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Review

Treatment of unruptured intracranial aneurysms: a review

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Abstract

Introduction: Unruptured brain aneurysms (UIAs) present a challenge due to the lack of definitive understanding of their natural history and treatment outcomes. As the treatment of UIAs is aimed at preventing the possibility of rupture, the immediate risk of treatment must be weighed against the risk of rupture in the future. As such, treatment for a large proportion of UIAs is currently individualized.

Areas covered: In this article, we discuss the important natural history studies of UIAs and discuss the existing scientific evidence and recent advances that help identify the rupture risk guide management of UIAs. We also address the recent advances in pharmacological therapy of UIAs.

Expert Commentary: In the recent years, there have been great advances in understanding the pathophysiology of UIAs and determining the rupture risk going beyond the traditional parameter of aneurysm size. Aneurysm morphology and hemodynamics play a pivotal role in growth and rupture. A true randomized trial for the management of UIAs is the need of the hour.

Keywords: unruptured, intracranial aneurysm, rupture, natural history, pharmacology, neuroendovascular, neurointerventional

1.0 Introduction

Incidentally discovered unruptured brain aneurysms (UIAs) are common[1]; but their management remains one of the most controversial topics in cerebrovascular medicine. There have been a number of empiric studies to evaluate the natural history of UIAs and, recently, the focus has shifted to characterizing the risk of rupture based on morphological and hemodynamic characteristics of UIAs. Over the last three decades, there have been significant advances in neurosurgical and neurointerventional treatment techniques, increasing their safety and efficacy to occlude complex shaped UIAs. However, due to the lack of prospective randomized clinical trials on the available treatments for UIA's, consensus regarding their evaluation and management is lacking. It is all the more relevant now to be able to clearly define the hemorrhage risk of an unruptured aneurysm and weigh it against the risk of available therapies.

In this review, we discuss the current state of knowledge regarding unruptured brain aneurysms and their management.

2.0 Epidemiology and Natural history of UIAs

The prevalence of UIAs has been variously cited between 1% and 6% in general population.[2–8] Studies have reported varying rates of prevalence of intracranial aneurysms in different ethnic populations. The prevalence was 1.8% of adults in a European population based study, 7% in a Chinese study and 1.9% in a Norwegian study.[9] About 85% are located in the anterior circulation, the common sites being the internal carotid artery, the anterior communicating artery, the middle cerebral artery bifurcation, and the posterior communicating artery and ophthalmic artery origins. In the posterior circulation, the common locations include basilar artery bifurcation and the origin of posterior inferior cerebellar artery. UIAs occur about three times more often in women than in men. Studies have reported varying rates of prevalence of intracranial aneurysms in different ethnic populations. The prevalence was 1.8% of adults in a European population based study, 7% in a Chinese study and 1.9% in a Norwegian study.[9]

In a large systematic review of over 56,000 patients, the prevalence of UIAs in adults

without specific risk factors was 2.3% and tended to increase with age. The prevalence was higher in patients with autosomal dominant polycystic kidney disease (relative risk [RR] 4.4), familial predisposition (RR 4.0) and history of atherosclerosis (RR 2.3).[10] The prevalence of UIAs in Finland and Japan is similar to that in other countries but they have higher risk of rupture than in other Western counties.[11–13,1]

Several multicenter studies for UIAs have shed light on their natural history. The International Study of Unruptured Intracranial Aneurysms (ISUIA) is a multicenter study of natural history of UIAs. The study had two arms. In the retrospective arm patients were divided into 2 groups, first group consisting of patients without history of subarachnoid hemorrhage (SAH) (n=727) and second group of patients with history of SAH (n=722). The mean follow-up duration was 8.3 years. For Group 1, the 5-year cumulative rate of SAH for aneurysms <10 mm was 0.05%, whereas that for aneurysms ≥10 mm was approximately 1%/year. For Group 2, the 5-year cumulative SAH rate was 0.5% for aneurysms <10 mm and 1% for aneurysms ≥10 mm. Aneurysms in the posterior circulation and internal carotid-posterior communicating artery (Relative Risk, RR 2.1) had a higher risk of rupture in Group 1 whereas increasing age and basilar bifurcation location (RR 2.3) were risk factors for higher risk of rupture in Group 2.[14]

In the prospective arm, the patients were divided into the same two groups. Group I consisted of 1077 patients without a previous SAH and Group II had 615 patients with a history of SAH. All aneurysms were confirmed with angiography and followed for 14.1 years. The annual rate of rupture during 5-year follow-up period in internal carotid artery, middle cerebral artery, anterior cerebral artery and anterior communicating artery (anterior circulation) for aneurysm less then 7mm, 7-12mm, 13-24mm and 25 mm or greater was noted to be 0%, 0.5%, 2.9% and 8% respectively. On the other hand rate of rupture for aneurysms of the same sizes located in the internal carotid-posterior communicating artery and posterior circulation were noted to be 0.5%, 2.9%, 3.7%, and 10% respectively[15]. The major limitation of the study was in regard to patient selection. For the retrospective cohort, all patients receiving treatment within 30 days of diagnosis were excluded, and the number of these patients was not known. These

aneurysms likely comprised the highest risk group as judged by treating clinicians. Aneurysms in low-risk locations, such as the cavernous segment of the internal carotid artery, were over-represented in this study. Data from thirty-six patients who had both an aneurysm and another potential source of SAH were not included in the primary analysis of endpoints. Also, in the ISUIA study, many patients were enrolled if they were deemed extremely low risk of rupture or high risk of treatment or both.

One of the other large prospective studies of natural history of UIAs comes from the Japanese cohort of 5720 subjects with 6697 aneurysms, Unruptured Cerebral Aneurysm Study (UCAS). Majority of aneurysms were either in middle cerebral artery (36%) or the internal carotid artery (34%). The mean size of aneurysms was 5.7±3.6 mm. During the follow-up period of 11,660 aneurysm-years, the authors reported an annual rupture rate of 0.95% [CI, 0.79 -1.15]. Aneurysms that were 5–6 mm in maximum diameter were not at higher risk of rupture than those with a maximum diameter of 3–4 mm, but the risk was increased for aneurysms that were ≥7mm in diameter. The hazard ratios for size categories, compared with the aneurysms with a diameter of 3–4 mm, were as follows: 5–6 mm, 1·13 (95% CI 0·58–2·22); 7–9 mm, 3·35 (1·87–6·00); 10–24 mm, 9·09 (5·25–15·74); and 25 mm or greater, 76·26 (32·76–177·54). They also observed that aneurysms in anterior communicating, internal carotid-posterior communicating arteries and those with daughter sac were more likely to rupture when compared to those located in the middle cerebral artery or those without a daughter sac respectively.[16]. One of the major limitations of this study was the selection bias as not all patients that were eligible were enrolled. Also in the UCAS, approximately 50% of patients were treated and removed from the study during the follow up time.

There are some differences in the risk of rupture in UIAs between the ISUIA and UCAS. In ISUIA study risk of rupture in the posterior circulation is higher than that in the anterior circulation, whereas in UCAS study UIAs in the posterior circulation are similar risk of rupture to that in the anterior circulation except for UIAs in the internal carotid-posterior communicating artery. For less than 7mm UIAs in the anterior circulation, in

ISUIA study risk of rupture is very low. However in UCAS study UIAs in the anterior communicating artery are as high as that in the internal carotid-posterior communicating artery. And in former studies, history of subarachnoid hemorrhage and smoking, multiple aneurysms, hypertension are thought to be risk factors, however in UCAS study they are not.

In a study by Juvela et al followed up 142 patients with 181 intracranial aneurysms for the rest of their lives. The median follow-up period was 21 years. The annual incidence of rupture in this cohort of patients was 1.1%. Cigarette smoking, patient age, and the size and location of the aneurysm emerged as the risk factors for aneurysm rupture.[17] However, there are some limitations of the study. Patients were enrolled at a time when there was no coiling and many aneurysms were untreated. Moreover, the patients were younger than in the other studies and mostly had multiple aneurysms, with the ruptured aneurysm clipped at the start of the follow-up

Other studies of UIA's show that small aneurysms are not always safe as to a risk of rupture. Kassell et al reported that 13% of 1092 ruptured brain aneurysm cases in North America are less than 5mm.[18] Ishibashi et al noticed that small aneurysms less than 5mm with a history of SAH have 5.5 times higher risk of rupture than those without SAH history.[19] The Small Unruptured Intracranial Aneurysm Verification Study (SUAVe) from Japan is presenting some information about aneurysms smaller than 5mm.[20] 448 aneurysms (374 cases) smaller than 5mm had been followed-up for 42.5 months in average. In this study, UIAs smaller than 4mm were 70.8%. During the follow-up period, 7 aneurysms were ruptured and overall rupture rate was 0.54%/year. 30 aneurysms (25 cases) showed aneurysmal growth more than 2mm, and significant predictive factors for rupture were patient <50 years of age, aneurysm diameter of ≥4.0mm, hypertension, and aneurysm multiplicity.

A recent retrospective study followed 140 patients for 21 years and reported a rate of rupture around 1.1%/year. Aneurysm diameter >7 mm (P=0.028), current cigarette smoking (P=.024) and heavy alcohol consumption (P=.043) were significantly

associated with the higher aneurysmal rupture rate[17]. The mean diameter of aneurysms that ruptured during follow-up was 5.6mm as compared to 4.9mm in the group of patients in whom the aneurysms did not rupture.

Table 1 lists the important studies describing the natural history of UIAs.

3.0 Identifying the risk of rupture of UIAs

Rupture of brain aneurysms will cause intracranial hemorrhage, including subarachnoid hemorrhage. These hemorrhages can be life-threatening in many cases. In a meta-analysis that covered 39 studies from 1972 to 2003 showed case fatality varied from 8.3% to 66.7% between studies. [A] The fatality rate decreased by 0.8% per year (95% CI 0.2 to 1.3), 23% decrease over the 30 years. Nevertheless, we still have mean case fatality between 20-50% recently. Thus we need to identify the risk of rupture of UIAs.

While the rupture risk in a particular subset of patients may be very small and subjecting these patients to any treatment (surgical or endovascular) may put them at a higher risk of complications than would be with natural history. At the same time, another subset of patients may be at a higher risk of aneurysm rupture and intervention rather than watchful waiting may be warranted. The factors determining the rupture risk of unruptured aneurysms and not completely known. A number of clinical, morphological, hemodynamic and genetic characteristics have been studied. In this section we discuss the putative factors that have a role in influencing rupture risk of cerebral aneurysms and should be taken into consideration while individualizing therapy

3.1 Patient characteristics

Race, age, gender, hypertension, smoking, prior history of subarachnoid hemorrhage (SAH) and multiplicity of aneurysms in a patient, have all been proposed to influence the risk of rupture. It is suggested that Finnish have 3-6 times and the Japanese have 2-6 times increased risk of aneurysm rupture than North Americans and Europeans countries other than Finland.[15,16] This difference spans across UIAs of all sizes. In

the International Study of Unruptured Intracranial Aneurysms (ISUIA) which involved predominantly Caucasian patients, the 5-year cumulative rupture risk in patients with anterior circulation aneurysms less than 7mm in size and without a prior history of SAH was 0%.[15] Whereas, the annual rate of rupture in the UCAS study, which was performed in a Japanese cohort, was between 0.23% and 1% for anterior circulation aneurysms[16].

Increasing age elevates the rupture risk in an unruptured aneurysm. In a cumulative analysis of 8382 patients with 10,272 unruptured aneurysms from six cohort studies from North America and Europe, only 12% of patients with ruptured and 5% with unruptured aneurysms were under 40 years of age. The 5-year predicted absolute risk of rupture ranged from 0.25% in individuals younger than 70 years without vascular risk factors and with an internal carotid artery aneurysm <7mm size to about 15% in patients ≥ 70 years with hypertension, a history of SAH and a >20mm posterior circulation aneurysm.[21] In a meta-analysis, patients >60 years had two times the rupture risk of those under 60 years age.[11]

With regards to UIA multiplicity, in the Small Unruptured Intracranial Aneurysm Verification Study (SUAVe), the annual rupture risk of single aneurysm <5mm diameter was 0.34%/year and that of multiple aneurysms was 0.95%/year with an overall rate of 0.54%/year[20].

More than two-thirds of all intracranial aneurysms occur in women. Among women, over half aneurysms are located in the ICA (54%) while anterior cerebral artery (ACA) is the most common location in men (29%). In a Finnish study, unruptured sporadic aneurysms were most frequent at the middle cerebral artery (MCA) bifurcation (44% vs 39%) and the anterior communicating artery (12% vs 13%), in contrast to the ruptured sporadic aneurysms that occurred at the anterior communicating artery (37% vs 29%) and MCA bifurcation (29% vs 29%). [22] Females also tend to present later in life, with multiple aneurysms and with SAH.[23] The reason for most females presenting with ruptured aneurysms later in life may be linked to the protective effect of estrogen through the activation of estrogen receptor-β.[24]

About 85% are located in the anterior circulation, the common sites being the internal carotid artery, the anterior communicating artery, the middle cerebral artery bifurcation, and the posterior communicating artery and ophthalmic artery origins. In the posterior circulation, the common locations include basilar artery bifurcation and the origin of posterior inferior cerebellar artery.[8] In a meta-analysis study showed that the most common sites were internal carotid artery (ICA) including posterior communicating artery (42%) and middle cerebral artery (MCA; 35%), followed by anterior cerebral artery (18%).[13] In a Finnish study, unruptured sporadic aneurysms were most frequent at the MCA bifurcation (39%) followed by ICA (26%) and the anterior communicating artery (13%), in contrast to the ruptured sporadic aneurysms that occurred at the anterior communicating artery (29%), MCA bifurcation (29%) and ICA (22%). [22]

Hypertension and cigarette smoking have long been recognized as risk factors for aneurysm rupture. Presence of hypertension alone increases the risk of rupture three-fold even in small aneurysms less than 7mm.[25] It has been demonstrated that cigarette smoking increases wall shear stress at the site of aneurysm initiation. It also promotes aneurysm growth and increases the rupture risk simultaneously by acting as a catalyst in a complex interplay of hemodynamic stress, vascular inflammation and cerebral aneurysm formation.[26] Meta-analysis also showed that relative risk of SAH associated with smoking was 2.93 (95% CI; 2.48 - 3.46).[27]

Connective tissue diseases are thought to be related to aneurysmal formation and its rupture[28], but there is no randomized, multicenter trial. In the UCAS, there is no relationship between Polycystic kidney disease and aneurysmal rupture [16].

Prior history of SAH and the presence of multiple aneurysms have been shown increase the risk of subsequent SAH in two Japanese studies. However, this effect has not been uniform across other studies.[19,20] In the study by Juvela et al, prior SAH was inversely associated with the rupture risk of UIAs whereas in the ISUIA study, patients with a prior history of SAH had a higher risk of rupture than those without.[15,17]

3.2 Morphological characteristics

A number of morphological indices have been proposed to correlate and predict the rupture risk. The most powerful predictor is aneurysm size. The ISUIA demonstrated that aneurysms less than 10mm have a very low risk of rupture and the 5-year cumulative rupture rate of aneurysms less than 7mm was between 0 and 2.5%, 2.6%-14.5% for aneurysms 7-12mm, 14.5%-18.4% for aneurysms 12-24mm and 40%-50% for aneurysms larger than 25mm size.[14,15] However, Finnish and Japanese studies revealed 1.3%-2.3% risk of rupture even in patients with less than 7mm size.[17,29,30]

Aneurysmal growth has been also thought to be a risk for rupture of brain aneurysms. In SUAVe study, 25 out of 374 (6.7%) patients had aneurysmal enlargement, and significant factors for this were female patients, aneurysm diameter of ≥4.0mm, smoking, and aneurysm multiplicity. And although the sizes of aneurysms were not changed during follow-up, 4 out of 7 ruptured aneurysm cases showed aneurysmal enlargement at the time of rupture in this study.

Aneurysms with daughter sacs and wall irregularity have also been reported to have a higher rupture risk.[16,31–34] In UCAS, aneurysms with a daughter sac were likely to rupture with hazard ratio of 1.63 (95%, CI 1.08 to 2.48).

Aspect ratio (AR) is defined as the ratio of the maximum perpendicular height to the average neck diameter, where the average neck diameter was calculated as twice the average distance from the neck centroid to the edge of the neck.[35] Ruptured aneurysms have been reported to have a higher AR than unruptured aneurysms. Ujiie noted that a significantly higher proportion of unruptured aneurysms had AR <1.6.[36] Weir reported that the mean AR of unruptured and ruptured aneurysms was 1.8 and 3.4 respectively.[37] Other authors have variously reported the mean AR in ruptured aneurysms to be 2.24 and 2.7.[34,38]

Size ratio (SR) refers to the ratio of maximum aneurysm height to the average parent vessel diameter. The average parent vessel diameter is obtained by calculating the average of two vessel cross-sections upstream of the aneurysm. The maximum height is the maximum distance from the centroid of the aneurysm neck to any point on the

aneurysm dome.[35] A SR of >2 has been associated with large areas of low Wall Shear Stress (WSS) in the aneurysm that in turn predisposes to aneurysm growth and rupture[39].

Other more complex parameters such as Ellipticity Index, Nonsphericity Index, Undulation Index, vessel angle, aneurysm (inclination) angle, relationship among aneurysm neck, parent artery and daughter branches, daughter artery ratio and lateral angle ratio have been proposed to predict the risk of rupture in unruptured aneurysms but not yet established as such [34,35,40].

3.3 Hemodynamic parameters

Blood flow hemodynamics play a pivotal role in the initiation, growth and rupture of intracranial aneurysms. WSS is a dynamic frictional force induced by a blood moving along the vessel wall. Hassan et al. demonstrated that high wall shear stress (WSS) may be responsible for growth and rupture of high flow intracranial aneurysms whereas high intra-aneurysmal pressure and flow stasis are responsible for rupture in low-flow aneurysms.[41] Low WSS can affect vascular remodeling and induce apoptosis of endothelial cells resulting in vessel wall degeneration and aneurysm growth and rupture.[41–44] On the other hand, high WSS has been proposed to induce degradation of the internal elastic lamina resulting in aneurysm formation.[45] Another parameter is the oscillatory shear index (OSI) , which measures the directional change of WSS during a cardiac cycle in another study, WSS and OSI were the only independent hemodynamic parameters that were significantly different in ruptured and unruptured aneurysms.[46] We should note that these analysis about ruptured aneurysm is made based on the images of ruptured aneurysms, not those of pre-rupture aneurysms. Aneurysms may change its shape by rupture, for example due to perianeurysmal hematoma.[47] Takao et al analyzed pre-rupture aneurysmal images together with unruptured ones and found that there were no significant corelations between unruptured/ruptured aneurysms and WSS.[48]

Other proposed hemodynamic parameters under study for their role in aneurysm growth and rupture include Maximal intra-aneurysmal Wall Shear Stress (MWSS), Low WSS

area, WSS gradient (WSSG), Number of Vortices (NV) and Relative Resistance Time (RRT).[46]

Table 2 lists the factors affecting rupture of intracranial aneurysms

4.0 Decision making in the treatment of UIAs

Management of UIAs is challenging. The various issues in decision making in the management of UIAs include (1) Observation versus Treatment (2) Surgical Clipping vs Endovascular Therapy (3) Management of aneurysm remnants.

4.1 Observation versus Clipping/Endovascular therapy

With the increasing use of high-resolution neuroimaging techniques, more people with UIAs will be diagnosed each year and a clear understanding of the current literature is paramount to optimal treatment. Treatment of UIAs would be indicated when the risk of rupture from natural history is higher than the risk of treatment and follow-up. Not only does this imply that, despite guidelines, therapy should be individualized, but also the expertise of the individual center should be taken into consideration. The risk of treatment at a center varies depending upon the cerebrovascular expertise of the neurosurgeons, neurointerventionists. Also, while there is some consensus that treatment should be offered in patients with aneurysms with known high rupture risk features such as female sex, young age, maximum size ≥ 7mm, basilar bifurcation location, internal carotid-posterior communicating artery and possibly anterior communicating artery, past history of subarachnoid hemorrhage, Finnish and Japanese descent, smoking and hypertension, management of small aneurysms still remains a matter of debate.

While natural history studies provide some information on the rupture risk of UIAs, they have certain limitations such as selection bias and not being applicable to all the people across the world. Greving et al developed the PHASES score to estimate the risk of aneurysm rupture based on a pooled analysis of six studies including ISUIA, SUAVe and UCAS.[21] To calculate the PHASES risk score, it uses Population (North American or European, Japanese or Finnish descent), Hypertension, Age (<70years or ≥70years),

Size (<7mm, 7-9.9mm, 10-19.9mm and ≥20mm), Earlier SAH and Site of aneurysm to predict the risk of rupture. Every factor has its own points, and the number of points is added up to obtain the total risk score, which corresponds to a 5-year risk of rupture. The 5-year absolute aneurysm rupture risk ranges from 0.25% in population with North American or European descent other than Finland in individuals younger than 70 years without vascular risk factors with a small sized (<7mm) internal carotid artery aneurysm to >15% in patients aged ≥70 years with hypertension, a history of prior subarachnoid hemorrhage and a large (>20mm) posterior circulation aneurysm. However, sex, smoking status and presence of multiple aneurysms were not found to bear significant effect on the risk of rupture. More recently, the PHASES score has been correlated with aneurysm growth as well.[49] The unruptured intracranial aneurysm treatment score (UIATS) model includes and quantifies the key factors for clinical decision-making in the management of UIAs, developed based on a multidisciplinary expert consensus. It takes into account 14 factors pertaining to the patient, aneurysm morphology and treatment risk. For cases with a score difference of ≥3 points, the direction, i.e., the difference between the calculated numerical values on each side of the recommendation columns, will suggest an individual management recommendation (i.e., aneurysm treatment or conservative management). For cases that have similar aneurysm treatment and conservative management scores (2 point difference or less), the recommendation is “not definitive” and either management approach could be chosen. For cases with multiple aneurysms, every aneurysm must be evaluated separately, which will then also result in separate recommendations for each aneurysm.[50] However, it should be noted that the PHASES score only estimates the risk of rupture and does not take into consideration the risk of treatment. The UIATS takes into consideration both the risk of rupture and treatment, but, is based only on expert review and not rupture risk data.

In our opinion, patients with newly diagnosed UIAs are considered for treatment when they have any one of the risk factors related to the patient (strong family history of SAH, prior SAH, associated genetic conditions such as autosomal polycystic kidney disease and age <70 years) or the aneurysm morphology (location on MCA/anterior and posterior communicating artery, presence of daughter sac, size ≥7mm, subarachnoid

location) and when the risk of treatment is lower than the risk of rupture due to conservative management. It is to be remembered that the risk of treatment denotes the likelihood of morbidity and mortality at the time of treatment and that of natural history is cumulative during the patient's lifetime. In patients with age >60 years, the cognitive effects of clipping and endovascular therapy have not been studied, and hence, treatment in this age group should be considered in selected cases only.

The TEAM trial (Trial on Endovascular Aneurysm Management) was an international, randomized, multicenter controlled trial comparing endovascular treatment and conservative management of UIAs. However, the study was suspended due to logistic reasons.

Other factors are also thought to be related to aneurysms themselves and surgical treatment; depression, cognitive dysfunction, QOL, and more. They are multifactorial and complex, thus a treatment plan for each aneurysm should be tailor-made. We believe that 'No observation" is an option that should be chosen only in rare situations. Even in elderly patients with small aneurysms, periodic imaging is recommended.

4.2 Surgical Clipping versus Endovascular Therapy (EVT)

Very few areas in cerebrovascular medicine have created as much differences in opinion as the treatment of UIAs. With the rapid refinement of endovascular techniques and the introduction of flow diversion devices, EVT has become the first line treatment of most UIAs. There has been no randomized trial of surgical clipping versus EVT for UIAs; however, numerous meta-analyses and systematic reviews have demonstrated the efficacy of EVT over clipping.[51–53] In a systematic review, clipping resulted in significantly higher disability using the Modified Rankin Scale (Odds Ratio OR, 2.83; 95% CI, 1.42–5.63) when compared with coiling. ORs for complications were also higher with clipping (ORs for neurological and cardiac complications were 1.94 and 2.51 respectively). Clipping resulted in significantly greater disability in the short term (≤6 months), but not in the long term (>6 months). However, EVT was associated with higher rate of retreatment than clipping.[52] On the other hand, Teleb et al reported that

endovascular retreatment for aneurysms initially treated by EVS is safe.[54] 111 aneurysms (13%) out of 871 treated with EVS underwent retreatment, and overall symptomatic complication rate were 2.7%, with no recurrent SAH or mortality event. In an analysis of the Nationwide Inpatient Sample from the United States, the cohort of patients that underwent surgical clipping had a significantly higher percentage of discharge to long-term facilities than that of patients that underwent EVT (14% and 4.9% respectively). Clipping was also associated with a higher mortality rate than EVT (1.2% versus 0.6% respectively).[51] Similar results were observed in another study that showed a significantly higher incidence of complications following surgical clipping.[55] Lad et al compared the economic burden of clipping and coiling. Reoperation rates were significantly lower in the clipping group compared to the coiling group at 1- ($P < .001$), 2- ($P < .001$), and 5 years ($P < .001$) following the procedure. However, postoperative complications (immediate, 30 and 90 days) were significantly higher in those undergoing surgical clipping. They observed that although hospital length of stay and costs were higher in the clipping group for the initial procedure, whereas the overall costs at 2 and 5 years were similar in the clipping and coiling cohorts.[56] However, there is no true blinded randomized study that compares surgical clipping and Endovascular therapy.

The Canadian Unruptured Endovascular versus Surgery Trial (CURES) is a two-phase trial: the pilot Canadian phase intends to examine the incidence of treatment failure by one year, using a composite primary end-point which includes anatomic outcomes.[57] The second international phase aims to compare the clinical efficacy and safety of a surgical or endovascular management strategy at 1 and 5 years. The primary outcome measure is treatment failure and the secondary outcome measures are morbidity and mortality, hospitalization > 5 days and discharge other than to home. The study is currently recruiting participants. (https://www.clinicaltrials.gov/ct2/show/NCT01139892?term=NCT01139892&rank=1)

4.3 New devices in EVT

There are some new devices for EVT at various stages of approval for clinical use.. The use of flow-diverting devices[58] (Silk, SFD; Balt Extrusion, Montmorency, France; Pipeline Embolization Device, PED, ev3-Covidien, Irvine, California, USA; Surpass, Stryker Neurovascular, Fremont, CA; Flow-Redirection Endoluminal Device, FRED, MicroVention, Tustin, CA), intrasaccular flow disrupting devices (Woven EndoBridge, WEB, Sequent Medical, Aliso Viejo, California)[59] have expanded the therapeutic options for aneurysms and represent a paradigm shift. However, they also have a risk of later aneurysmal rupture especially in giant aneurysms, which might come from flow alteration ending up increasing intra-aneurysmal pressure.[60] Even so, they hold a potential to be one of the standard cares in the future. Figure 1 illustrates a patient with left vertebral artery aneurysm treated with flow diversion (Off-label use of PED).

4.4 Management of aneurysm remnants or recanalization

Management of aneurysm remnant and recanalization following surgical clipping or EVT is another matter of debate. Retreatment is a major event in that, in addition to being costly, it puts the patient at some risk, although much lower than what it was during the actual treatment. In the long-term follow-up of patients in the ISAT trial, patients in the endovascular group were more likely to be alive and independent at 10 years compared to patients in the neurosurgery group. The cumulative risk of a rebleeding from the target aneurysm was 0·0216 for patients in the endovascular group and 0·0064 for patients in the neurosurgery group. Although the rebleeding risk was small, the probability of disability-free survival was significantly greater in the endovascular group than in the neurosurgical group at 10 years[61]. It is not known whether the recurrent hemorrhages occurred only in patients with residual aneurysm filling or recanalized aneurysms. There is no such data following treatment of UIAs. The term Target Aneurysm Recurrence (TAR) refers to occurrence of ≥1 of the following events (1) target aneurysm rupture (2) sudden unexplained death and (3) target aneurysm retreatment. It is not yet known which aneurysm recurrences or residuals need to be treated to prevent delayed re-hemorrhage. Until then, the decision to treat aneurysm recurrence or recanalization depends upon individual patient and surgeon preference.

5.0 Prognosis and long-term outcome of UIAs

Initial prospective data on 798 patients that underwent clipping in the ISUIA study, the mortality was 2.3% at 1 month and 3% at 1-year, which was slightly higher than that mentioned in previous studies. The combined morbidity (which included substantial functional disability or cognitive impairment) was around 13% in patients with history of previous hemorrhage from another aneurysm as compared to 17.5% in subjects with no history of aneurysms. The morbidity noted in ISUIA was higher than previous studies, primarily due to the addition of cognitive impairment as measure of morbidity as this aspect was largely ignored in previous studies.[14] In larger prospective cohort from ISUIA consisting of 1917 subjects, the morbidity and mortality rates at 1 year in patients with open surgical repair were 12·6% for subjects with no history of SAH as compared to 10·1% for subjects with history of SAH from other aneurysms. In both of these studies large size, location in posterior circulation and advance age was noted to be predictor of bad outcome.[14,15] King et al did meta-analysis of mortality and morbidity of elective surgery for asymptomatic aneurysm, which included 28 studies with over 700 patients, demonstrated morbidity rate of 4.1% (95% CI 2.8- 5.8), and a mortality rate of 1.0% (CI 0.4- 2.0).[62] In larger met-analysis consisting of more than 2400 patients undergoing surgical clipping a mortality of 2·6% and morbidity of 10·9% was reported. The authors also reported that aneurysm location in anterior circulation and small size are associated with lower mortality and morbidity as compared to aneurysm in posterior location and large size.[63] In a recent study of patients with unruptured aneurysms with follow-up of more than 30 years, the cumulative death rate was 20% (95% confidence interval 14%-27%) at 10 years and 60% (52%-68%) at 30 years. Patient age, male sex, heavy alcohol consumption and cigarette smoking were the only independent factors predicting subsequent death.[64] Korja et al followed up 118 patients diagnosed with UIAs between 1956 and 1978 until death or SAH. They observed that 34 (29%) of the patients had SAH during the lifelong follow-up. The annual rupture rate was 1.6% per patient. Female sex, current smoking, and aneurysm size of ≥7 mm in diameter were risk factors for a lifetime SAH. 25% of patients with UIAs<7mm in size experienced SAH during the follow-up.[65]

Currently, with advancement in angiographic techniques, endovascular approach is rapidly becoming the treatment of first choice at many centers across the world. Johnston et al observed that in-hospital death, discharge to a nursing home or rehabilitation hospital occurred in 10% of patients with UIAs treated with endovascular therapy compared with 25% of those treated surgically.[66] Prospective data from 498 patients that were treated with endovascular therapy in the ISUIA, the combined mortality and morbidity at 30 days and one year were 9.1% and 9.5% respectively. Advanced age was not a predictor of bad outcome in subgroup analysis suggesting that endovascular therapy might be more suitable for older patients.[15]

6.0 Pharmacological treatment of UIAs

Treatment of aneurysm in human involves microvascular surgery or endovascular procedures. But the choice of either depends on patient's intra-cranial aneurysm (IA) anatomy, age and comorbidities. There may be utility of non-invasive strategies to manage unruptured aneurysms which include blood pressure control, anti-fibrinolytics, statins, calcium channel blockers.[67]

Blood pressure (BP) lowering drugs are useful to control hypertension and to prevent rupture of IA in both human and experimental model[68]. Previous studies suggest that in experimental animal model with IA, hydralazine, a BP reducing drug was able to normalize blood pressure and was also able to significantly reduce the incidence of IA rupture. However, this observation is based only on retrospective studies and animal studies.

Statins may have potential benefits in UIAs. Statins are hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which are widely used as cholesterol-lowering drugs. These have cholesterol-lowering effect and also have potential anti-inflammatory property especially anti-NF-κB effect. NF-κB is a transcription factor that regulates the expressions of various pro-inflammatory genes. These regulate inflammatory responses following aneurysm and contribute to its pathogenesis.[69–73] NF-κB is activated in the endothelial cells as a stress response to the arterial walls.[74] Administration of statins in rodent model of IA have produced beneficial effects.[75–77] However, one report

demonstrates its deleterious effect on IA progression.[78] Pravastatin, simvastatin and pitavastatin administered orally to rat model of intra cranial aneurysms significantly suppress the formation, progression or enlargement of induced intra cranial aneurysm, independent of their cholesterol- lowering effects.[75–77]

Preclinical studies have shown that intracranial aneurysms are often caused due to the disappearance of the internal elastic lamina.[79] The balance between synthesis and degradation of the extracellular matrix is compromised which breaches the structural integrity of the vessel wall. This causes thinning of wall leading to aneurysm. Previous studies have shown that intracranial aneurysms accompanies increased expression of MMPs (MMP-2 and MMP-9) that contributes to the extracellular matrix disruption especially elastin and collagen.[80–82] MMP-9 deficiency reduced the incidence of IA in animal model of intracranial aneurysm.[83] Doxycycline, a broad-spectrum MMP inhibitor has shown promising results in reducing incidence of IA from 70% to 10% in an animal model of IA.[83] Doxycycline and minocycline had preventive role in the rupture of IA induced by deoxycorticosterone acetate and elastase.[84] In contrary, studies have also shown that SB-3CT, a selective inhibitor of MMP-2/9 failed to inhibit the rupture of IA. Tissue inhibitors of matrix metalloproteinases (TIMP 1 and 2) expression are elevated in human IA and exhibits preventive effects due to their ability to inhibit the activity of MMPs.[82]

Chemokine like stromal cell derived factor-1 (SDF-1) plays an important role in promoting angiogenesis and inflammation.[85,86] Studies have reported that human intracranial aneurysms show increased SDF-1 expression.[87] SDF-1 inhibition by intravenous administration of its antibody reduces intracranial aneurysm formation, which may be due to decrease in inflammation. Inhibition of TNF-α has also shown beneficial effects in IA. These reported to decrease UIA rupture in animals.[88]

Mast cell number increases in arterial wall during aneurysm formation. Inhibitors of mast cell degranulation have reported to inhibit the size and medial thinning of induced IA through the inhibition of chronic inflammation. Hence, inhibitors of mast cell degranulation can be therapeutic drugs for IA in future.[89] Other preclinical studies suggest that IA formation can be prevented by inhibition of nitric oxide synthase.

Aminoguanidine, an NOS inhibitor attenuated both early aneurysmal changes and the incidence of induced aneurysms. A defibrinogenic agent, batroxobin, that diminished shear stress by reducing blood viscosity prevented iNOS induction and early aneurysmal changes.[90] Other factors that may contribute towards aneurysm are loss of mural cells[91] and hyperhomocysteinemia.[92]

Inhibiting the renin-angiotensin system may be one of the potential therapies to prevent intracranial aneurysm rupture. Studies have reported that angiotensin converting enzyme inhibition with the administration of captopril or angiotensin type I receptor inhibition with the administration of losartan can decrease the incidence of ruptured aneurysms without affecting the blood pressure.[68] Postmenopausal women have been observed to have a higher rate of intracranial aneurysm rupture than premenopausal women.[93] Studies have shown that α and β estrogen receptors are expressed in human intracranial aneurysms.[24] Stimulation of estrogen receptor-β protected mice against intracranial aneurysm rupture. These results strongly suggest that estrogen signaling plays a prominent role in intracranial aneurysm rupture and may be used as a pharmacological target for intervention. Estrogen replacement therapy reduces the risk for subarachnoid hemorrhage in post-menopausal women. Studies have also reported the protective role of estrogen against the formation and progression of cerebral aneurysms.[94]

Aspirin has emerged as a major candidate for noninvasive pharmacotherapy of cerebral aneurysms. it exerts its effect through irreversible inhibition of cyclooxygenase-2. Among patients enrolled in ISUIA, those with a history of aspirin use 3 times weekly, or greater had a lower risk of cerebral aneurysm rupture and subarachnoid hemorrhage compared with those who never used aspirin.[95] Gross et al, in a study of 747 patients, noted that SAH occurred in 28% of patients with a history of aspirin use versus 40% of patients without a history of aspirin use.[96] To take aspirin seems to exacerbate SAH, but they also reported that there was no difference in clinical and radiographic grade of SAH between patients who take aspirin and those who does not.

Table 3 lists the important preclinical studies in animal model of intracranial aneurysms (IA)

7.0 Expert commentary

UIAs represent a unique category of intracranial lesions without consensus about their management. While a small subset of aneurysms clearly falls in the category for observation or treatment, a large proportion of aneurysms are managed based on the treating physician and patient preferences and bias. Much of the earlier research was based on understanding the natural history and rupture risk based on the patient characteristics and basic aneurysm morphology. However, recent data show that a number of morphological and hemodynamic changes and the perianeurysmal environment affect the rupture risk of these aneurysms. Given the uncertainity in the determination of rupture risk of a large proportion of unruptured brain aneurysms, we recommend that therapy should be individualized based on the outcomes at the treating center and patient preference. Designing and conducting a true randomized controlled trial for management of UIAs is the need of the hour.

8.0 Five-year view

In the coming five years, we envisage that more in-vivo and in-vitro studies will shed light on the complex interaction between the morphology and blood flow hemodynamics of the aneurysm and the perianeurysmal environment. Inflammation has been shown to play a major role in the formation, growth and rupture of aneurysms.[97] The inflammatory cascade is likely interrelated with mechanical flow-induced vascular dysfunction leading to aneurysm destabilization and rupture.[98][88] Future studies will help us understand the role of inflammation in the pathogenesis of intracranial aneurysms. Ferumoxytol-enhanced MRI is a very promising method for assessing inflammation in the walls of aneurysms and arteriovenous malformations and for studying the natural course of the disease. Future studies will focus on refining the technique to objectively assess the risk of aneurysm rupture and identify the ruptured aneurysm in patients with multiple intracranial aneurysms.[99] The association of UIAs and connective tissue disorders also needs to be investigated further. We envisage more genetic studies relating to the association of specific mutations in patients with connective tissue diseases and development and rupture of intracranial aneurysms.

Key issues

- The natural history of unruptured brain aneurysms varies depending upon a number of, morphological and hemodynamic characteristics.
- Race, age, gender, prior subarachnoid hemorrhage, familial and genetic predisposition also affect rupture risk of unruptured aneurysms
- Controlled studies till date have established only size and location as the morphological factors affecting the risk of rupture.
- Aspect ratio, size ratio and wall shear stress are the three most promising factors that might have a role in predicting the risk of rupture
- PHASES score has been proposed to reliably predict the risk of aneurysm growth and rupture in the North American, European and Japanese population
- Endovascular therapy and clipping remain the established therapies in UIA patients with a significant risk of rupture.
- Endovascular therapy may be superior to clipping especially in patients above 60 years of age.
- Novel therapies for unruptured aneurysms will focus on stabilizing the growth and preventing rupture through pharmacological targets

Declaration of interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Reference annotations

** Of interest*
*** Of considerable interest*

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Figure Legend

Figure 1: 57 year old lady with incidentally detected left vertebral artery (LVA) aneurysm. Anteroposterior (AP) view of LVA angiogram showing a saccular aneurysm arising off the intracranial segment of the LVA. 1B, 1C AP views of LVA angiogram following embolization using the Pipeline Embolization Device (PED) showing contrast stagnation within the aneurysm. 1D AP view of LVA angiogram showing complete remodeling of the artery and occlusion of the aneurysm at 6 months' follow-up.

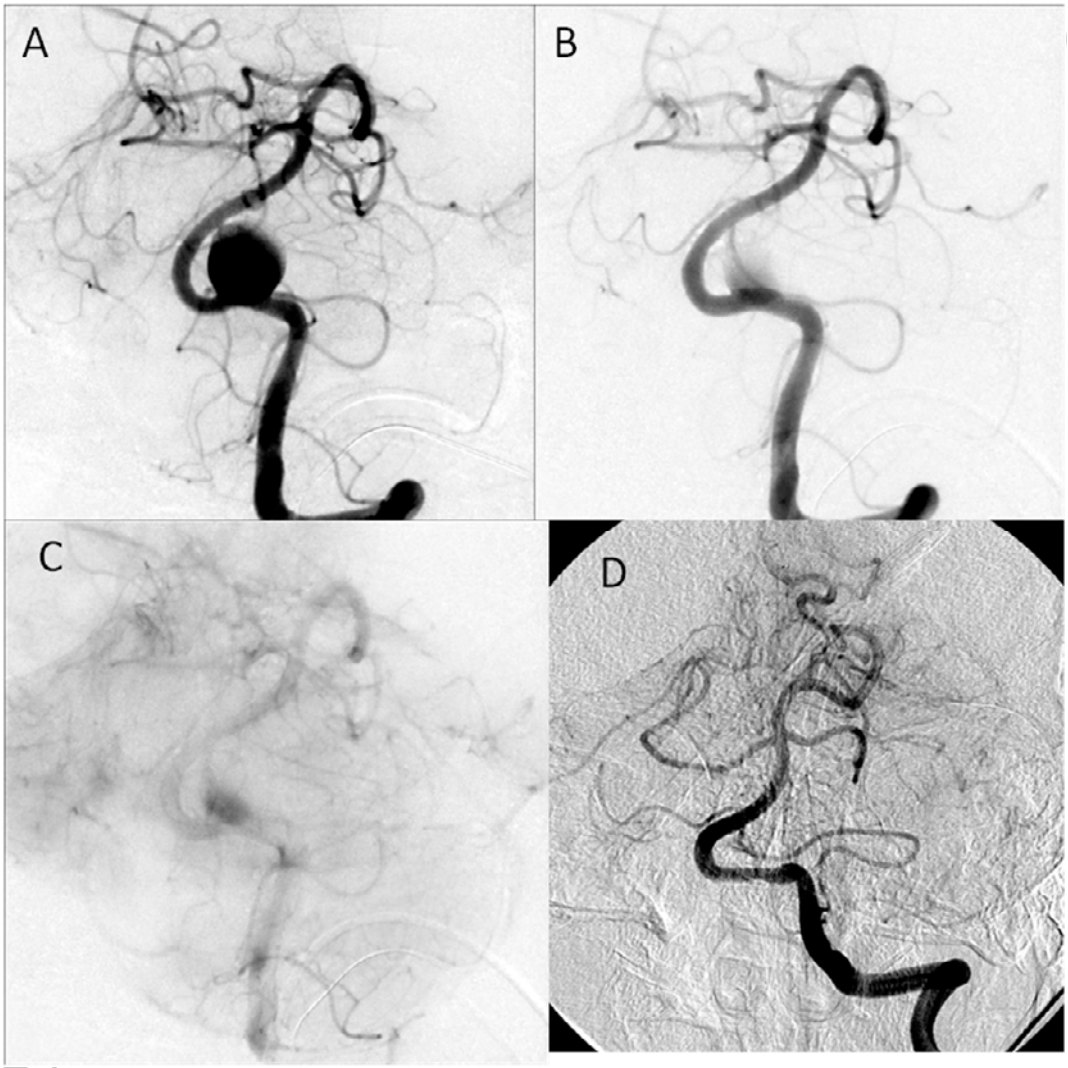

Table 1: Important studies of natural history of unruptured brain aneurysms

	Number of patients	Inclusion criteria	Mean age in years (range)	Median follow-up duration (range, years)	No. of SAHs during follow-up	Rupture risk	Factors affecting rupture risk
Wiebers et al **[13]**	130	Saccular aneurysm	56.2 (17-79)	8.3 (NA)	15	24% at 7 years for age <59 years; 48% at 7 years for age ≥59 years	Aneurysm size
Juvela et al**[12]**	142	Non-fusiform, nonmycotic aneurysm	41 (14–60)	21·0 (0–52)	34	10.5% at 10 years, 23.0% at 20 years, and 30.1% at 30 years	Cigarette smoking, AcoA location, patient age inversely and aneurysm diameter ≥7 mm
ISUIA**[9]**	1691	Saccular aneurysm ≥2 mm, mRS <3	55 (10–90)	9·0 (0–15)	59	Size <7mm 0-2.5%; 7-12mm 2.6%-14.5%; 13-24mm 14.5%-18.4%; ≥25mm 40%-50%	Aneurysm location, size
SUAVe**[13]**	374	Saccular aneurysm ≤5 mm, mRS <3	62 (23–90)	3·2 (0–20)	7	0.54% overall (single aneurysm 0.34%; multiple aneurysms 0.95%)	Age <50 years, aneurysm diameter ≥4.0 mm, hypertension and multiple aneurysms
UCAS**[11]**	5720	Saccular aneurysm ≥3 mm, mRS <3	63 (23–98)	1·0 (0–9)	111	0.95% per year	Size, aneurysm location, presence of daughter sac
Wermer et al**[14]**	93	Non-fusiform aneurysm ≤5 mm	50 (19–69)	2·2 (0–15)	1	2.2%	History of SAH, Family history of intracranial aneurysm
Ishibashi et al**[15]**	419	Saccular aneurysm	60 (17–86)	2·1 (0–22)	19	1.4% per year	History of SAH, PComA location, large size

Abbreviations: ISUIA = International Study of Unruptured Intracranial Aneurysms; SUAVe = Small Unruptured Aneurysms Verification Study; UCAS = Unruptured Cerebral Aneurysm Study, SAH=Subarachnoid Hemorrhage, PComA=Posterior communicating artery

Table 2: Variables affecting risk of rupture of UBAs

Variables affecting rupture risk of unruptured brain aneurysms	Definite	Probable
Patient characteristics	Race	Hypertension
	Age	Current cigarette smoking
	Gender	Multiple aneurysms
	Prior SAH	
	Family history of intracranial aneurysms	
	Associated genetic conditions (ADPKD, etc)	
Morphological characteristics	Size	Aspect ratio
	Location	Size ratio
		Presence of daughter sac
		Ellipticity index
		Nonsphericity index
		Undulation index
		Vessel angle
		Aneurysm (inclination) angle
		Daughter artery ratio
		Lateral angle ratio
Hemodynamic characteristics		Wall shear stress
		Wall shear stress area
		Wall shear stress gradient
		Oscillatory shear index
		Number of vortices
		Relative resistance time

Table 3: Important preclinical studies in animal model of intracranial aneurysms (IA)

Study title	Therapy	Animal Model	Findings
Tada et al**[46]**	Hydralazine/Captopril/Losartan/discontinuation of DOCA-salt	Deoxycorticosterone + acetate-salt with elastase	Hydralazine normalized blood pressure of mice with intracranial aneurysms. Significant reduction in the incidence of ruptured IA.
Hoh et al**[70]**	Inhibition of stromal cell derived factor-1 (SDF-1)	Ligation of the left common carotid artery and the right renal artery + angiotensin II,β-aminopropionitrile and elastase	Intravenous administration of SDF-1 antibody reduced intracranial aneurysm formation from 89% to 33%.Decrease in angiogenesis and inflammation.
Tada et al**[18]**	Estrogen receptor-β agonists	Deoxycorticosterone + acetate-salt with elastase	Treatment with an estrogen receptor-β agonist (diarylpropionitrile) protected mice against aneurysm rupture mediated by nitric oxide production.
Makino et al**[67]** Nuki et al**[66]**	MMP inhibition	Angiotensin II + elastase	Doxycycline (MMP inhibitor) reduced intracranial aneurysm in mice
Starke et al**[71]**	Inhibition of TNF-α	Deoxycorticosterone + acetate-salt with elastase	Pre-treatment with TNF-α inhibitor (3,6′-dithiothalidomide) decreased intracranial aneurysm formation and rupture in mice.
Tada et al**[46]**	Inhibition of RAS	Deoxycorticosterone + acetate-salt with elastase	Inhibition of angiotensin-converting enzyme with captopril or inhibition of the angiotensin type I receptor with losartan decreased the incidence of ruptured aneurysms without affecting blood pressure.
Fukuda et al**[78]**	Prostaglandin F2α antagonist AS604872	Ligation of the left carotid artery and ligation of the left renal artery. Fed chow containing 8% sodium chloride and 0.12% 3-aminopropionitrile	AS604872 exacerbates vascular inflammation in hypertensive rats and facilitates IA and aortic dissection
Aoki et al**[79]**	TNF-alpha-TNFR1 signaling as a potential therapeutic target for IAs	Ligation of the left carotid artery and systemic hypertension+ salt overloading and ligation of the left renal artery	Nuclear factor (NF)-kappaB as a critical mediator of inflammation regulating IA formation, by inducing downstream pro-inflammatory genes such as MCP-1, a chemoattractant for macrophages, and COX-2

Xu et al**[80]**	EPO Treatment	Ligation of the left carotid artery and systemic hypertension+ salt overloading and ligation of the left renal artery	Erythropoietin (EPO) mobilizes erythropoietin progenitor cells(EPCs) from the bone marrow and promotes their homing. EPO increased levels of circulating EPCs and VEGF. It also decreases iNOS, MMP-2, and MMP-9 mRNA levels and increases eNOS mRNA in aneurysm tissue
Xu et al**[74]**	Water containing methionine (1g/kg/d)	Surgical induction of aneurysm	Methionine diet significantly increased plasma homocysteine levels, accelerates IA formation after ligation of the left common carotid artery
Eldawoody et al**[81]**	Fasudil powder added to the drinking water at concentrations of 0.5 and 1.0mg/mL, respectively	Surgical induction of aneurysm	Fasudil attenuated the formation of aneurysmal lesions at arterial branching sites. No dose-dependency was observed in the present settings, and no effect was seen at non-branching sites

Abbreviations: MMP = matrix metalloproteinase; RAS = renin-angiotensin system; SDF-1 = stromal cell-derived factor-1; TNF-α = tumor necrosis factor-α