

Evidence That a Subset of Aneurysms Less Than 7 mm Warrant Treatment

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The management of unruptured intracranial aneurysms (UAs) has been a very controversial topic in neurosurgery. There is no clear consensus at present as to when a small UA should be treated and when it should be observed. The magnitude of this problem is increasing with advances in imaging, its widespread use, and the introduction of family screening,¹ which have led to an increased rate of identification of small UAs. The prevalence of cerebral aneurysms (CAs) in the general population is thought to be somewhere between 1% and 7%.^{2–4} However, aneurysmal subarachnoid hemorrhage (SAH) remains a rare event with an incidence of 6 to 20 cases per 100 000 persons per year.² This highlights the importance of patient selection for treatment. The estimated 1% annual risk of rupture, even though small, has a tremendous impact on the patient's health, given its high mortality and morbidity rate.⁵ This estimated risk, however, is not absolute, as it may be decreased to 0.1% to 0.7% depending on certain characteristics.^{3,6} The best evidence we have thus far comes from the ISUIA (International Study of Unruptured Intracranial Aneurysms) trial,^{7,8} which stratified the risk of rupture according to aneurysm size. This study reported a 5-year ruptured rate of 0% for aneurysms smaller than 7 mm in the anterior circulation and 2.5% for those smaller than 7 mm in the posterior circulation. The standard of care has been to observe these lesions, especially in the absence of high-risk factors based on patient history or aneurysm characteristics and geometry.² A 2012 study evaluating the natural history of unruptured cerebral

aneurysm in a Japanese cohort⁹ showed that larger size, posterior circulation aneurysm, and presence of a daughter sac confers a higher risk of rupture.

In contrast to the findings of the ISUIA, several studies^{10–12} have reported results showing that the majority of SAHs result from aneurysms <10 mm in size and a significant proportion of patients present with ruptured aneurysms <5 mm in diameter.^{2,9,13} Korja et al¹³ evaluated the lifelong rupture risk of intracranial aneurysms in a Finnish cohort and concluded that treatment decisions of UIAs should be based on the risk factor status since even small UIAs still ruptured. It is still unknown whether it is safe to observe patients harboring small aneurysms, especially if they are planning on engaging in strenuous activities, or planning on getting pregnant, or if there are any anticipated future events that may carry significant hemodynamic changes (diving, athletic sports, etc). It is also not well established whether it is sufficient to advise treatment in this subpopulation based on hypertension, smoking, or some geometrical characteristics such as aspect ratio (defined by height/neck width), nonsphericity index, and size ratio.¹⁴

On the basis of hemodynamic factors and inflammatory changes, we review the evidence that goes against the traditional dogma: A subset of aneurysms smaller than 5 to 7 mm are at high risk of rupture and warrant treatment. The predictors of elevated risk of rupture can be categorized into 2 main variables: Inflammatory index and Hemodynamic instability.

Inflammation and Rupture

It is becoming clearer that inflammation is a major player in the pathophysiology of CAs.¹⁵ This has been well studied in human and animals.^{16,17} The previous model of aneurysms that assumes a static passive dilatation of tissue is being abandoned for a more comprehensive model focusing on inflammation, hemodynamic factors, tissue degeneration, and genetic and environmental factors.¹⁸ The currently adopted model presumes that an inflammatory process is initiated by a hemodynamic insult that leads to matrix metalloproteinase–mediated degradation of the extracellular matrix and apoptosis of smooth-muscle cells, which are the predominant matrix-

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synthesizing cells of the vascular wall. These processes act in concert to weaken the arterial wall progressively, resulting in dilatation, aneurysm formation, and ultimately rupture. Although several constituents of the inflammatory response may be involved, recent data indicate that macrophages play the central role in the process of aneurysm formation and rupture,^{19,20} through the secretion of cytokines and metalloproteinases responsible for inflammation and digestion of the arterial wall. Macrophages are present early in ruptured aneurysms and have been linked to rupture.¹⁷ Effectively, inhibition of metalloproteinase has been shown to decrease the incidence of advanced aneurysms in animal studies.²¹ It is postulated, based on human studies, that a predominance of macrophage subtype (M1 over M2) and upregulation of mastocytes may increase the risk of rupture. Given the critical role of macrophages in the pathophysiology of CA rupture, several studies were conducted to investigate the inflammatory status of human CAs through direct macrophage imaging. Along these lines, Hasan et al^{22,23} have investigated the feasibility and optimal parameters for imaging macrophages in human CAs using ferumoxytol-enhanced magnetic resonance imaging (MRI). Ferumoxytol, a member of the class of nanoparticles known as ultrasmall superparamagnetic iron oxide, is a useful intravascular contrast agent and an inflammatory marker when imaging is delayed because it is cleared by macrophages, usually within 24 to 72 hours. In their initial work, Hasan et al found that the optimal technique for imaging macrophages in human CA walls is infusion of 5 mg/kg of ferumoxytol and imaging at 72 hours after injection.²³ Aneurysm tissue harvested from patients infused with ferumoxytol stained positive for CD68 (marker of macrophage lineage), demonstrating macrophage infiltration, and stained positive for Prussian blue, demonstrating uptake of iron particles. Tissue harvested from controls (ie patients who underwent clipping but were not previously infused with ferumoxytol) stained positive for CD68 but not Prussian blue. This study helped to establish that infusion dosing of 5 mg/kg of ferumoxytol and imaging at 72 hours postinjection using T2* GE MRI constitute the optimal dose and timing parameters for imaging of macrophages within the aneurysm wall.

However, some aneurysms showed early uptake (at 24 hours), well before the others. The significance of early uptake, however, was not clear at the time, but the authors thought it might be associated with a more active inflammation and thus linked to a higher risk of rupture. Hence, a subsequent study was conducted to verify this hypothesis,²⁴ where 25 aneurysms were imaged to compare early (24 hours) versus late (72 hours) or no uptake. Seven of the 25 aneurysms demonstrated early uptake. Of these 7 aneurysms, 4 were clipped and 3 were observed. All 3 observed aneurysms progressed to rupture, including a <7-mm aneurysm. On the other hand, 18 of the 25 aneurysms did

not show early uptake. Of these, 9 were clipped and 9 were observed. None of the observed progressed to rupture, including a giant aneurysm (The authors elected not to treat the aneurysm due to the patient age and morbidity). In conclusion, all aneurysms with early uptake ruptured and those with no or late uptake did not rupture or change in size/morphology, despite a follow-up period of 2 years (as of the current time). Furthermore, the authors found that CAs with early uptake had increased M1 cells and exhibited a more intense inflammation in their walls, similar in magnitude to ruptured aneurysms (harvested tissue from control patients) and significantly higher than patients with late uptake ($P<0.05$). Interestingly, early MRI signal change was independent of aneurysm size. Late MRI signal change was noted in 50% of aneurysms <7 mm, and 44% in aneurysms 7 to 14 mm. To sum up, there were no subarachnoid hemorrhages (SAHs) in 9 patients without uptake compared to all 3 patients with uptake (Figure). We performed a Fischer exact test and found this difference to be statistically significant (Fischer exact =0.0045). Aneurysms with early uptake of ferumoxytol on MRI may be prone to rupture and thus may warrant early operative intervention, regardless of size.

These observations support the hypothesis that inflammation is an important cause, rather than a consequence of aneurysm rupture. Although previous studies that reported inflammatory changes in the walls of ruptured aneurysms fell short of demonstrating that the inflammatory response preceded the rupture,¹⁹ recent literature is showing increasing evidence that links inflammation to a prerupture state, which may lead the way for ferumoxytol-enhanced MRI to be applied in clinical practice as a noninvasive tool to differentiate unstable aneurysms requiring early intervention from stable aneurysms in which observation may be safe. Specifically, this technique could prove particularly useful in identifying rupture-prone aneurysms in patients that often pose a therapeutic dilemma, namely, elderly patients (>70 years) and patients harboring small aneurysms (<5–7 mm).^{2,24}

Hemodynamic Factors Predisposing to Rupture

The physiopathology that leads to the development of aneurysms and their subsequent rupture has been partially explained by hemodynamic components in a multitude of studies; high wall shear stress seems to play the predominant role in high-flow aneurysm, whereas high intra-aneurysmal pressure and low-flow stasis are the main factors in low-flow aneurysms.²⁵ It is hypothesized that the lower the flow, the higher the degenerative changes, and the higher the risk of rupture. Ruptured aneurysms (RAs) can have areas with higher than average and more concentrated wall shear stress with smaller impingement zones (where the inflow jet impacts

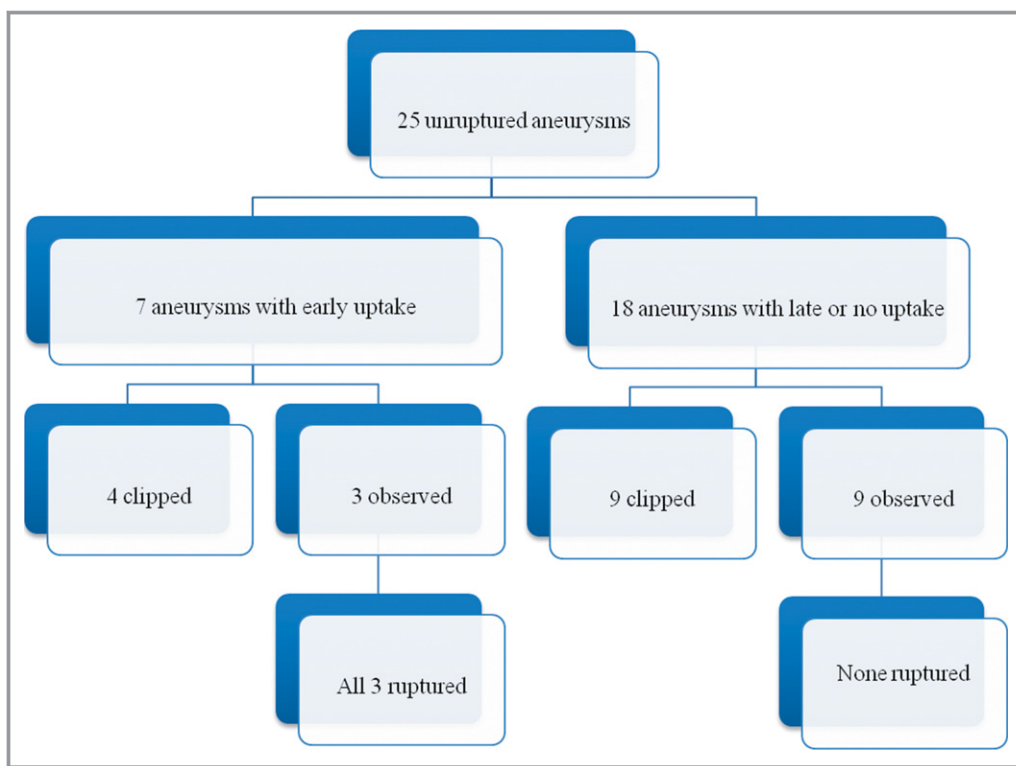


Figure. Early versus late uptake. Twenty-five aneurysms were imaged to compare early (24 hours) vs late (72 hours) or no uptake. Seven of the 25 aneurysms demonstrated early uptake. Of these 7 aneurysms, 4 were clipped and 3 were observed. All 3 observed aneurysms progressed to rupture, including a <7-mm aneurysm. On the other hand, 18 of the 25 aneurysms did not show early uptake. Of these, 9 were clipped and 9 were observed. None of the observed progressed to rupture, including a giant aneurysm (The authors elected not to treat the aneurysm due to the patient’s age and morbidity).

against the aneurysm wall) when compared with unruptured ones.^{26–28} Furthermore, it is reported that hemodynamic variables are dependent on the morphology of the aneurysm and on its feeding vessels.^{25,29,30} Chronic hypertension seems to play a major role in aneurysm formation since it is more prevalent in patients with CAs compared to the general population.³¹ It is also a well-established independent risk factor.³¹ Lin et al introduced the parent–daughter angle parameter,³² which is formed by the vector of flow in the feeding artery with the vector of flow in the aneurysm. They found that a smaller angle was associated with increased rupture rate, a finding consistent with previous studies that showed increased wall shear stress when the angle of bifurcation decreases.³² Hasan and colleagues directly measured the pressure changes between the aneurysm and the systemic circulation.³³ Dual-sensor microwires with the capacity to simultaneously measure flow velocity and pressure were used to measure systolic, diastolic, and mean pressure inside the aneurysm sac and to measure both pressures and flow velocities in the feeder vessel just outside the aneurysm in patients undergoing endovascular treatment. Measurements were taken at baseline and then during a gradual increase in systemic systolic blood pressure to a

target value of ≈25 mm Hg above baseline. This study demonstrated several important points. First, peak and mean flow velocities in the parent arteries did not change significantly with increased systolic blood pressure, nor did vessel diameters as measured by angiography. This is an important finding since traditionally, investigators have studied geometrical characteristics and variables governing the aneurysm risk of rupture since geometry could indirectly reflect hemodynamic variables. One example would be the aspect ratio (defined as the maximum perpendicular distance between the neck and the dome, divided by the neck width), with the rationale that the smaller the aneurysm neck, the slower the flow and subsequently the higher the risk of rupture.^{29,34–36} A common threshold of the aspect ratio, above which there is a significant risk of rupture, varied between studies and was hard to define. This could be possibly attributable to the fact that velocity alone cannot explain the rupture mechanism, since low-flow velocity may lead to the opposite outcome, which is aneurysm thrombosis.³⁵ Another reason would be that mean and peak flow velocities do not significantly change.³³

Second, there was a clear linear relationship between changes in radial and aneurysm pressures: An acute change in

systemic arterial pressure resulted in nearly equal changes in arterial pressure inside the aneurysm, with the intra-aneurysm pressure being almost always below that of the systemic one. This highlights that hypertension may result in an increased intra-aneurysm pressure and stresses the aneurysm wall. More importantly, the authors found a significant variation in the slopes of this relationship from patient to patient. This means that some aneurysms were more vulnerable to changes in pressure. The authors measured this vulnerability index and found that it is independent of the aneurysm size or location. In fact, 1 aneurysm of <5 mm had the steepest slope in pressure changes, showing an exaggerated response to pressure variation. This could potentially explain why some smaller aneurysms progress to growth and even rupture. Furthermore, in a different patient, the intra-aneurysm pressure was consistently higher than the systemic one, possibly due to vessel sclerosis and poor autoregulation. The clinical implications of this study were that a subpopulation of patients may have an exaggerated aneurysmal pressure response and would be particularly prone to rupture, and that in some individuals with chronic hypertension and vessel sclerosis, the intra-aneurysm pressure can even supersede the systemic one. In fact, Takao et al indicated that RAs have a significantly lower pressure loss coefficient that can be translated to lesser resistance to blood flow.²⁸ This facilitation to flow renders the vessel susceptible to sudden changes in pressure, thereby increasing the risk of rupture.²⁸ The findings of these studies suggest that a subcategory of small aneurysms (<7 mm) can be considered hemodynamically unstable and may proceed to rupture.

Discussion

Traditional Dogma

The ISUIA trial aimed to provide the neurosurgeon with the evidence needed for making decisions regarding patients who would benefit from treatment of UIAs. It was reported that the rupture risk among patients with a UIA of <7 mm in diameter in the anterior circulation was 0% (no prior SAH from other aneurysm) and 1.5% (prior SAH) over 5 years. The rupture risk in the posterior circulation or posterior communicating artery site was 2.5% (no prior SAH) and 3.4% (prior SAH) over 5 years. However, other studies have reported conflicting results from the ISUIA. Wermer et al³⁷ conducted a comprehensive meta-analysis of the natural history of aneurysms. It was noted that the UIA rupture rate was approximately 1% for smaller UIAs (5/565 measuring <5 mm in diameter, and 1% [23/2249] for <7 mm in diameter with follow-up of 3.7 and 7.7 years, respectively). The rupture rate was 0.24% per year in those <5 mm and 0.13% per year in those <7 mm in diameter. Zylkowski et al³⁸ studied 110 UIAs <7 mm in 70

patients and reported a rupture risk of 2.7%. With the ISUIA study, more emphasis has been given to size, location, and history of subarachnoid hemorrhage, so that these variables became the most important factors used in day-to-day clinical practice guiding the management of incidental aneurysms with addition of several other clinical factors such as life expectancy, family history, and smoking.^{39–42} Traditionally, aneurysms <10 mm are given a 0.5% to 0.7% annual risk of rupture.⁷ This estimate was found to be nonhomogeneous since a large percentage of RAs fall in this size category, and many are as small as 5 mm, making the relationship between size and rupture more sophisticated.^{4,29,39,43–45} In addition, shape, a potential indirect estimator of underlying hemodynamic changes, seems to play a role in RAs, as Ryu et al found that irregular aneurysms (multilobular or had 1 or more daughter sacs) tend to rupture more than simple-lobed ones.⁴⁶ In a multitude of studies, the daughter sacs were significantly related to rupture, which may be due to higher shear stress values present at or adjacent to the blebs.^{9,41,47} One study found that for anterior communicating aneurysms, size >5 mm, the presence of blebs, and an anterior direction of the dome are significantly associated with RAs, and recommended that aneurysms with these characteristics should be treated.⁴¹ This study also challenges the IUSIA trial that estimated the risk of rupture to be 0% for small anterior circulation aneurysm. Furthermore, Chalouhi et al reported their experience with treating 151 patients between 2004 and 2011 who presented with small ruptured aneurysm with a diameter size of <3 mm.⁴⁸

Multiple attempts to predict the hemodynamic characteristics of an aneurysm and to quantify the wall shear stress have been made throughout the literature by focusing on shape as a principal estimator. However, direct measurements of the pressure changes showed that it was independent of size,³³ suggesting that a subset of small aneurysms tend to rupture.

Incidence and Rate of Growth in Small Aneurysms (<7 mm)

Villablanca et al⁴⁹ showed that the risk of aneurysm growth in UIAs <7 mm in diameter is 14% over a mean follow-up of 2.2 years. They also found an overall 12-fold increased risk of rupture for growing aneurysms when compared to nongrowing aneurysms. In their series, 3 UIA aneurysms <7 mm (1.6%) progressed to rupture. Burns et al⁵⁰ showed the risk of rupture of <8 mm UIAs is 6.9% over a mean follow-up of 3.9 years. Ramachandran et al⁵¹ studied 198 aneurysms, and detected growth in 10.1% of UIAs of <7 mm, over a mean follow-up of 4 years. Zylkowski et al³⁸ studied 110 UIAs <7 mm in 70 patients, and 21% of UIAs enlarged, the majority (75%) of which in the first 3 years of observation. Jeon et al⁵² retrospectively evaluated 524 patients harboring 568

paraclinoid UIAs (≤ 5 mm) during a mean follow-up of 35.4 months. Two aneurysms (0.35%) ruptured and 17 grew (3%). The criticism of this study was limiting UIAs to a specific location, which is known to have a lower rupture/growth rate. Bor et al⁵³ reported in a prospective study whereby they defined aneurysm growth as ≥ 1 mm that the risk of aneurysm growth in UIAs < 7 mm was 9% (37/403) and the mean likelihood of growth during the first 4 years of follow-up was 2.75% per year. Inoue et al⁵⁴ found that among 18 patients with UIAs that grew during follow-up, the annual rupture risk after growth was 18.5%/person-year. Mehan et al⁵⁵ noted that UIA morphology and interval growth are characteristics predictive of a higher risk of subsequent rupture during follow-up using computed tomographic angiography. Brinjikji et al⁵⁶ showed that growth of UIAs was associated with a rupture rate of 3.1% per year compared with 0.1% per year for stable UIAs ($P < 0.01$). Juvola et al⁵⁷ found that rupture of UIAs was associated ($P < 0.001$) with UIAs growth during follow-up. For these reasons, most UIAs that demonstrate growth during follow-up are treated because of concern regarding the rupture risk, leading to few such patients being followed over the long term. There has always been the consideration that a subset of smaller aneurysms are “unstable” for some reason and are at risk of growth and rupture, as opposed to those that reach a steady state and remain stable over the long term. This would reconcile the low rupture rates in many small aneurysms followed over the long term (ISUIA and other cohorts), and the reality of clinical practice in which one sees smaller aneurysms that have ruptured. Whether documented growth with intermittent imaging may precede rupture of these smaller aneurysms, or whether growth occurs over a

short period of time such that intermittent imaging would not pick it up (or would occur in people who have never had imaging) is also unclear but needs to be answered. So far the standard of care for small IAs has been observation except in a small minority of cases. Chalouhi et al, after reviewing the literature, defined Type A and Type B risk factor based on geometrical consideration as well as past medical history (Table).² After carefully assessing the evidence in the literature, they recommended that aneurysms measuring 5 to 7 mm should be treated if any risk factor (Type A or B) is present, while aneurysms < 5 mm in diameter should only be treated in the presence of 2 or more Type A risk factors or in the presence of any of the Type B risk factors. However, there is no report in the literature where active inflammation or active hemodynamic changes were investigated.

Challenges of Treating < 7 mm Aneurysm

Treatment of unruptured small aneurysms carries a high morbidity–mortality. The National Inpatient Sample was used to evaluate the morbidity and mortality in patients who underwent coiling/clipping of their UIA between 2001 and 2008.^{58,59} A total of 34 054 patients underwent coiling and 29 886 patients underwent clipping; in 30% of these, aneurysms were ≤ 7 mm. The morbidity and mortality for coiling were 4.8% and 0.6%, respectively, and those for clipping were 16.2% and 1.2%. Both surgical and endovascular repair of incidental anterior circulation aneurysms ≤ 7 mm (with the exception of posterior communicating artery UIAs) results in a net loss of quality-adjusted life-years at all ages over 20 years old.⁶⁰ Another obstacle to treating small aneurysm is the cost. The average cost of treatment is \$24 000 per aneurysm, assuming zero periprocedural complications.⁶¹ This would amount to a total cost of \$288 million per year.⁶¹

Table. Types A and B Risk Factors Dictating Treatment

Types A and B Risk Factors	
Type A: factors that favor intervention over observation	Type B: factors that warrant a strong consideration for treatment independent of size
Active smoking	Young patient age
Arterial hypertension	Change in the size or configuration of the aneurysm
Posterior circulation aneurysm	Presence of multiple aneurysms
Prior subarachnoid hemorrhage	Multilobed configuration
Familial subarachnoid hemorrhage	Symptomatic aneurysm (emboli or mass effect)
Aspect ratio > 3	

Chalouhi et al² recommended that an aneurysm measuring 5 to 7 mm should be treated if any risk factor (type A or B) is present while aneurysms < 5 mm in diameter should only be treated in the presence of 2 or more Type A risk factors or in the presence of any of the Type B risk factors. Reproduced with permission from Journal of Neurosurgery Publishing Group.²

Conclusions

In conclusion, larger size means higher risk, but small aneurysms need to be carefully evaluated by relying on different indicators. A multitude of studies have reported that a significant portion of SAHs have resulted from small aneurysms.^{2,11,12,62} A subset of small aneurysms < 5 to 7 mm may be highly unstable and warrant treatment, based on hemodynamic and inflammatory components. Future research is required to individualize aneurysm treatment based on age, anatomy, and possibly molecular/investigational imaging, instead of grouping all aneurysms together.

Disclosures

None.

References

- Vernooij MW, Ikram MA, Tanghe HL, Vincent AJPE, Hofman A, Krestin GP. Incidental findings on brain MRI in the general population. *N Eng J Med*. 2007;357:1821–1828.
- Chalouhi N, Dumont AS, Randazzo C, Tjounakaris S, Gonzalez LF, Rosenwasser R, Jabbour P. Management of incidentally discovered intracranial vascular abnormalities. *Neurosurg Focus*. 2011;31:E1.
- Rinkel GJE, Djibuti M, Algra A, van Gijn J. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. *Stroke*. 1998;29:251–256.
- Amenta PS, Yadla S, Campbell PG, Maltenfort MG, Dey S, Ghosh S, Ali MS, Jallo JI, Tjounakaris SI, Gonzalez LF, Dumont AS, Rosenwasser RH, Jabbour PM. Analysis of nonmodifiable risk factors for intracranial aneurysm rupture in a large, retrospective cohort. *Neurosurgery*. 2012;70:693–699; discussion 699–701.
- Zacharia BE, Hickman ZL, Grobelny BT, DeRosa P, Kotchetkov I, Ducruet AF, Connolly, ES. Epidemiology of aneurysmal subarachnoid hemorrhage. *Neurosurg Clin N Am*. 2010;21:221–233.
- Wiebers DO, Whisnant JP, Huston J III, Meissner I, Brown RD Jr, Piepgras DG, Forbes GS, Thielens K, Nichols D, O'Fallon WM, Peacock JL, Jaeger L, Kassell NF, Kongable-Beckman GL, Torner JC; International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet* 2003;362:103–110.
- International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms—risk of rupture and risks of surgical intervention. *N Engl J Med*. 1988;339:1725–1733.
- Wiebers DO, Whisnant JP, Huston J III, Meissner I, Brown RD Jr, Piepgras DG, Forbes GS, Thielens K, Nichols D, O'Fallon WM, Peacock J, Jaeger L, Kassell NF, Kongable-Beckman GL, Torner JC; International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet*. 2003;361:103–110.
- UCAS Japan Investigators, Morita A, Kirino T, Hashi K, Aoki N, Fukuhara S, Hashimoto N, Nakayama T, Sakai M, Teramoto A, Tominari S, Yoshimoto T. The natural course of unruptured cerebral aneurysms in a Japanese cohort. *N Engl J Med*. 2012;366:2474–2482.
- Berenstein A, Flamm ES, Kupersmith MJ. Unruptured intracranial aneurysms. *N Engl J Med*. 1999;340:1439–1442.
- Connolly ES Jr, Mohr JP, Solomon RA. Unruptured intracranial aneurysms. *N Engl J Med*. 1999;340:1440–1442.
- King JT Jr, Berlin JA, Flamm ES. Morbidity and mortality from elective surgery for asymptomatic, unruptured, intracranial aneurysms: a meta-analysis. *J Neurosurg*. 1994;81:837–842.
- Korja M, Lehto H, Juvela S. Lifelong rupture risk of intracranial aneurysms depends on risk factors: a prospective finnish Cohort study. *Stroke*. 2014;45:1958–1963.
- Zanaty M, Chalouhi N, Tjounakaris SI, Fernando Gonzalez L, Rosenwasser RH, Jabbour PM. Aneurysm geometry in predicting the risk of rupture. A review of the literature. *Neurol Res*. 2014;36:308–313.
- Hashimoto T, Meng H, Young WL. Intracranial aneurysms: links among inflammation, hemodynamics and vascular remodeling. *Neurol Res*. 2006;28:372–380.
- Frosen J, Piippo A, Paetau A, Kangasniemi M, Niemela M, Hernesniemi J, Jaaskelainen J. Growth factor receptor expression and remodeling of saccular cerebral artery aneurysm walls: implications for biological therapy preventing rupture. *Neurosurgery*. 2006;58:534–541; discussion 534–541.
- Frosen J, Piippo A, Paetau A, Kangasniemi M, Niemela M, Hernesniemi J, Jaaskelainen J. Remodeling of saccular cerebral artery aneurysm wall is associated with rupture: histological analysis of 24 unruptured and 42 ruptured cases. *Stroke*. 2004;35:2287–2293.
- Chalouhi N, Hoh BL, Hasan D. Review of cerebral aneurysm formation, growth, and rupture. *Stroke*. 2013;44:3613–3622.
- Chalouhi N, Ali MS, Jabbour P, Tjounakaris SI, Gonzalez LF, Rosenwasser RH, Koch WJ, Dumont AS. Biology of intracranial aneurysms: role of inflammation. *J Cereb Blood Flow Metab*. 2012;32:1659–1676.
- Chalouhi N, Ali MS, Starke RM, Jabbour PM, Tjounakaris SI, Gonzalez LF, Rosenwasser RH, Koch WJ, Dumont AS. Cigarette smoke and inflammation: role in cerebral aneurysm formation and rupture. *Mediators Inflamm*. 2012;2012:271582.
- Aoki T, Kataoka H, Morimoto M, Nozaki K, Hashimoto N. Macrophage-derived matrix metalloproteinase-2 and -9 promote the progression of cerebral aneurysms in rats. *Stroke*. 2007;38:162–169.
- Hasan DM, Amans M, Tihan T, Hess C, Guo Y, Cha S, Su H, Martin AJ, Lawton MT, Neuwelt EA, Saloner DA, Young WL. Ferumoxytol-enhanced MRI to image inflammation within human brain arteriovenous malformations: a pilot investigation. *Transl Stroke Res*. 2012;3:166–173.
- Hasan DM, Mahaney KB, Magnotta VA, Kung DK, Lawton MT, Hashimoto T, Winn HR, Saloner D, Martin A, Gahramanov S, Dósa E, Neuwelt E, Young WL. Macrophage imaging within human cerebral aneurysms wall using ferumoxytol-enhanced mri: a pilot study. *Arterioscler Thromb Vasc Biol*. 2012;32:1032–1038.
- Hasan D, Chalouhi N, Jabbour P, Dumont AS, Kung DK, Magnotta VA, Young WL, Hashimoto T, Winn HR, Heistad D. Early change in ferumoxytol-enhanced magnetic resonance imaging signal suggests unstable human cerebral aneurysm: a pilot study. *Stroke*. 2012;43:3258–3265.
- Hassan T, Timofeev EV, Saito T, Shimizu H, Ezura M, Matsumoto Y, Takayama K, Tominaga T, Takahashi A. A proposed parent vessel geometry-based categorization of saccular intracranial aneurysms: computational flow dynamics analysis of the risk factors for lesion rupture. *J Neurosurg*. 2005;103:662–680.
- Shojima M, Oshima M, Takagi K, Torii R, Hayakawa M, Katada K, Morita A, Kirino T. Magnitude and role of wall shear stress on cerebral aneurysm: computational fluid dynamic study of 20 middle cerebral artery aneurysms. *Stroke*. 2004;35:2500–2505.
- Cebral JR, Castro MA, Burgess JE, Pergolizzi RS, Sheridan MJ, Putman CM. Characterization of cerebral aneurysms for assessing risk of rupture by using patient-specific computational hemodynamics models. *AJNR Am J Neuroradiol*. 2005;26:2550–2559.
- Takao H, Murayama Y, Otsuka S, Qian Y, Mohamed A, Masuda S, Yamamoto M, Abe T. Hemodynamic differences between unruptured and ruptured intracranial aneurysms during observation. *Stroke*. 2012;43:1436–1439.
- Ujiie H, Tachibana H, Hiramatsu O, Hazel AL, Matsumoto T, Ogasawara Y, Nakajima H, Hori T, Takakura K, Kajiya F. Effects of size and shape (aspect ratio) on the hemodynamics of saccular aneurysms: a possible index for surgical treatment of intracranial aneurysms. *Neurosurgery*. 1999;45:119–129.
- Hoi Y, Meng H, Woodward SH, Bendok BR, Hanel RA, Guterman LR, Hopkins LN. Effects of arterial geometry on aneurysm growth: Three-dimensional computational fluid dynamics study. *J Neurosurg*. 2004;101:676–681.
- Taylor CL, Yuan Z, Selman WR, Ratcheson RA, Rimm AA. Cerebral arterial aneurysm formation and rupture in 20 767 elderly patients: hypertension and other risk factors. *J Neurosurg*. 1995;83:812–819.
- Lin N, Ho A, Gross BA, Pieper S, Frerichs KU, Day AL, Du R. Differences in simple morphological variables in ruptured and unruptured middle cerebral artery aneurysms. *J Neurosurg*. 2012;117:913–919.
- Hasan DM, Hindman BJ, Todd MM. Pressure changes within the sac of human cerebral aneurysms in response to artificially induced transient increases in systemic blood pressure. *Hypertension*. 2015;66:324–331.
- Ozdamar N, Celebi G. Pressure distribution on the wall of experimental aneurysms. *Acta Neurochir (Wien)*. 1978;45:27–34.
- Nader-Sepahi A, Casimiro M, Sen J, Kitchen ND. Is aspect ratio a reliable predictor of intracranial aneurysm rupture? *Neurosurgery*. 2004;54:1343–1348.
- Tateshima S, Chien A, Sayre J, Cebral J, Vinuela F. The effect of aneurysm geometry on the intra-aneurysmal flow condition. *Neuroradiology*. 2010;52:1135–1141.
- Wermer MJ, van der Schaaf IC, Algra A, Rinkel GJ. Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: an updated meta-analysis. *Stroke*. 2007;38:1404–1410.
- Zylkowski J, Kunert P, Jaworski M, Rosiak G, Marchel A, Rowinski O. Changes of size and shape of small, unruptured intracranial aneurysms in repeated computed tomography angiography studies. *Wideochir Inne Tech Maloinwazyjne*. 2015;10:178–188.
- Dhar S, Tremmel M, Mocco J, Kim M, Yamamoto J, Siddiqui AH, Hopkins LN, Meng H. Morphology parameters for intracranial aneurysm rupture risk assessment. *Neurosurgery*. 2008;63:185–196; discussion 196–197.
- Rinkel G, Djibuti M, Algra A, van Gijn J. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. *Stroke*. 1988;29:251–256.
- Matsukawa H, Uemura A, Fujii M, Kamo M, Takahashi O, Sumiyoshi S. Morphological and clinical risk factors for the rupture of anterior communicating artery aneurysms. *J Neurosurg*. 2013;118:978–983.
- You SH, Kong DS, Kim JS, Jeon P, Kim KH, Roh HK, Kim GM, Lee KH, Hong SC. Characteristic features of unruptured intracranial aneurysms: predictive risk factors for aneurysm rupture. *J Neurol Neurosurg Psychiatry*. 2010;81:479–484.
- Raghavan ML, Ma B, Harbaugh RE. Quantified aneurysm shape and rupture risk. *J Neurosurg*. 2005;102:355–362.
- Nakagawa T, Hashi K. The incidence and treatment of asymptomatic, unruptured cerebral aneurysms. *J Neurosurg*. 1994;80:217–223.

45. Forget TR, Benitez R, Veznedaroglu E, Sharan A, Mitchell W, Silva M, Rosenwasser RH. A review of size and location of ruptured intracranial aneurysms. *Neurosurgery*. 2001;49:1322–1325.
46. Ryu CW, Kwon OK, Koh JS, Kim EJ. Analysis of aneurysm rupture in relation to the geometric indices: aspect ratio, volume, and volume-to-neck ratio. *Neuroradiology*. 2011;53:883–889.
47. Morita A, Kirino T, Hashi K, Aoki N, Fukuhara S, Hashimoto N, Nakayama T, Sakai M, Teramoto A, Tominari S, Yoshimoto T. The natural course of unruptured cerebral aneurysms in a Japanese cohort. *N Engl J Med*. 2012;336:2474–2482.
48. Chalouhi N, Penn DL, Tjoumakaris S, Jabbour P, Gonzalez LF, Starke RM, Ali MS, Rosenwasser R, Dumont AS. Treatment of small ruptured intracranial aneurysms: comparison of surgical and endovascular options. *J Am Heart Assoc*. 2012;1:e002865.
49. Villablanca JP, Duckwiler GR, Jahan R, Tateshima S, Martin NA, Frazee J, Gonzalez NR, Sayre J, Vinuela FV. Natural history of asymptomatic unruptured cerebral aneurysms evaluated at CT angiography: growth and rupture incidence and correlation with epidemiologic risk factors. *Radiology*. 2013;269:258–265.
50. Burns JD, Huston J 3rd, Layton KF, Piepgras DG, Brown RD Jr. Intracranial aneurysm enlargement on serial magnetic resonance angiography: frequency and risk factors. *Stroke*. 2009;40:406–411.
51. Ramachandran M, Retarekar R, Raghavan ML, Berkowitz B, Dickerhoff B, Correa T, Lin S, Johnson K, Hasan D, Ogilvy C, Rosenwasser R, Torner J, Bogason E, Stapleton CJ, Harbaugh RE. Assessment of image-derived risk factors for natural course of unruptured cerebral aneurysms. *J Neurosurg*. 2016;124:288–295.
52. Jeon JS, Ahn JH, Huh W, Son YJ, Bang JS, Kang HS, Sohn CH, Oh CW, Kwon OK, Kim JE. A retrospective analysis on the natural history of incidental small paraclinoid unruptured aneurysm. *J Neurol Neurosurg Psychiatry*. 2014;85:289–294.
53. Bor AS, Tiel Groenestege AT, terBrugge KG, Agid R, Velthuis BK, Rinkel GJ, Wermer MJ. Clinical, radiological, and flow-related risk factors for growth of untreated, unruptured intracranial aneurysms. *Stroke*. 2015;46:42–48.
54. Inoue T, Shimizu H, Fujimura M, Saito A, Tominaga T. Annual rupture risk of growing unruptured cerebral aneurysms detected by magnetic resonance angiography. *J Neurosurg*. 2012;117:20–25.
55. Mehan WA Jr, Romero JM, Hirsch JA, Sabbag DJ, Gonzalez RG, Heit JJ, Schaefer PW. Unruptured intracranial aneurysms conservatively followed with serial CT angiography: could morphology and growth predict rupture? *J Neurointerv Surg*. 2014;6:761–766.
56. Brinjikji W, Zhu YQ, Lanzino G, Cloft HJ, Murad MH, Wang Z, Kallmes DF. Risk factors for growth of intracranial aneurysms: a systematic review and meta-analysis. [published online ahead of print November 26, 2015]. *Stroke*. 2014. <http://www.ajnr.org/content/early/2015/11/26/ajnr.A4575.long>. Accessed January 20, 2015.
57. Juvela S, Poussa K, Lehto H, Porras M. Natural history of unruptured intracranial aneurysms: a long-term follow-up study. *Stroke*. 2013;44:2414–2421.
58. Brinjikji W, Rabinstein AA, Lanzino G, Kallmes DF, Cloft HJ. Effect of age on outcomes of treatment of unruptured cerebral aneurysms: a study of the national inpatient sample 2001–2008. *Stroke*. 2011;42:1320–1324.
59. Brinjikji W, Rabinstein AA, Lanzino G, Kallmes DF, Cloft HJ. Patient outcomes are better for unruptured cerebral aneurysms treated at centers that preferentially treat with endovascular coiling: a study of the national inpatient sample 2001–2007. *AJNR Am J Neuroradiol*. 2011;32:1065–1070.
60. Health Quality Ontario. Coil embolization for intracranial aneurysms: an evidence-based analysis. *Ontario Health Technology Assessment Series*. 2006;6:1–114.
61. Hao Q, Su H, Palmer D, Sun B, Gao P, Yang GY, Young WL. Bone marrow-derived cells contribute to vascular endothelial growth factor-induced angiogenesis in the adult mouse brain by supplying matrix metalloproteinase-9. *Stroke*. 2011;42:453–458.
62. Winn HR, Jane JA Sr, Taylor J, Kaiser D, Britz GW. Prevalence of asymptomatic incidental aneurysms: review of 4568 arteriograms. *J Neurosurg*. 2002;96:43–49.

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