Curr Cardiol Rep (2016) 18: 86
DOI 10.1007/s11886-016-0763-4

STROKE (JF MESCHIA, SECTION EDITOR)

Management of Unruptured Intracranial Aneurysms

Deena M. Nasr[1] · **Robert D. Brown Jr.**[1]

Published online: 21 July 2016

Abstract Unruptured intracranial aneurysms (UIA) occur in approximately 2–3 % of the population. Most of these lesions are incidentally found, asymptomatic and typically carry a benign course. Although the risk of aneurysmal subarachnoid hemorrhage is low, this complication can result in significant morbidity and mortality, making assessment of this risk the cornerstone of UIA management. This article reviews important factors to consider when managing unruptured intracranial aneurysms including patient demographics, comorbidities, family history, symptom status, and aneurysm characteristics. It also addresses screening, monitoring, medical management and current surgical and endovascular therapies.

Keywords Intracranial aneurysms · Subarachnoid hemorrhage · Natural history · Epidemiology · Treatment

Introduction

Saccular aneurysms, also known as berry aneurysms, are the most common type of intracranial aneurysm (IA). These arterial wall outpouchings commonly occur at proximal arterial bifurcations in the Circle of Willis. The prevalence of unruptured intracranial aneurysms (UIAs) in the general population has been estimated to be anywhere from 1 to 10 % [1, 2] with most studies suggesting a frequency of about 2–3 % for unruptured intracranial aneurysms [1]. UIAs are typically discovered as an incidental finding on head imaging performed for unrelated reasons [3]. While most UIAs are asymptomatic, some present with symptoms including headache, seizure, focal deficit, or cranial nerve palsy from mass effect and rarely with ischemic stroke from emboli distal to the aneurysm [4–6]. Intracranial aneurysms can also present with subarachnoid hemorrhage (SAH), with associated potentially significant morbidity and mortality [7, 8]. In order to optimally manage UIAs, it is important to identify factors associated with the presence of a UIA and predictors of rupture once detected and carefully compare these risks of rupture to the risks of interventional management.

This article is part of the Topical Collection on *Stroke*

✉ Deena M. Nasr
nasr.deena@mayo.edu

Robert D. Brown, Jr.
brown@mayo.edu

[1] Department of Neurology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Risk Factors

There are several non-modifiable risk factors associated with the presence of IA including the female gender (3:1 prevalence), older age (>50 years), family history of IA or SAH, and hereditary diseases associated with intracranial aneurysms such as autosomal dominant polycystic kidney disease (ADPKD). Ethnicity has also been shown to be a risk factor, as individuals of Finnish or Japanese descent appear to have both an increased prevalence and rate of rupture when compared to North American and other European populations (3.6 and 2.8×, respectively) [9, 10••].

Screening

Current studies and guidelines typically recommend screening individuals with a family history of two or more first-degree relatives with UIA or SAH, as the prevalence of aneurysms in these populations is 8–10 % [11••]. There is a 4 % risk of UIA in those with one affected relative, and although not typically

recommended, it would not be inappropriate to consider screening in those individuals, particularly if there are other risk factors present. The role of screening in patients with only affected second-degree relatives is less certain.

Screening for IA is also advised in patients with hereditary or congenital diseases that predispose to intracranial aneurysms. These diseases include ADPKD, Ehlers Danlos-vascular type IV, microcephalic osteodysplastic primordial dwarfism, coarctation of the aorta, and bicuspid aortic valve [11••]. In population-based studies of patients with ADPKD, approximately 10 % had UIA and the prevalence rose to 20 % if there was a family history of IA [1, 12], leading to the recommendation to strongly consider screening of those family members affected with ADPKD, especially if there is a family history of UIA or SAH.

Radiographic screening is recommended with either a magnetic resonance angiography (MRA) or a computer-tomography angiography (CTA). Screening is generally recommended to begin in the fourth decade for high-risk patients (i.e., ADPKD or a strong family history), as aneurysm occurrence typically increases with age [13]. However, studies show that de novo aneurysm formation can occur in up to 7 % of cases following a negative initial screening study [14]. For this reason, high-risk patients with a negative initial screen are advised to undergo repeat screening every 5 years.

Natural History

There are seven large prospective UIA natural history studies to date, which estimate the overall annual rupture risk of UIA to be 0.5–1.4 %/year [15–21]. The International Study of Unruptured Intracranial Aneurysms (ISUIA) is a North American prospective study that followed 1692 patients with UIA and found that larger aneurysm size, location of the aneurysm (posterior circulation and posterior communicating artery (PCOM)), and previous subarachnoid hemorrhage are the strongest predictors of rupture. The largest prospective cohort published to date is the Unruptured Cerebral Aneurysm Study (UCAS) from Japan which followed 6697 patients and found that along with aneurysm size (>7 mm), factors associated with increased risk of rupture were aneurysm location (anterior and posterior communicating arteries) and the presence of a daughter sac, defined as an irregular protrusion of the aneurysm wall [19].

Several of the other prospective studies have also suggested that larger size and posterior circulation location are associated with risk of rupture. Other factors that have been reported to be associated with rupture of a UIA include previous history of SAH [15, 16, 21], presence of daughter sac [19, 21] multiple aneurysms [17], hypertension, cigarette smoking, and heavy alcohol consumption [20]. Two smaller prospective studies from Finland and Japan have shown that age <50 years was associated with risk of rupture [17, 20].

Pooled data from large prospective series on the natural history of UIAs have been essential to developing predictive models for aneurysm growth and rupture. In a recent study, investigators from six large prospective natural history studies pooled data on 8382 patients to develop a prognostication scoring system called PHASES [10••, 22]. The PHASES scoring system individualizes the 5-year UIA rupture risk based on six risk factors: (1) population, (2) hypertension, (3) age, (4) size of aneurysm, (5) earlier SAH from another aneurysm, and (6) site of aneurysm. A summary of the PHASES scoring system is provided in Table 1. Population-based risk factors include Japanese or Finnish ancestry. Site-based risk factors include middle cerebral artery (MCA) bifurcation location and anterior cerebral artery (ACA)/posterior communicating artery (PCom)/posterior circulation location. Scoring systems such as PHASES can only be used as a guide since there are several aspects that should be considered that are not included in this scoring system including aneurysm sac and neck morphology, hemodynamics, history of growth on sequential angiographic studies, history of smoking, medical comorbidities that would affect surgical/endovascular treatments, family history of subarachnoid hemorrhage, and a history of connective tissue disease.

Table 1 Summary of PHASES score

	Number of points
Population	
North America or European (not Finnish)	0
Japanese	3
Finnish	5
Hypertension	
No	0
Yes	1
Age	
<70 years	0
≥70	1
Size of aneurysm	
<7 mm	0
7–9.9 mm	3
10–19.9 mm	6
≥20 mm	10
Earlier SAH from another aneurysm	
No	0
Yes	1
Site of aneurysm	
ICA	0
MCA	2
ACA/Pcom/posterior	4

Five-year rupture risk ranges from 0.4 % for ≤2 points to 17.8 % for ≥12 points

Aneurysm growth on serial imaging is a risk factor for UIA aneurysm rupture. The definition of aneurysm enlargement is variably defined, but an increase of ≥1 mm would be considered as enlargement for small aneurysms, ≤5 mm in diameter, and an increase of ≥2 mm for aneurysms ≥5 mm in diameter. Aneurysms that demonstrate growth on long-term follow-up (~4 years) have rupture rates of about 3 % per year compared to about 0.1 % per year for aneurysms that demonstrate stability on follow-up [23]. Growth of an aneurysm on follow-up imaging will often trigger endovascular or surgical intervention due to the higher rate of rupture. The PHASES score has been shown to be predictive of aneurysm growth as well as rupture [10••, 22]. Other factors that have been shown to be associated with aneurysm growth in one recently published meta-analysis include age (>50 years), female sex, smoking history, shape (non-saccular, lobulated, or daughter sac), location, and size >10 mm [23].

Management

Once an incidental and asymptomatic unruptured intracranial aneurysm is detected, an individualized assessment of the balance of risk of rupture versus risk of intervening should be performed in order to determine the best management option for each patient (Table 2). If an incidental asymptomatic IA is deemed to have a low risk of rupture, then conservative management is warranted. This includes optimizing modifiable risk factors such as smoking cessation and blood pressure control in conjunction with radiographic monitoring for growth by serial CTA or MRA as growing aneurysms are associated with a high risk of rupture [23, 24••]. There are no guidelines regarding the optimal interval in which to serially image these patients. However, annual MRA or CTA for at least 3–5 years with reduction in imaging frequency once stability is established is reasonable.

In addition to aneurysm growth during follow-up, new neurological symptoms caused by compressive or ischemic phenomena from a UIA would lead to a recommendation for treatment. It is generally thought that these symptoms are due to aneurysm growth and therefore portend a higher risk of rupture. Furthermore, compressive and ischemic symptoms from an aneurysm can be debilitating, and it is possible that treatment of the UIA could mitigate these symptoms.

In addition to predictive models of rupture risk and close monitoring of brain aneurysm patients, clinicians have other tools that they can rely on to decide whether or not to treat an aneurysm. There is a new treatment risk model named the Unruptured Intracranial Aneurysm Treatment Score (UIATS), which has been developed based on consensus of multidisciplinary experts in the field and indirect data from natural history and intervention studies. This model is an attempt to individualize the comparison of risks of intervention compared to conservative management [24••]. The UIATS model accounts for 29 factors in UIA management, including demographic factors, symptoms, life expectancy, aneurysm size and morphology, and treatment-related factors.

Once a decision is made to take an interventional approach to the UIA; the type of intervention depends on several characteristics, including patient's age, co-morbidities, aneurysm location, morphology, size, and procedure-related risk factors. The most common approaches are craniotomy with clipping or endovascular therapies such as coiling alone, device-assisted coiling (i.e., stent or balloon angioplasty), and flow-diverting stenting.

In general, aneurysms with a narrow neck may be considered for coiling of the sac, as opposed to those with a wide neck. If endovascular therapies are pursued for wide-necked aneurysms, these may include stent-assisted coiling to keep the coils within the aneurysm sac or flow diversion; these aneurysms may also be treated with surgical clipping. Over the past several years, flow diversion has emerged as the method of choice for treating large and wide-necked unruptured aneurysms of the internal carotid artery (ICA) with high cure rates and low complication rates [25, 26]. Meanwhile, coiling is preferred for treating narrow-necked ICA aneurysms as well as aneurysms of the posterior circulation aneurysms and ACA/anterior communicating artery complex [26]. Patients who are treated with simple coiling (i.e., without stent placement) do not require dual antiplatelet therapy while patients who are treated with stent-assisted coiling or flow diversion require dual antiplatelet therapy for at least 5 days prior to the procedure and then 3–6 months following treatment. After 3–6 months, these patients are kept on aspirin for life.

Contemporary endovascular management of UIAs is generally considered to be associated with a periprocedural morbidity and mortality rate of 2 and 0.5 % for coiling and 3 and 1 % for flow diversion, respectively [26, 27]. The primary

Table 2 Summary of considerations for management of unruptured aneurysms

Factors favoring conservative management	Small aneurysm; few risk factors (see Table 1); low PHASES score; older age, medical factors suggesting short life expectancy
Factors favoring clipping, if interventional treatment is indicated	Age <50 years; small aneurysms; anterior circulation; wide-neck aneurysms or branches from aneurysm sac/neck
Factors favoring endovascular treatment, if interventional treatment is indicated	Age >50 years; patients with increased surgical risk; narrow neck; posterior circulation location

causes of morbidity from endovascular procedures are perioperative infarction and intraoperative rupture. Rates of perioperative morbidity and mortality depend on a variety of risk factors including aneurysm size (giant aneurysms and tiny aneurysms are often associated with higher complication rates), location (posterior circulation is associated with higher complication rates), and morphology [26]. Close postoperative follow-up is recommended for all endovascular-treated patients as recurrence rates range from 5 to 15 % [26]. Catheter angiography is the preferred imaging modality for follow-up of these patients in the short term. Contrast-enhanced MRA is also useful [28]. Modern endovascular implants are MRI compatible.

There are some situations in which surgical clipping is favored over endovascular treatment. In general, clipping is often considered for MCA bifurcation aneurysms [27, 29]. Furthermore, clipping is a reasonable option for very small aneurysms as these aneurysms are harder to treat with endovascular techniques [30]. Complex aneurysm morphologies may also favor clipping, especially aneurysms with branches arising from the sac/neck or those with a wide neck. Surgical clipping requires an open craniotomy to visualize and clip the aneurysm. The clip is typically made of platinum metal and placed at the neck of the aneurysm. Surgical clipping is effective in eliminating the aneurysm, and recurrence risks are generally very low. There are two randomized controlled trials comparing outcomes of clipping compared to coiling in ruptured aneurysms, but none comparing these outcomes in unruptured aneurysms [31, 32]. There is, however, a trial underway called The Canadian Unruptured Endovascular Versus Surgery Trial. Outcomes for this trial include treatment success, overall morbidity and mortality, perioperative morbidity and mortality, hospital length of stay, and angiographic outcomes [33]. A meta-analysis comparing clipping and endovascular treatment of unruptured aneurysms demonstrated that in general, coiling is associated with lower short-term complications and morbidity as compared to clipping [27]. However, treatment decisions need to be made on a case-by-case basis, carefully weighing the risks and benefits of all potential management options [34].

Medical Management

Antithrombotics are not contraindicated in the setting of unruptured intracranial aneurysms. It is generally recommended that antiplatelet and anticoagulation medications be used if there is a specific indication for treatment (i.e., atrial fibrillation, cardiac stenting, DVT prophylaxis, etc). While there have been a few case-control studies that suggest an increased association with dipyramidole and non-traumatic subarachnoid hemorrhage [35] and worsened outcomes in patients with subarachnoid hemorrhage on anticoagulation; there are no studies demonstrating an association between aneurysm rupture and anticoagulant or antiplatelet use [36, 37].

There is some experimental evidence suggesting that aspirin therapy could potentially reduce aneurysm wall inflammation and thus risk of rupture [38, 39]. In an analysis of the ISUIA cohort, the UIA rupture risk was somewhat lower in patients who were taking aspirin most frequently, but the data are not definitive in terms of leading to a change in clinical practice [40]. In one small randomized controlled trial including 11 patients randomized to daily aspirin therapy or placebo, Hasan et al found that patients on aspirin therapy had decreased macrophage activity and aneurysm wall inflammation when compared to those on placebo. Ultimately, further randomized controlled trials are needed to validate these findings [41].

For hypertension management, there is no level 1 evidence supporting the use of one antihypertensive over another. The best treatment strategy is to find an antihypertensive that is effective and well tolerated. There is some experimental evidence that suggests that angiotensin-converting enzyme (ACE)-inhibitors and angiotensin receptor blockers are effective in reducing aneurysm rupture in animal models; however, no human studies to date have validated these findings [42]. These agents are thought to prevent aneurysm rupture by decreasing elastin degradation.

Statin therapy is recommended for aneurysm patients only if a specific separate indication exists (i.e., hypercholesterolemia, coronary artery disease, and cerebrovascular disease). In general, large studies have demonstrated no association between statin therapy and aneurysm growth or rupture [43]. One large study of 1200 patients found no association between statin use and incidence of intracranial aneurysm formation [44]. These findings contrast those of animal models which indicated that statin therapy is associated with a reduced incidence of aneurysm formation through pleiotropic effects including inhibition of inflammation and improved endothelial function [45].

Conclusions/Main Points

Over the last two decades, natural history studies have clarified factors that may predict a higher risk of rupture in certain saccular aneurysms. Aneurysms with low rupture risk can be monitored for growth with serial radiographic imaging. Those with a predicted risk of rupture that is greater than management risks should be considered for intervention such as craniotomy with clipping or endovascular therapies (i.e., coiling, assisted coiling, flow diversion stent, or flow disruption). Aneurysm screening should be considered for patients with a high risk of aneurysm detection (i.e., >2 affected first degree relatives with UIA or SAH, ADPKD, other disorders

associated with a high frequency of UIA detection) who would be candidates for intervention. Antithrombotics have not been shown to increase rupture risk in patients with unruptured intracranial aneurysms and may be used for a specific indication. Aspirin may actually lower the risk of rupture in UIAs, but this issue requires further study before aspirin would be recommended for all patients with a UIA. However, despite the evolving available data, the optimal management of all UIAs is uncertain. Additional study is needed to clarify many of the key clinical questions that occur when managing a patient with a UIA. Clarification of the optimal imaging interval and frequency for those managed conservatively is important. Data regarding specific surgical or endovascular outcomes based on particular aneurysmal morphology, size, and location are important. Lastly, medical strategies aimed at reducing the risk of UIA rupture, and studies aimed at determining the influence of genetic factors on outcomes are essential.

Compliance with Ethical Standards

Conflict of Interest Deena M. Nasr and Robert D. Brown, Jr. declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Vlak MH, Algra A, Brandenburg R, et al. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. Lancet Neurol. 2011;10(7):626–36.
2. Li MH, Chen SW, Li YD, et al. Prevalence of unruptured cerebral aneurysms in Chinese adults aged 35 to 75 years: a cross-sectional study. Ann Intern Med. 2013;159(8):514–21.
3. Vernooij MW, Ikram MA, Tanghe HL, et al. Incidental findings on brain MRI in the general population. N Engl J Med. 2007;357(18):1821–8.
4. Qureshi AI, Mohammad Y, Yahia AM, et al. Ischemic events associated with unruptured intracranial aneurysms: multicenter clinical study and review of the literature. Neurosurgery. 2000;46(2):282–9. discussion 9–90.
5. Guillon B, Daumas-Duport B, Delaroche O, et al. Cerebral ischemia complicating intracranial aneurysm: a warning sign of imminent rupture? AJNR Am J Neuroradiol. 2011;32(10):1862–5.
6. Arauz A, Patino-Rodriguez HM, Chavarria-Medina M, et al. Embolic stroke secondary to spontaneous thrombosis of unruptured intracranial aneurysm: report of three cases. Interv Neuroradiol. 2016;22(2):196–200.
7. Menghini VV, Brown Jr RD, Sicks JD, et al. Clinical manifestations and survival rates among patients with saccular intracranial aneurysms: population-based study in Olmsted County, Minnesota, 1965 to 1995. Neurosurgery. 2001;49(2):251–6. discussion 6–8.
8. van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. Lancet. 2007;369(9558):306–18.
9. Wermer MJ, van der Schaaf IC, Algra A, et al. Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: an updated meta-analysis. Stroke. 2007;38(4):1404–10.
10. •• Greving JP, Wermer MJ, Brown Jr RD, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. Lancet Neurol. 2014;13(1):59–66. **This reference details the development of the PHASES score and demonstrates the association between the PHASES score and risk of rupture. This study provides a nice summary of the six largest and most comprehensive natural history studies of unruptured intracranial aneurysms to date**.
11. •• Thompson BG, Brown Jr RD, Amin-Hanjani S, et al. Guidelines for the management of patients with unruptured intracranial aneurysms: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015;46(8):2368–400. **This reference summarizes the most up to date guidelines for the management of patients with unruptured intracranial aneurysms. It is a comprehensive review of screening guidelines, treatment guidelines and role of risk factor modification**.
12. Xu HW, Yu SQ, Mei CL, et al. Screening for intracranial aneurysm in 355 patients with autosomal-dominant polycystic kidney disease. Stroke. 2011;42(1):204–6.
13. Lee JS, Park IS, Park KB, et al. Familial intracranial aneurysms. J Korean Neurosurg Soc. 2008;44(3):136–40.
14. Wermer MJ, Rinkel GJ, van Gijn J. Repeated screening for intracranial aneurysms in familial subarachnoid hemorrhage. Stroke. 2003;34(12):2788–91.
15. Wiebers DO, Whisnant JP, Huston 3rd J, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet. 2003;362(9378):103–10.
16. Ishibashi T, Murayama Y, Urashima M, et al. Unruptured intracranial aneurysms: incidence of rupture and risk factors. Stroke. 2009;40(1):313–6.
17. Sonobe M, Yamazaki T, Yonekura M, et al. Small unruptured intracranial aneurysm verification study: SUAVe study, Japan. Stroke. 2010;41(9):1969–77.
18. Lee EJ, Lee HJ, Hyun MK, et al. Rupture rate for patients with untreated unruptured intracranial aneurysms in South Korea during 2006-2009. J Neurosurg. 2012;117(1):53–9.
19. Morita A, Kirino T, Hashi K, et al. The natural course of unruptured cerebral aneurysms in a Japanese cohort. N Engl J Med. 2012;366(26):2474–82.
20. Juvela S, Poussa K, Lehto H, et al. Natural history of unruptured intracranial aneurysms: a long-term follow-up study. Stroke. 2013;44(9):2414–21.
21. Murayama Y, Takao H, Ishibashi T, et al. Risk analysis of unruptured intracranial aneurysms: prospective 10-year cohort study. Stroke. 2016;47(2):365–71.
22. Backes D, Vergouwen MD, Tiel Groenestege AT, et al. PHASES score for prediction of intracranial aneurysm growth. Stroke. 2015;46(5):1221–6.
23. Brinjikji W, Zhu YQ, Lanzino G, et al. Risk factors for growth of intracranial aneurysms: a systematic review and meta-analysis. AJNR Am J Neuroradiol. 2016;37(4):615–20.

24.•• Etminan N, Brown Jr RD, Beseoglu K, et al. The unruptured intracranial aneurysm treatment score: a multidisciplinary consensus. Neurology. 2015;85(10):881–9. **This reference summarizes the development of the Unruptured Intracranial Aneurysm Treatment Score and details the various components of the score. This score can serve as a general guideline to inform practitioners regarding the best treatment options for unruptured intracranial aneurysms**.

25. Brinjikji W, Murad MH, Lanzino G, et al. Endovascular treatment of intracranial aneurysms with flow diverters: a meta-analysis. Stroke. 2013;44(2):442–7.

26. Petr O, Brinjikji W, Cloft H, et al. Current trends and results of endovascular treatment of unruptured intracranial aneurysms at a single institution in the flow-diverter era. AJNR Am J Neuroradiol 2016. Epub 2016/01/23.

27. Falk Delgado A, Andersson T. Clinical outcome after surgical clipping or endovascular coiling for cerebral aneurysms: a pragmatic meta-analysis of randomized and non-randomized trials with short- and long-term follow-up. J Neurointerventional Surg 2016. Epub 2016/04/08.

28. Levent A, Yuce I, Eren S, et al. Contrast-enhanced and time-of-flight MR angiographic assessment of endovascular coiled intracranial aneurysms at 1.5 T. Interv Neuroradiol. 2014;20(6):686–92.

29. Tenjin H, Yamamoto Y, Goto Y, et al. Factors for achieving safe and complete treatment for unruptured saccular aneurysm smaller than 10 mm by simple clipping or simple coil embolization. World Neurosurg 2016. Epub 2016/04/14.

30. Yamaki VN, Brinjikji W, Murad MH, et al. Endovascular treatment of very small intracranial aneurysms: meta-analysis. AJNR Am J Neuroradiology 2015. Epub 2016/01/02.

31. Molyneux A, Kerr R, Stratton I, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet. 2002;360(9342):1267–74.

32. Spetzler RF, McDougall CG, Zabramski JM, et al. The Barrow Ruptured Aneurysm Trial: 6-year results. J Neurosurg. 2015;123(3):609–17.

33. Darsaut TE, Findlay JM, Raymond J. The design of the Canadian UnRuptured Endovascular versus Surgery (CURES) trial. Can J of Neurol Sci. 2011;38(2):236–41.

34. Chua MH, Griessenauer CJ, Stapleton CJ, et al. Documentation of improved outcomes for intracranial aneurysm management over a 15-year interval. Stroke. 2016;47(3):708–12.

35. Schmidt M, Johansen MB, Lash TL, et al. Antiplatelet drugs and risk of subarachnoid hemorrhage: a population-based case-control study. J Thromb Haemost. 2010;8(7):1468–74.

36. Rinkel GJ, Prins NE, Algra A. Outcome of aneurysmal subarachnoid hemorrhage in patients on anticoagulant treatment. Stroke. 1997;28(1):6–9.

37. Tarlov N, Norbash AM, Nguyen TN. The safety of anticoagulation in patients with intracranial aneurysms. J Neurointerventional Surg. 2013;5(5):405–9.

38. Hasan DM, Chalouhi N, Jabbour P, et al. Imaging aspirin effect on macrophages in the wall of human cerebral aneurysms using ferumoxytol-enhanced MRI: preliminary results. J Neuroradiol. 2013;40(3):187–91.

39. Welling LC, Welling MS, Teixeira MJ, et al. Vessel wall magnetic resonance imaging, inflammatory cascade, aspirin, and aneurysm rupture: future paradigms? World Neurosurg. 2015;84(2):206–7.

40. Hasan DM, Mahaney KB, Brown Jr RD, et al. Aspirin as a promising agent for decreasing incidence of cerebral aneurysm rupture. Stroke. 2011;42(11):3156–62.

41. Hasan DM, Chalouhi N, Jabbour P, et al. Evidence that acetylsalicylic acid attenuates inflammation in the walls of human cerebral aneurysms: preliminary results. J Am Heart Assoc. 2013;2(1):e000019.

42. Tada Y, Wada K, Shimada K, et al. Roles of hypertension in the rupture of intracranial aneurysms. Stroke. 2014;45(2):579–86.

43. Bekelis K, Smith J, Zhou W, et al. Statins and subarachnoid hemorrhage in Medicare patients with unruptured cerebral aneurysms. Int J Stroke. 2015;10(Suppl A100):38–45.

44. Marbacher S, Schlappi JA, Fung C, et al. Do statins reduce the risk of aneurysm development? A case-control study. J Neurosurg. 2012;116(3):638–42.

45. Bambakidis NC, Selman WR. Statins and aneurysms. J Neurosurg. 2012;116(3):636–7. discussion 7.