Endovascular and Medical Management of Unruptured Intracranial Aneurysms

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Abstract

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Unruptured intracranial aneurysms are often discovered incidentally on noninvasive imaging. As use of noninvasive imaging has increased, our understanding of the presumed prevalence of intracranial aneurysms in adults has increased. Incidentally found aneurysms are often asymptomatic; however, they can rarely rupture and cause life-threatening illness. Elective treatment of intracranial aneurysms carries risks which need to be considered along with patient-specific factors (e.g., anatomy, medical comorbidities, personal preferences). In this article, we review the natural history, risk factors for cerebral aneurysm formation and rupture, evidence for medical management, and the safety profile and efficacy of available endovascular treatment options.

Cerebral aneurysms can be characterized as an abnormal dilatation and weakening of the arterial wall of cerebral blood vessels. They most commonly occur in segments of the artery near bifurcation points, often secondary to an underlying structural abnormality. An examination of the layers of the diseased vessel wall will often reveal a thin or absent tunica media, thin or fragmented internal elastic lamina, and fibrinous tunica adventitia.[1] Most commonly (approximately 90%), cerebral aneurysms take a saccular (or berry) morphology, and most discussion regarding rupture risks and treatments focuses on these types of aneurysms.[2] However, other aneurysm types include fusiform (affecting a longer segment of artery), mycotic (related to an underlying infectious process), and dissecting (secondary to a previous injury to the arterial wall).

Since the early 2000s, there has been an increasing proportion of aneurysms, both ruptured and unruptured, that are now treated with endovascular therapy compared with surgical clipping, as well as an increase in the overall number of unruptured intracranial aneurysms that are treated with endovascular therapy.[3,4] Furthermore, there has been a concomitant decline in procedures for aneurysmal subarachnoid hemorrhage, suggestive of a beneficial effect of treatment for unruptured intracranial aneurysms.[4]

Risk Factors for Cerebral Aneurysm Formation

Several risk factors have been identified in association with the development of cerebral aneurysms, including cigarette smoking, female sex, positive family history, alcohol abuse, hypertension, older age, and certain genetic conditions.[5,6] Hormonal therapy, including estrogens, remains a controversial topic regarding cerebral aneurysm formation and rupture risk. On one side, there are data suggesting higher prevalence of subarachnoid hemorrhage in postmenopausal women compared with premenopausal women and risk reduction with use of hormone replacement therapy in postmenopausal women (suggestive of estrogen deficiency as a risk factor); however, there are also data to suggest hormone replacement therapy in postmenopausal women may increase the risk of subarachnoid hemorrhage.[7] Inflammation or an inflammatory state has also been proposed as a risk factor for cerebral aneurysm formation.

Overall, the mean prevalence of unruptured intracranial aneurysms was 2.8% from a comprehensive systematic review that included 68 studies on 83 populations.[5]

Natural History of Unruptured Intracranial Aneurysms

Our understanding of the natural history of intracranial aneurysms is informed and supported in part by two large studies (International Study of Unruptured Intracranial Aneurysms [ISUIA], Unruptured Cerebral Aneurysm Study of Japan [UCAS]) as well as a large, pooled analysis (population, hypertension, age, size of aneurysm, earlier subarachnoid hemorrhage from another aneurysm, and site of aneurysm [PHASES]). From these data, we understand that the majority of unruptured aneurysms will never rupture in a patient's lifetime. In the rare event of aneurysmal rupture, in-hospital mortality is estimated to occur in one in five patients.[8] There is a large discrepancy between the annual prevalence of unruptured aneurysms (2,000–4,000 per 100,000) and the annual nontraumatic subarachnoid hemorrhage incidence (10 per 100,000), which suggests that only 1 rupture occurs per 200 to 400 patients per year.[9] However, certain factors identified from these studies may play a role in increasing the risk of aneurysm rupture.

ISUIA reported on the 5-year rupture risk of 2,686 unruptured and untreated cerebral aneurysms in North America and Europe, most of which were discovered incidentally. This study reported that the risk of rupture varies with the cerebral aneurysm's size and location within the cerebrovasculature (anterior circulation, cavernous carotid, or posterior circulation including the posterior communicating artery). A summary of ISUIA data is shown in ►Table 1.[10]

UCAS reported annualized aneurysm rupture risk on 6,697 cerebral aneurysms. The overall aneurysm rupture rate for the study was 1% and the rupture risk increased with aneurysm size, with an annualized rupture rate of 1.1% for 5–6 mm, 3.4% for 7–9 mm, 9.1% for 10–24 mm, and 76.3% for >25 mm.[11]

The PHASES score was developed from a large, pooled analysis of six prospective studies on unruptured intracranial aneurysms (including ISUIA and UCAS). Data were analyzed from 8,382 patients and 10,272 unruptured aneurysms. The PHASES score considers the following six predictors to model a patient's 5-year aneurysm rupture risk: population, hypertension, age, size of the aneurysm, prior subarachnoid hemorrhage from another aneurysm, and site of the aneurysm (►Table 2).[12]

Observational studies have also noted an increased cerebral aneurysm formation rate with cigarette smoking, and other studies have shown increased risk of subarachnoid hemorrhage in patients with a combination of cigarette smoking and hypertension.[13] In addition, patients with a familial history of aneurysms in first-degree relatives tend toward aneurysm rupture at smaller sizes and younger ages compared with patients with sporadic aneurysms.[14]

Morphology of cerebral aneurysms appears to be a factor associated with risk of rupture. In particular, multiple lobes, increased aneurysm-to-vessel size ratio, and aneurysm angle may be associated with increased rupture risk.[15,16]

In clinical practice, the UIATS (Unruptured Intracranial Aneurysm Treatment Score) is sometimes used to assist with patient counseling, differing from the PHASES score in that it accounts for risk of aneurysm treatment into its scoring system. Developed by Delphi consensus among a multidisciplinary group of 69 specialists, UIATS incorporates patient-specific factors (age, risk factors, clinical symptoms, and quality of life), aneurysm risk factors (size, morphology, location, and growth), and treatment risks (age, size, complexity, and a constant intervention-related risk), as shown in ►Fig. 1. Points scored under patient- and aneurysm-related risks are tallied together (as points in favor of aneurysm repair) and compared against treatment-related risks plus adjustments for specific comorbidities or expected reduction of life expectancy (as points favoring conservative management).[17]

Growth of Intracranial Aneurysms

Cerebral aneurysm growth can occur in two ways: an increase in the size of an existing aneurysm (in situ), or formation of a de novo aneurysm at a different location. An increase in the size of cerebral aneurysms detected by imaging studies is considered macroscopic growth, although aneurysm growth may also occur on a microscopic level not detected by conventional imaging (e.g., computed tomography angiography [CTA], magnetic resonance angiography [MRA], digital subtraction angiography [DSA]). Growth of intracranial aneurysms has been associated with female sex, cigarette smoking, excessive alcohol consumption, and multiplicity of aneurysms.[18,19]

Macroscopic cerebral aneurysm growth has been associated with an increased risk of aneurysm rupture and is considered an indication to refer patients for evaluation of aneurysm repair.[20–22] For example, one prospective

Table 1 ISUIA 5-year rupture risk in patients without previous history of SAH[a]

	<7 mm	7–12 mm	13–24 mm	>25 mm
Cavernous carotid	0	0	3%	6.4%
Anterior circulation[b]	0	2.6%	14.5%	40%
Posterior/posterior communicating artery[c]	2.5%	14.5%	18.4%	50%

Abbreviations: ISUIA, International Study of Unruptured Intracranial Aneurysms; SAH, subarachnoid hemorrhage.
[a]Adapted from Wiebers et al.[10]
[b]Anterior circulation includes anterior communicating or anterior cerebral arteries, internal carotid artery (excluding cavernous carotid), and middle cerebral artery.
[c]Posterior circulation includes vertebrobasilar, posterior cerebral, or posterior communicating artery.

Table 2 PHASES score for aneurysm rupture risk

PHASES[a] aneurysm rupture risk model[b]	
PHASES aneurysm risk score	Points
(P) Population	
North American, European (other than Finnish)	0
Japanese	3
Finnish	5
(H) Hypertension	
No	0
Yes	1
(A) Age	
< 70 y	0
≥70 y	1
(S) Size of aneurysm	
< 7–0 mm	0
7–9.9 mm	3
10–19.9 mm	6
≥20 mm	10
(E) Earlier SAH from another aneurysm	
No	0
Yes	1
(S) Site of aneurysm	
ICA	0
MCA	2
ACA/Pcomm/Posterior	4
PHASES risk score	5-year risk of aneurysm rupture
≤2	0.4 (0.1–1.5)
3	0.7 (0.2–1.5)
4	0.9 (0.3–2)
5	1.3 (0.8–2.4)
6	1.7 (1.1–2.7)
7	2.4 (1.6–3.3)
8	3.2 (2.3–4.4)
9	4.3 (2.9–6.1)
10	5.3 (3.5–8)
11	7.2 (5–10.2)
≥12	17.8 (15.2–20.7)

Abbreviations: ACA, anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery; SAH, subarachnoid hemorrhage.
[a]PHASES = population, hypertension, age, size of aneurysm, earlier subarachnoid hemorrhage from another aneurysm, and site of aneurysm.
[b]Adapted from Greving et al.[12]

observational study evaluating 1,325 aneurysms followed with serial MRAs identified 18 patients with interval aneurysm growth, with a reported annualized hemorrhage rate of 18.5%. The study estimated that 90% of growing aneurysms

would be detected before hemorrhage with screening performed at 6-month intervals.[23]

Mathematical simulations of prospective aneurysm series have suggested that intracranial aneurysm growth has a nonlinear trajectory.[24] Notably, cerebral aneurysm growth has been reported to be more likely to be detected for larger aneurysms than smaller ones.[25] De novo growth of cerebral aneurysms (i.e., formation of aneurysms not previously present) over weeks to months has been reported in some patients after an index aneurysmal subarachnoid hemorrhage.[24]

Unruptured but Symptomatic Intracranial Aneurysms

Although uncommon, approximately 10 to 15% of unruptured intracranial aneurysms are symptomatic. Cranial neuropathies, seizures, facial pain, headaches, and visual disturbances have all been reported as presenting symptoms.[1] The development of new symptoms of an unruptured aneurysm is often considered a harbinger of impending rupture, and newly symptomatic aneurysms are often treated on an urgent basis.[26]

An unruptured aneurysm may present with cranial nerve palsy secondary to mass effect. Acute-to-subacute ipsilateral oculomotor nerve palsy due to the compressive effect of a posterior communicating artery aneurysm is a classic example. Some observational studies have reported improvement of cranial nerve function after aneurysm treatment.[27]

Headaches have been associated with unruptured as well as ruptured aneurysms, often with distinct features. The classic "thunderclap" headache feature of aneurysm rupture includes the sudden onset of maximal pain intensity and nuchal rigidity. However, sentinel headaches can also occur days to weeks prior to aneurysm rupture.[28] In general, treatment of unruptured intracranial aneurysms does not provide headache relief.[18,29]

In patients with acute headache, a noncontrast head computed tomography (CT) is highly sensitive for aneurysmal subarachnoid hemorrhage and has been reported to be positive in 98 to 100% of cases in the first 12 hours from symptom onset, and up to 93% in the first 24 hours from symptom onset, with yield dropping as time increases.[30] If noncontrast head CT is unrevealing and a strong clinical suspicion remains, a diagnostic lumbar puncture remains the gold standard for diagnosis, with detection of xanthochromia (secondary to metabolization of hemoglobin from red blood cells into pigmented oxyhemoglobin and bilirubin) which may take up to 12 hours to form.[2]

Some intracranial aneurysms may be discovered as part of the work-up for ischemic cerebrovascular disease or another neurological event. Management of an aneurysm found proximal to a territory of ischemia remains controversial, and there are no prospective randomized trials to compare the risk of subsequent ischemic events after aneurysm repair or medical management. Aneurysms with clearly defined intrasaccular thrombus proximal to ischemic territory may warrant consideration for treatment,[31] but there is lack of

Patient	Age (single)	< 40 years	4		
		40-60 years	3		
		61-70 years	2	☐	
		71-80 years	1		
		> 80 years	0		
	Risk factor incidence (multiple)	Previous SAH from a different aneurysm	4		
		Familial intracranial aneurysms or SAH	3		
		Japanese, Finnish, Inuit ethnicity	2		
		Current cigarette smoking	3		
		Hypertension (systolic BP > 140 mm Hg)	2	☐	
		Autosomal-polycystic kidney disease	2		
		Current drug abuse (cocaine, amphetamine)	2		
		Current alcohol abuse	1		
	Clinical Symptoms related to UIA (multiple)	Cranial nerve deficit	4		
		Clinical or radiological mass effect	4		
		Thromboembolic events from the aneurysm	3	☐	
		Epilepsy	1		
	Other (multiple)	Reduced quality of life due to fear of rupture	2	☐	
		Aneurysm multiplicity	1		
	Life expectancy due to chronic and/or malignant Diseases (single)	< 5 years	4		
		5 - 10 years	3		☐
		> 10 years	1		
	Comorbid disease (multiple)	Neurocognitive disorder	3		
		Coagulopathies, thrombophilic diseases	2		☐
		Psychiatric disorder	2		
Aneurysm	Maximum diameter (single)	≤ 3.9 mm	0		
		4.0-6.9 mm	1		
		7.0-12.9 mm	2	☐	
		13.0-24.9 mm	3		
		≥ 25 mm	4		
	Morphology (multiple)	Irregularity or lobulation	3	☐	
		Size ratio > 3 or aspect ratio > 1.6	1		
	Location (single)	BasA bifurcation	5		
		Vertebral/basilar artery	4	☐	
		AcomA or PcomA	2		
	Other (multiple)	Aneurysm growth on serial imaging	4		
		Aneurysm de novo formation on serial imaging	3	☐	
		Contralateral stenoocclusive vessel disease	1		
Treatment	Age-related risk (single)	< 40 years	0		
		41-60 years	1		
		61-70 years	3		
		71-80 years	4		☐
		> 80 years	5		
	Aneurysm size-related risk (single)	< 6.0 mm	0		
		6.0-10.0 mm	1		
		10.1-20.0 mm	3		☐
		> 20 mm	5		
	Aneurysm complexity-related risk	High	3		☐
		Low	0		
	Intervention-related risk	Constant*			5
				Favors UIA repair ☐	Favors UIA conservative management ☐

Fig. 1   Unruptured intracranial aneurysm treatment score (UIATS). (Adapted from Etminan et al[17].)

prospective data regarding any benefits to reducing the risk of subsequent ischemic events.

Screening for Unruptured Intracranial Aneurysms

To be effective, screening must be targeted to high-risk populations; the most recent American Heart Association/ American Stroke Association guidelines do not support widespread screening for intracranial aneurysms in the general population. However, noninvasive imaging (CTA, MRA) is recommended for patients with two or more family members with intracranial aneurysms or subarachnoid hemorrhage, especially with a history of hypertension or cigarette smoking.[18] Furthermore, patients with a history of autosomal-dominant polycystic kidney disease, particularly those with a family history of cerebral aneurysms, should also be offered screening with CTA or MRA. It is also reasonable to offer screening CTA or MRA to patients with fibromuscular dysplasia, aortic aneurysms, coarctation of the aorta, and microcephalic osteodysplastic primordial dwarfism.[18]

Diagnostic Imaging

Initial diagnosis of an unruptured aneurysm is most often made by noninvasive imaging such as CTA or MRA. Invasive DSA offers more specific anatomic details to better characterize the aneurysm and is useful for operative or procedural planning if aneurysm repair is being considered.

DSA remains the gold standard for diagnostic imaging of cerebral aneurysms, especially for those that are diminutive, <3 mm in size. As an invasive study, the DSA does entail procedural risks including cerebral infarction, aneurysmal rupture, arterial injury, contrast-related injury, and radiation injury. Risk is considered low, reported to be approximately 0.07% following DSA in a cohort of patients with cerebral aneurysms and arteriovenous malformations.[32]

CTA has a high sensitivity for detecting cerebral aneurysms, ranging from 95 to 100%, but dropping to as low as 82% for smaller aneurysms (<3 mm).[33] CTA can also identify mural calcification and thrombus which can inform management of the aneurysm. However, reconstructed CTA images may not accurately display the aneurysm of neck, dome, or adjacent small vessel anatomy, which are important to ascertain before aneurysm repair.[34] Furthermore, image artifact from bone and metal obscuring the demonstration of vessels can significantly reduce the value of CTA imaging used in follow-up after aneurysm repair.[35] ►**Fig. 2** demonstrates an example of CTA image artifact that can reduce diagnostic utility.

MRA uses either time-of-flight (TOF) or contrast methods for detection of cerebral aneurysms, although it is unclear which method is more useful. Overall, the sensitivity of MRA for detecting cerebral aneurysms is 74 to 98%, with higher sensitivity associated with aneurysms >3 mm.[36] Although MRA can also be prone to susceptibility artifact from the skull base and metal implants, contrast-enhanced MRA appears to have high sensitivity (92%) and specificity (96%) for residual or recurrent aneurysm detection compared with
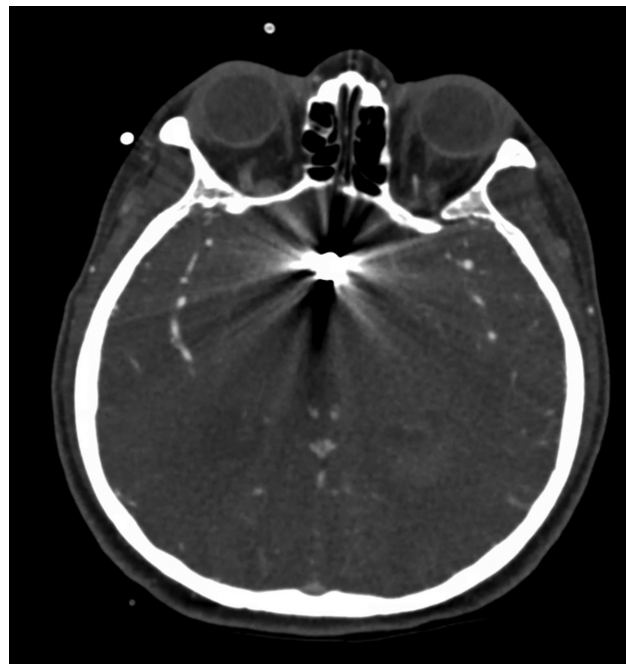

Fig. 2 CTA image artifact from aneurysm coil. Example of coil artifact on CTA, from a patient following anterior communicating artery aneurysm coiling. In this case, image artifact impaired ability to assess for focal vasospasm. CTA, computed tomography angiography.

DSA, although the size of any recurrent aneurysm may be underestimated.[37] Overall, the lack of ionizing radiation and contrast exposure (with TOF MRA) makes it a superior choice for patients in which radiation exposure risks and renal impairment are relevant concerns.

High-resolution vessel wall imaging (HR-VWI) has gained attention as a modality for identifying unstable aneurysms at high risk for potential rupture; however, it has not yet been validated for clinical use.[38,39] In this technique, MR technology is utilized in combination with contrast administration, and the degree of enhancement of the aneurysm wall is then visualized. One study showed that HR-VWI wall enhancement was associated with larger aneurysm size (>7 mm), and localization to the anterior cerebral, posterior communicating, and posterior circulation.[40] However, data from computational flow dynamics studies have suggested that increased turbulent flow within larger or irregular aneurysms might produce contrast stagnation and a pseudo-enhancement effect.[41] There is no standard accepted definition or grading scale for contrast enhancement, and a consistent histological correlation to aneurysm enhancement has not been observed, which has so far limited wider adoption of this modality for the management of unruptured intracranial aneurysms.

Conservative Management

In patients considered to be at low risk for cerebral aneurysm rupture (e.g., size <5 mm, asymptomatic, and without other risk factors), conservative management with serial noninvasive imaging is reasonable.[42] The optimal interval and duration of obtaining follow-up imaging is uncertain; however,

serial MRA every 1 to 2 years (depending on patient and aneurysm factors) is commonly used.[18,43] In older patients with a limited life expectancy or patients with other comorbidities in whom treatment risk may outweigh benefits, repeat imaging may be deemed unnecessary as it may not change management unless new symptoms arise.

Patients often have anxiety related to their diagnosed cerebral aneurysms, and proper patient education and counseling is an important part of their care. Education regarding symptoms to monitor for (sudden-onset severe headache, cranial nerve palsies) as well as reassurance for long-term follow-up are essential. For anxious patients, it may be useful to describe the aneurysmal rupture risk in terms of the likelihood of nonrupture to help with reassurance. Patients who are taking antithrombotics (antiplatelets and anticoagulants) for other indications should generally be advised to continue their medications, as the risk of an ischemic event is generally higher than the risk of aneurysm rupture for an asymptomatic intracranial aneurysm with low-risk features.[44] Antithrombotic medications are not known to cause aneurysm rupture, but can impair coagulation mechanisms in the event of a rupture. Furthermore, general anesthesia appears safe for patients with unruptured intracranial aneurysms, with one retrospective study reporting 0 cases of subarachnoid hemorrhage in a patient sample of 134 unsecured aneurysms and 208 inductions over a 5.7-year follow-up period.[45]

Medical Treatments

Currently there is no strong evidence to support the routine use of medications as prophylaxis for aneurysm formation or rupture. The role of anti-inflammatory medications in the prevention of growth and rupture of cerebral aneurysms has been hypothesized; however, there is a lack of prospective data to inform specific recommendations.

In animal models, treatment with aspirin and genetic inactivation of cyclooxygenase-2 decreased aneurysm formation and rupture, whereas selective inhibition of cyclooxygenase-1 did not decrease aneurysm rupture.[46,47] In ISUIA, patients who used aspirin three times weekly to daily were noted to have lower odds of hemorrhage compared with aspirin-naïve patients. Furthermore, in patients with cerebral aneurysms, patients taking aspirin were noted to have lower rates of aneurysmal subarachnoid hemorrhage.[48] The PROTECT-U (Acetylsalicylic Acid plus Intensive Blood Pressure Treatment in Patients with Unruptured intracranial aneurysms, NCT03063541) trial is an ongoing randomized trial testing whether aspirin plus intensive blood pressure management (<120 mm Hg) reduces risk of aneurysm growth or rupture compared with standard care.

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have also been proposed as anti-inflammatory agents with the potential to reduce cerebral aneurysm growth and rupture.[49] Statins can reduce inflammation of the vessel wall and mobilize endothelial progenitor cells for possible aneurysm wall repair, and have also been shown to inhibit expression of matrix metalloproteinases by smooth muscle cells and macrophages. Retrospective reviews have shown that the use of statins is inversely associated with risk of cerebral aneurysm rupture.[50] One completed open-label, randomized controlled trial compared treatment with atorvastatin versus no statin on the risk of small (3–5 mm) cerebral aneurysm growth and rupture (as measured by >0.5 mm growth on MRA, new bleb formation on MRA, and rupture); 231 patients with 275 intracranial aneurysms were enrolled and randomly assigned to 10 mg daily atorvastatin or control. There was no statistically significant difference between the two treatment groups, but the study was ended prematurely due to slow enrollment.[51]

Management of hypertension is recommended for reduction of aneurysm rupture risk. While there is no prospective randomized controlled trial data yet available, one prospective study included 272 patients with unruptured intracranial aneurysms, and found that patients with uncontrolled hypertension, in comparison to nonhypertensive patients, had a high hazard ratio for aneurysm growth (6.1, 95% confidence interval [CI]: 2.4–15.4), compared with controlled hypertensive patients (1.6, 95% CI: 0.6–3.8).[52] Another study found that, in comparison to nonhypertensive patients, uncontrolled hypertension patients had a hazard ratio for aneurysm rupture of 16.7 (95% CI: 2.1–132.1) and controlled hypertension patients had a hazard ratio of 3.5 (95% CI: 0.3–38.5).[53]

Counseling for cigarette smoking cessation is also advised for patients with unruptured intracranial aneurysms, even though there are no randomized controlled trial data to support this recommendation. One small observational study found that in smokers who had unruptured intracranial aneurysms, patients who continued to smoke had a 41% rate of rupture (14/34) compared with 0% (0/11) of those who stopped smoking.[54]

Safety of Endovascular Treatments

Treatment of cerebral aneurysms involves consideration of open surgical as well endovascular approaches. Aneurysm clipping was first reported by Walter Dandy in 1938 and continues to be used as a treatment option for cerebral aneurysms.[55]

Coil Embolization

Endovascular coil embolization of intracranial aneurysms was first reported in 1990 to 1991 by Guido Guglielmi using detachable platinum microcoils.[56] Since then, numerous advances in technology have allowed for efficacious endovascular treatment of complex intracranial aneurysms. Coil embolization involves deployment of an initial framing coil into the dome of the aneurysm under fluoroscopic guidance. Following this, additional filling coils of various softness and configuration are deployed in succession until angiographic evidence of satisfactory occlusion is achieved.

In the mid-2000s, ISAT (International Subarachnoid Aneurysm Trial) reported results of a randomized trial comparing 2,143 ruptured cerebral aneurysm patients amenable to treatment with either endovascular coiling or surgical

clipping. The results showed that patients treated with endovascular coiling had better clinical outcomes at 1-year follow-up.[57,58] In 2015, the final ISAT results, after a follow-up period of 10 to 18 years, reported that patients treated with endovascular coiling were more likely to be alive and independent at 10 years.[59]

In the prospective phase of ISUIA, 1,917 patients underwent surgical clipping, and 451 underwent coil embolization of their aneurysms. The combined surgical morbidity and mortality at 1 year was 10.1% for patients without previous subarachnoid hemorrhage and 12.6% for patients with previous subarachnoid hemorrhage, compared with 7.1 and 9.8% respectively for patients who underwent coil embolization. Moreover, endovascular treatment in patients >50 years old appeared safer than clipping, although the result was not statistically significant.[10] However, the endovascular group was relatively small in comparison to the surgical group, limiting the ability to make comparisons.

Further data on the safety of unruptured intracranial aneurysm treatment with endovascular coil embolization are reported in the ATENA (Analysis of Treatment by Endovascular Approach of Non-ruptured Aneurysms) study; 649 patients with 1,100 unruptured aneurysms were prospectively treated at centers in France and Canada. The overall rate of treatment-associated adverse events, including thromboembolism, was 15.4%. Intraprocedural rupture occurred in 2.6%, of which 50% were asymptomatic and 16.7% were fatal. Complications attributed to thromboembolic events occurred in 5.4%, were permanent in 2.6%, and led to death in 0.9%. However, for patients with a preprocedure modified Rankin Scale (mRS) of 0, 96% had postprocedure mRS of 0, 3.4% had postprocedure mRS of 1, 0.4% had postprocedure mRS of 2, and 0.2% had postprocedure mRS of 3.[60] This suggests complications were more common in patients with pre-existing morbidities.

Additionally, retrospective studies have shown that patients treated with endovascular therapy have fewer adverse outcomes at the time of discharge, decreased mortality, decreased hospital length of stay, and decreased hospital charges.[61–63] Patients over age 50 treated with endovascular therapy appear to have decreased morbidity and mortality compared with those treated with surgical clipping.[64,65]

Efficacy of Endovascular Coiling Treatments

In addition to safety, the durability of aneurysm occlusion with coil embolization is an important consideration, as well as techniques to improve the likelihood of effective endovascular obliteration. In ISAT, aneurysm recanalization was associated with recurrent subarachnoid hemorrhage, although still a relatively low risk (10 episodes after 1 year in 1,073 patients).[57,58]

Additional data on the efficacy of endovascular therapy versus surgical clipping can be found in studies on patients with ruptured intracranial aneurysms. The Barrow Ruptured Aneurysm Trial (BRAT) was a randomized trial including 408 patients with aneurysmal subarachnoid hemorrhage; patients were randomized to a surgical clipping arm and

an endovascular coiling arm. It found no significant difference in the proportion of patients with an mRS >2 (lack of functional independence) in the two treatment arms. However, in a subsection of patients with ruptured posterior circulation aneurysms, outcomes favored patients treated with endovascular coiling, although higher rates of complete obliteration and rate of retreatment at 6 years favored the surgical treatment group.[66]

The Cerebral Aneurysm Rerupture After Treatment (CARAT) study was an ambidirectional cohort study of patients with ruptured intracranial aneurysms treated with coil embolization or surgical clipping at 9 high volume centers in the United States between 1996 and 1998. The study showed that the degree of aneurysm occlusion after treatment correlated with risk of rerupture, and that while there was a tendency for greater risk of rerupture after coil embolization (3.4 vs. 1.3% for surgical clipping, $p = 0.092$), the difference did not persist after adjustment for confounders ($p = 0.83$).[67]

Balloon-Assisted Remodeling

To achieve better aneurysm occlusion, methods such as balloon-assisted remodeling and stent-assisted occlusion have been reported. Balloon-assisted remodeling was initially described by Moret et al and is used to treat board-neck aneurysms (>4 mm) by inflating and deflating a small balloon microcatheter across the aneurysm neck. This provides temporary support for coils, which are then deployed through a second microcatheter placed into the aneurysm sac. ►Fig. 3 demonstrates balloon-assisted coil embolization of an anterior communicating artery aneurysm.

Moret et al reported complete angiographic occlusion in 20 of 21 broad-necked cerebral aneurysms treated via this method with complication rates comparable to primary coil embolization.[68] Similar results were reported in the ATENA study for patients who underwent balloon-assisted remodeling.[60] An additional advantage of this method for the treatment of wide-neck aneurysms in the acute phase is that it can be performed without the need for antiplatelet therapy, typically necessary to prevent thrombosis in stent-assisted coiling or flow diversion techniques. Furthermore, in the event of intraprocedural rupture, rapid hemostasis can be achieved by inflation of the balloon in the parent vessel to prevent blood from entering the aneurysm while coil embolization of the aneurysm is performed with a second microcatheter. In one case series of patients with intraprocedural aneurysm rupture, those treated with a hemostatic balloon had better clinical outcomes than those who did not.[69]

Stent-Assisted Coiling

Stent-assisted coil embolization involves the deployment of a nitinol (metal alloy of nickel and titanium) self-expanding stent across the aneurysm neck and placing the coiling microcatheter into the aneurysm sac through the stent interstices. Useful for cases of broad-neck or bifurcation aneurysms, it is typically reserved for treatment of
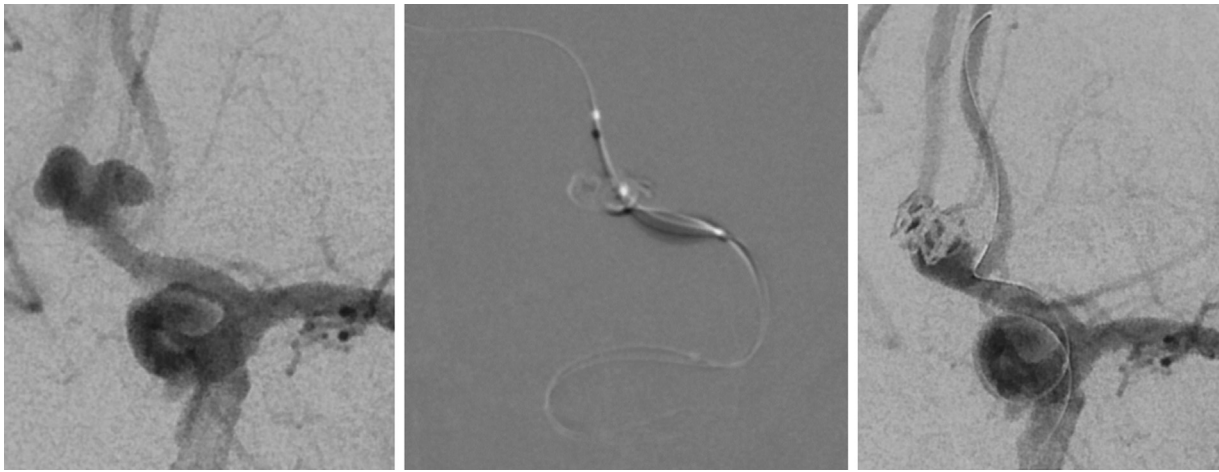
Fig. 3 Balloon-assisted remodeling Left: bilobed, wide-neck (4.7 mm) left anterior cerebral artery aneurysm demonstrated by DSA. Middle: inflation of the balloon to assist with coil embolization of anterior communicating artery. Right: left anterior cerebral artery aneurysm post balloon-assisted coil embolization, with near-complete occlusion. DSA, digital subtraction angiography.
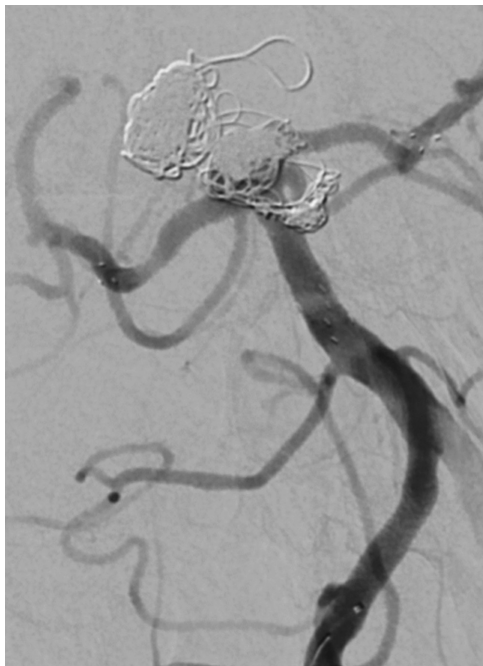

Fig. 4 Y-stent of basilar tip aneurysm. Digitally subtracted angiography (DSA) run of the right vertebral artery, following Y-stent-assisted coil embolization of a wide-neck basilar tip aneurysm.

unruptured aneurysms due to the requirement for dual antiplatelet therapy following stent placement. Single-center retrospective studies have reported increased rates of progressive aneurysm occlusion with stent-assisted coiling[70]; however, stent use in the Hydrocoil and Endovascular Aneurysm Occlusion and Packing (HELPS) trial did not show greater rates of aneurysm occlusion compared with primary coiling.[71] More recently, the Stent-Assisted Coiling in the Treatment of Unruptured Intracranial Aneurysms (STAT) randomized controlled trial reported interim data which showed no significant benefit of stent-assisted coiling over primary coiling for large, wide-neck, or recurrent aneurysms.[72]

"Y-stenting" is a technique sometimes employed to treat wide-neck bifurcation aneurysms, where two stents are placed at the bifurcation to provide support.[73] ►**Fig. 4** provides an example of a wide-neck basilar tip aneurysm that was treated with Y-stent-assisted coil embolization. The deployment of the second stent is performed through the interstices of the first stent, which can be technically challenging and overall involves a significant amount of implanted metal. As an alternative, the PulseRider device (Pulsar Vascular, Los Gatos, California) is a self-expanding nitinol implant that has been used to treat patients with wide-neck aneurysms at the carotid terminus or basilar tip, with less implanted metal. The study reported immediate occlusion rates of 82.4%, rising to 87.9% at 6-month follow-up, and 94% of patients having mRS of 2 or less at 6 months.[74]

Flow Diversion

Low-porosity stents divert blood flow away from an aneurysm while providing a scaffold for neointima to grow across the neck of an aneurysm. These flow-diverting devices are a newer technology aimed at achieving better aneurysm occlusion rates, especially for broad-neck aneurysms. The Pipeline Embolization Device (Medtronic, Minneapolis, Minnesota) was used successfully in the Pipeline for Uncoilable or Failed Aneurysms (PUFS) trial,[75] and led to Food and Drug Administration (FDA) approval for a specific segment of broad-neck aneurysms, although the current high rate of use in the United States suggests application beyond the FDA indication. ►**Fig. 5** shows an example of an ophthalmic internal carotid artery aneurysm treated with Pipeline embolization. Similar to conventional stents, dual antiplatelet therapy is required for maintenance of patency of the flow diversion device. Some proposed off-label uses of flow diversion techniques as treatment include distal aneurysms, bifurcation aneurysms, small aneurysms, and recurrent aneurysms.[76]
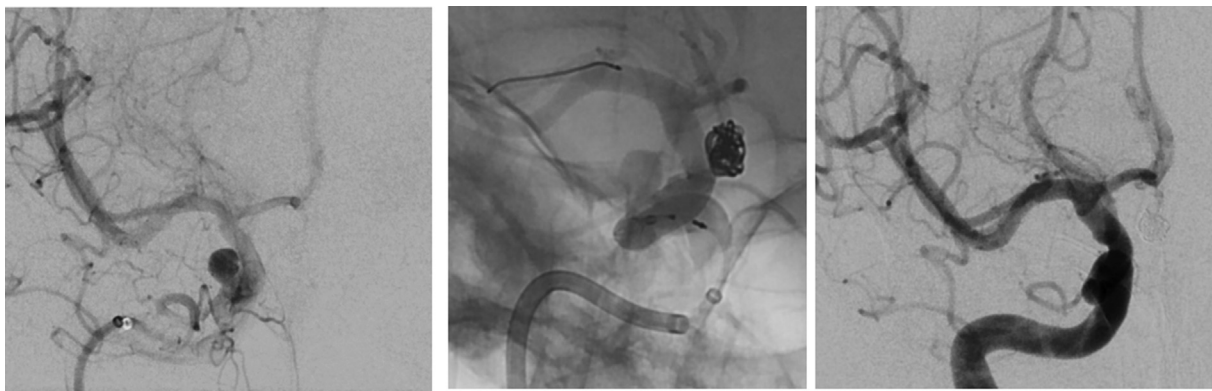
Fig. 5 Pipeline flow diversion for right ophthalmic ICA aneurysm embolization. Left: contrast stasis in the right ophthalmic ICA aneurysm following placement of the Pipeline embolization device. Middle: unsubtracted image showing deployment of Pipeline across right ICA aneurysm. A coil mass from a previously coiled right ICA aneurysm is also visible. Right: complete occlusion of the aneurysm at 6 month follow-up; of note, patient in this case also had previous coil embolization of an anterior communicating artery aneurysm. ICA, internal carotid artery.

Newer flow diversion devices are aiming to treat smaller aneurysms and improve useability. As one example, Flow Direction Endoluminal Device (FRED, MicroVention, Aliso Viejo, California) is a low-profile flow diversion device that can be delivered through a small 0.021-inch microcatheter (compared with a 0.027-inch microcatheter required for Pipeline).[77] During the deployment of a Pipeline device, the operator must use care to avoid perforation of small, distal branches with the inner wire as it is pushed forward while unsheathing the device. The smaller FRED device has a wire that remains within the stent during deployment, minimizing the risk of vessel perforation.[76]

Intrasaccular Devices

Intrasaccular flow disruptor devices have also been developed as treatment for wide-neck bifurcation aneurysm treatment. Common locations for these aneurysms include bifurcations of the middle cerebral artery, basilar artery, and/or anterior communicating artery. The Woven EndoBridge Intrasaccular Therapy (WEB-IT) study was a prospective study that evaluat-ed the safety of the WEB device for wide-neck bifurcation aneurysms. A total of 148 patients were treated with the WEB device and only 1 patient developed delayed parenchymal hemorrhage at 3 weeks after treatment. No primary safety events were reported between 30 days and 1 year follow-up, and adequate occlusion was reported in 85% of patients at 1-year follow-up.[78] Pretreatment with dual antiplatelet therapy is often used in anticipation of possible need for an adjunctive stent, although there is no requirement for antiplatelet therapy maintenance.[79,80] Nevertheless, many patients are often maintained on low-dose aspirin. ►**Fig. 6** shows an example of a patient with a wide-neck basilar tip aneurysm treated with the WEB intrasaccular device.

The Contour neurovascular device (Cerus, Fremont, California) is another intrasaccular flow disruptor device, consisting of a circular dual-layered structure of nitinol wires. In the CERUS study, the Contour device was implanted successfully into 32 of 34 wide-neck aneurysms, with reported adequate occlusion rates of 10, 77, and 90% at 0, 6, and 12 months, respectively. At 12-month follow-up, 30 of 32 patients who underwent device implant remained at mRS of 0.[81]

Fig. 6 WEB intrasaccular device. Left: wide-neck basilar tip aneurysm. Middle: contrast stasis in aneurysm following WEB placement. Right: complete occlusion. WEB, Woven EndoBridge.

Post-procedure Follow-Up

Follow-up after endovascular treatment with serial imaging is recommended, although the interval for imaging follow-up can vary with factors such as initial aneurysm size, presence of untreated aneurysms, and success of initial embolization treatment.[82] Factors associated with an increased risk of aneurysm recurrence following endovascular coiling include wide-neck aneurysms (>4 mm), large aneurysms (>10 mm), aneurysms in previously ruptured state, younger age, and incomplete aneurysm occlusion at the time of treatment.[83–85] Contrast-enhanced MRA has been shown to have high sensitivity and specificity for detection of residual or recurrent aneurysm compared with DSA, although DSA may be utilized when patient- or aneurysm-specific factors do not permit adequate imaging with MRA or when planning for re-treatment.[37,86,87] For practical purposes, many clinicians now utilize TOF MRA without contrast for surveillance imaging, as it often provides sufficient information to detect changes in aneurysm size or recurrence, and helps inform treatment decisions in most patients while minimizing risks related to radiation and contrast exposure.

Conclusion

The treatment of unruptured intracranial aneurysms has evolved over time, incorporating an increased understanding of the natural history and pathophysiology of aneurysm formation with technological advances in treatment options. Management of medical risk factors including hypertension and smoking cessation is important to mitigate arteriopathy, although a prophylactic medication for preventing aneurysm growth and rupture has remained elusive. Symptomatic unruptured aneurysms, large aneurysms, and growing aneurysms are considered higher risk for rupture and hemorrhage. When aneurysm treatment is considered, endovascular therapy appears to be safe and effective in comparison to surgical clipping, with a tendency toward decreased morbidity and mortality in older patients. This has led to greater utilization of endovascular therapy for aneurysm repair over time. Newer devices used in endovascular therapy have enabled more effective treatment for complex aneurysms, including wide-neck bifurcation aneurysms and small or distal aneurysms.

Conflict of Interest
None declared.

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