysms — risk of rupture and risks of surgical intervention. N Engl J Med 339:1725–1733
19. The UCAS Japan Investigators (2012) The natural course of unruptured cerebral aneurysms in a Japanese cohort. N Engl J Med 366:2474–2482
20. Rinaldo L, Shepherd DL, Murphy ME, Vine RL, Brown RD, Rabinstein AA, Lanzino G (2016) Natural history of untreated unruptured intracranial aneurysms in the elderly. J Neurosurg Sci
21. Sonobe M, Yamazaki T, Yonekura M, Kikuchi H (2010) Small unruptured intracranial aneurysm verification study: SUAVe study, Japan. Stroke 41:1969–1977. https://doi.org/10.1161/STROKEAHA.110.585059
22. Juvela S, Poussa K, Lehto H, Porras M (2013) Natural history of unruptured intracranial aneurysms: a long-term follow-up study. Stroke 44:2414–2421
23. Greving JP, Wermer MJH, Brown RD, Morita A, Juvela S, Yonekura M, Ishibashi T, Torner JC, Nakayama T, Rinkel GJE, Algra A (2014) Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. Lancet Neurol 13:59–66. https://doi.org/10.1016/S1474-4422(13)70263-1
24. Backes D, Vergouwen MDI, Groenestege ATT, Bor ASE, Velthuis BK, Greving JP, Algra A, Wermer MJH, van Walderveen MAA, terBrugge KG, Agid R, Rinkel GJE (2015) PHASES score for prediction of intracranial aneurysm growth. Stroke 46:1221–1226
25. Broderick JP, Brown RD Jr, Sauerbeck L, Hornung R, Huston J III, Woo D, Anderson C, Rouleau G, Kleindorfer D, Flaherty ML (2009) Greater rupture risk for familial as compared to sporadic unruptured intracranial aneurysms. Stroke 40:1952–1957
26. Okamoto K, Horisawa R, Kawamura T, Asai A, Ogino M, Takagi T, Ohno Y (2003) Family history and risk of subarachnoid hemorrhage: a case-control study in Nagoya, Japan. Stroke 34:422–426
27. Feigin V, Parag V, Lawes CMM, Rodgers A, Suh I, Woodward M, Jamrozik K, Ueshima H (2005) Smoking and elevated blood pressure are the most important risk factors for subarachnoid hemorrhage in the Asia-Pacific region: an overview of 26 cohorts involving 306 620 participants. Stroke 36:1360–1365. https://doi.org/10.1161/01.STR.0000170710.95689.41

28. de Rooij NK, Velthuis BK, Algra A, Rinkel GJE (2009) Configuration of the circle of Willis, direction of flow, and shape of the aneurysm as risk factors for rupture of intracranial aneurysms. J Neurol 256:45–50. https://doi.org/10.1007/s00415-009-0028-x

29. Hartman JB, Watase H, Sun J, Hippe DS, Kim L, Levitt M, Sekhar L, Balu N, Hatsukami T, Yuan C (2019) Intracranial aneurysms at higher clinical risk for rupture demonstrate increased wall enhancement and thinning on multicontrast 3D vessel wall MRI. Br J Radiol 92:20180950

30. Lv N, Karmonik C, Chen S, Wang X, Fang Y, Huang Q, Liu J (2019) Relationship between aneurysm wall enhancement in vessel wall magnetic resonance imaging and rupture risk of unruptured intracranial aneurysms. Neurosurgery 84:E385–E391

31. Edjlali M, Guédon A, Ben Hassen W, Boulouis G, Benzakoun J, Rodriguez-Régent C, Trystram D, Nataf F, Meder J-F, Turski P (2018) Circumferential thick enhancement at vessel wall MRI has high specificity for intracranial aneurysm instability. Radiology 289:181–187

32. Omodaka S, Endo H, Niizuma K, Fujimura M, Inoue T, Endo T, Sato K, Sugiyama S, Tominaga T (2018) Circumferential wall enhancement in evolving intracranial aneurysms on magnetic resonance vessel wall imaging. J Neurosurg 131:1262–1268

33. Etminan N, Beseoglu K, Barrow DL, Bederson J, Brown RD, Connolly ES, Derdeyn CP, Hänggi D, Hasan D, Juvela S, Kasuya H, Kirkpatrick PJ, Knuckey N, Koivisto T, Lanzino G, Lawton MT, LeRoux P, McDougall CG, Mee E, Mocco J, Molyneux A, Morgan MK, Mori K, Morita A, Murayama Y, Nagahiro S, Pasqualin A, Raabe A, Raymond J, Rinkel GJE, Rüfenacht D, Seifert V, Spears J, Steiger H-J, Steinmetz H, Torner JC, Vajkoczy P, Wanke I, Wong GKC, Wong JH, Macdonald RL (2014) Multidisciplinary consensus on assessment of unruptured intracranial aneurysms. Stroke 45:1523–1530

34. Etminan N, Brown RD, Beseoglu K, Juvela S, Raymond J, Morita A, Torner JC, Derdeyn CP, Raabe A, Mocco J, Korja M, Abdulazim A, Amin-Hanjani S, Al-Shahi Salman R, Barrow DL, Bederson J, Bonafe A, Dumont AS, Fiorella DJ, Gruber A, Hankey GJ, Hasan DM, Hoh BL, Jabbour P, Kasuya H, Kelly ME, Kirkpatrick PJ, Knuckey N, Koivisto T, Krings T, Lawton MT, Marotta TR, Mayer SA, Mee E, Pereira VM, Molyneux A, Morgan MK, Mori K, Murayama Y, Nakayama N, Niemelä M, Ogilvy CS, Pierot L, Rabinstein AA, Roos YBWEM, Rinne J, Rosenwasser RH, Ronkainen A, Schaller K, Seifert V, Solomon RA, Spears J, Steiger H-J, Vergouwen MDI, Wanke I, Wermer MJH, Wong GKC, Wong JH, Zipfel GJ, Connolly ES, Steinmetz H, Lanzino G, Pasqualin A, Rüfenacht D, Vajkoczy P, McDougall C, Hänggi D, LeRoux P, Rinkel GJE, Macdonald RL (2015) The unruptured intracranial aneurysm treatment score. Neurology 85:881–889. https://doi.org/10.1212/WNL.0000000000001891

35. Algra AM, Lindgren A, Vergouwen MDI, Greving JP, van der Schaaf IC, van Doormaal TPC, Rinkel GJE (2019) Procedural clinical complications, case-fatality risks, and risk factors in endovascular and neurosurgical treatment of unruptured intracranial aneurysms: a systematic review and meta-analysis. JAMA Neurol 76:282–293. https://doi.org/10.1001/jamaneurol.2018.4165

36. Burkhardt J-K, Benet A, Lawton MT (2017) Management of small incidental intracranial aneurysms. Neurosurg Clin N Am 28:389–396. https://doi.org/10.1016/j.nec.2017.02.006

37. Komotar RJ, Mocco J, Solomon RA (2008) Guidelines for the surgical treatment of unruptured intracranial aneurysms. Neurosurgery 62:183–194. https://doi.org/10.1227/01.NEU.0000311076.64109.2E

38. Hishikawa T, Date I, Tokunaga K, Tominari S, Nozaki K, Shiokawa Y, Houkin K, Murayama Y, Ishibashi T, Takao H, Kimura T, Nakayama T, Morita A (2015) Risk of rupture of

39. Williams LN, Brown RD (2013) Management of unruptured intracranial aneurysms. Neurol Clin Pract 3:99–108. https://doi.org/10.1212/CPJ.0b013e31828d9f6b

40. Sato K, Yoshimoto Y (2011) Risk profile of intracranial aneurysms: rupture rate is not constant after formation. Stroke 42:3376–3381. https://doi.org/10.1161/STROKEAHA.111.625871

41. Bijlenga P, Gondar R, Schilling S, Morel S, Hirsch S, Cuony J, Corniola M-V, Perren F, Rüfenacht D, Schaller K (2017) PHASES score for the management of intracranial aneurysm. Stroke 48:2105–2112

42. Britz GW, Salem L, Newell DW, Eskridge J, Flum DR (2004) Impact of surgical clipping on survival in unruptured and ruptured cerebral aneurysms: a population-based study. Stroke 35:1399–1403. https://doi.org/10.1161/01.STR.0000128706.41021.01

43. Kotowski M, Naggara O, Darsaut TE, Nolet S, Gevry G, Kouznetsov E, Raymond J (2013) Safety and occlusion rates of surgical treatment of unruptured intracranial aneurysms: a systematic review and meta-analysis of the literature from 1990 to 2011. J Neurol Neurosurg Psychiatry 84:42–48. https://doi.org/10.1136/jnnp-2011-302068

44. Rinkel GJE (2019) Management of patients with unruptured intracranial aneurysms. Curr Opin Neurol 32:49–53. https://doi.org/10.1097/WCO.0000000000000642

45. Lad SP, Babu R, Rhee MS, Franklin RL, Ugiliweneza B, Hodes J, Nimjee SM, Zomorodi AR, Smith TP, Friedman AH, Patil CG, Boakye M (2013) Long-term economic impact of coiling vs clipping for unruptured intracranial aneurysms. Neurosurgery 72:1000–1011; **discussion 1011-1013**. https://doi.org/10.1227/01.neu.0000429284.91142.56

46. Darsaut TE, Findlay JM, Magro E, Kotowski M, Roy D, Weill A, Bojanowski MW, Chaalala C, Iancu D, Lesiuk H, Sinclair J, Scholtes F, Martin D, Chow MM, O'Kelly CJ, Wong JH, Butcher K, Fox AJ, Arthur AS, Guilbert F, Tian L, Chagnon M, Nolet S, Gevry G, Raymond J (2017) Surgical clipping or endovascular coiling for unruptured intracranial aneurysms: a pragmatic randomised trial. J Neurol Neurosurg Psychiatry 88:663–668. https://doi.org/10.1136/jnnp-2016-315433

47. Regli L, Uske A, de Tribolet N (1999) Endovascular coil placement compared with surgical clipping for the treatment of unruptured middle cerebral artery aneurysms: a consecutive series. J Neurosurg 90:1025–1030. https://doi.org/10.3171/jns.1999.90.6.1025

48. Consoli A, Vignoli C, Renieri L, Rosi A, Chiarotti I, Nappini S, Limbucci N, Mangiafico S (2016) Assisted coiling of saccular wide-necked unruptured intracranial aneurysms: stent versus balloon. J NeuroInterventional Surg 8:52–57. https://doi.org/10.1136/neurintsurg-2014-011466

49. Fang S, Brinjikji W, Murad MH, Kallmes DF, Cloft HJ, Lanzino G (2014) Endovascular treatment of anterior communicating artery aneurysms: a systematic review and meta-analysis. Am J Neuroradiol 35:943–947. https://doi.org/10.3174/ajnr.A3802

50. Petr O, Brinjikji W, Cloft H, Kallmes DF, Lanzino G (2016) Current trends and results of endovascular treatment of unruptured intracranial aneurysms at a single institution in the flow-diverter era. AJNR Am J Neuroradiol 37:1106–1113. https://doi.org/10.3174/ajnr.A4699

51. Park HK, Horowitz M, Jungreis C, Kassam A, Koebbe C, Genevro J, Dutton K, Purdy P (2003) Endovascular treatment of paraclinoid aneurysms: experience with 73 patients. Neurosurgery 53:14–24

52. Chen PR, Frerichs K, Spetzler R (2004) Current treatment options for unruptured intracranial aneurysms. Neurosurg Focus 17:1–6. https://doi.org/10.3171/foc.2004.17.5.5

53. Rajah G, Narayanan S, Rangel-Castilla L (2017) Update on flow diverters for the endovascular management of cerebral aneurysms. Neurosurg Focus 42:E2. https://doi.org/10.3171/2017.3.FOCUS16427

54. Tonetti DA, Jankowitz BT, Gross BA (2019) Antiplatelet therapy in flow diversion. Neurosurgery 86:S47–S52

55. Comin J, Kallmes DF (2013) Platelet-function testing in patients undergoing neurovascular procedures: caught between a rock and a hard place. Am J Neuroradiol 34:730–734. https://doi.org/10.3174/ajnr.A3440

56. Batey M, Hecht J, Callahan C, Wahl W (2018) Direct oral anticoagulants do not worsen traumatic brain injury after low-level falls in the elderly. Surgery 164:814–819. https://doi.org/10.1016/j.surg.2018.05.060

57. Howard BM, Hu R, Barrow JW, Barrow DL (2019) Comprehensive review of imaging of intracranial aneurysms and angiographically negative subarachnoid hemorrhage. Neurosurg Focus 47:E20