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Aspirin Decreases Contrast Enhancement of the Wall of Unruptured Intracranial Aneurysms: A 3T HR-VWI Study

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Abstract

Introduction: Inflammation plays an integral role in the formation, growth and progression to rupture of unruptured intracranial aneurysms (UIAs). Animal and human studies have suggested that aspirin (ASA) may decrease risk of growth and rupture of UIAs due to its anti-inflammatory effect. High-resolution vessel wall imaging (HR-VWI) has emerged as a non-invasive biomarker of vessel wall inflammation and UIA instability. To date, no studies have found a significant correlation between use of ASA and contrast enhancement of UIAs on HR-VWI.

Methods: The University of Iowa HR-VWI Project database was analyzed. This database compiles patients with UIAs who prospectively underwent HR-VWI on a 3T Siemens MRI scanner. Presence of aneurysmal wall enhancement was objectively defined using the aneurysm-to-pituitary contrast ratio (CR_{stalk}). This ratio was calculated by measuring the maximal signal intensity in the aneurysmal wall and the pituitary stalk on post-contrast T1-weighted images. Aneurysm size, morphology, location and patients' demographics/comorbidities were collected. Use of ASA was defined as daily intake of ≥81 mg during the last 6 months or longer. Uni- and multivariate logistic regression analyses were performed to determine factors independently associated with increased contrast enhancement of UIAs on HR-VWI.

Results: Seventy-four patients harboring 96 UIAs were included in the study. Mean age was 64.7±12.4 years-old, and 60 (81%) were women. Multivariate analysis showed that age (OR 1.12,

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95% CI 1.05-1.19), aneurysm size ≥7 mm (OR 21.3, 95% CI 4.88-92.8) and location in the ACOM, PCOM and BA arteries (OR 10.7, 95% CI 2.45-46.5) were significantly associated with increased wall enhancement. On the other hand, use of ASA was significantly associated with decreased aneurysm enhancement on HR-VWI (OR 0.22, 95% CI 0.06-0.83, *P*=0.026).

Conclusions: Use of ASA daily for ≥ 6 months significantly decreases wall enhancement of UIAs on HR-VWI. This finding suggests that HR-MRI might be used as a non-invasive biomarker of aneurysm wall inflammation and UIA instability.

Keywords

aspirin; inflammation; high-resolution vessel wall imaging; magnetic resonance imaging; aneurysm; circumferential enhancement

INTRODUCTION

Unruptured intracranial aneurysms (UIAs) continue to pose a therapeutic dilemma where the risk-benefit analysis of therapeutic interventions has to be balanced against the natural history of the disease. UIAs are found in 3-5% of the adult population worldwide.[35] Although the large majority will never rupture, 27%-44% of patients who develop aneurysmal subarachnoid hemorrhage (aSAH) may die within 12 months,[10,25] and those who survive experience a 17% excess mortality after 20 years compared with the general population.[23] Results from large prospective trials such as the International Study of Unruptured Intracranial Aneurysms (ISUIA),[38] the Unruptured Cerebral Aneurysms Study (UCAS)[24] and the PHASES study[12] have identified demographics (age, sex, smoking), history of previous aSAH, aneurysm size, location and morphology as important determinants of rupture risk.

Currently, it is unclear what prompts the growth and rupture of cerebral aneurysms; inflammation of the arterial wall may have a pivotal role in this process.[5,15,18,20] Flow and histological studies have proposed that increased hemodynamic stress triggers infiltration of inflammatory cells (mostly M1 macrophages) into the arterial wall. Locally, these cells induce synthesis of cytokines, adhesion molecules and reactive oxygen species, inflammatory mediators that ultimately lead to endothelial dysfunction, proteolytic destruction of the vascular extracellular matrix by metalloproteinases, and weakening of the aneurysmal wall. Several animal and human studies have shown that aspirin (ASA) attenuates inflammation in the wall of UIA and decreases both growth and rupture of UIAs.[4,6,13,18,26,33]

High-resolution vessel wall imaging (HR-VWI) has also been used to study the structure, thickness and enhancement of the wall of brain aneurysms. Recently, a histological analysis of human aneurysm wall tissue suggested a significant correlation between increased enhancement and inflammation and therefore, aneurysm instability.[31] To date, the only longitudinal study that has prospectively assessed the association between aneurysmal wall enhancement on HR-MRI and risk of aneurysm growth and rupture in patients with UIAs was published by Vergouwen and colleagues.[34] They included a total of 57 patients harboring 65 UIAs. After a median follow-up of 27 months, growth (n = 2) or rupture (n =

2) was observed in 4 of 19 enhancing aneurysms, whereas none of 46 non-enhancing UIAs showed growth or progressed to rupture. Statistically, they found a mean risk difference of 21% for enhancing UIAs compared to non-enhancing aneurysms.[34]

In the current study, we aim to assess the correlation between increased enhancement of UIAs on HR-VWI and classic risk factors of aneurysm rupture, and to define the effect of ASA on the wall enhancement of UIAs.

METHODS

Patient Population and Data Collection

After Institutional Review Board approval, we conducted an analysis of the University of Iowa HR-VWI Project database (January 2015 – August 2019). This database collects patients who prospectively underwent HR-VWI at diagnosis as part of our institutional protocol to assess incidental UIAs. Non-saccular aneurysms were excluded from the study. Demographics and clinical information including age, sex and comorbidities were gathered from electronic medical records. Patients who were actively smoking or quitted within the last 6 months were categorized as positive. Use of ASA was defined as daily intake of ≥ 81 mg during the last 6 months or longer. These cut-offs were based on previous HR-VWI studies published by our group assessing the enhancement of the wall of unruptured intracranial aneurysms with ferumoxytol as contrast agent.[15,17]

Imaging Acquisition

Images were routinely acquired with a 3T Siemens MRI scanner (Siemens MAGNETOM Skyra, Munich, Germany). Our HR-VWI protocol included a 3D T1-weighted SPACE fast-spin-echo (FSE) and a 3D T2-weighted sequence. Five minutes after intravenous injection of 0.1 mmol/kg gadolinium-based contrast agent (GBCA) gadobutrol (Gadavist, Bayer Pharmaceuticals, Whippany, NJ), a post-contrast 3D T1-weighted SPACE FSE sequence and a contrast-enhanced magnetic resonance angiography (CE-MRA) were obtained. Technical parameters used for imaging acquisition are described in the Supplementary Material.

HR-VWI Assessment

All the images were analyzed with Picture Archiving Communication System (Carestream Vue PACS, Rochester, NY). Aneurysm size (diameter and neck) was measured based on CE-MRA images. After six-fold magnification and auto-correction of viewer windowing, the aneurysm was manually co-registered in both pre- and post-contrast T1-weighted sequences using the same slide in all 3 planes (axial, coronal and sagittal). A biplanar region of interest (ROI) covering the aneurysm wall was drawn at the level of maximal aneurysm diameter. CE-MRA images were used as a reference to correctly delineate the inner surface of the aneurysm wall, whereas T2-weighted sequence was used to distinguish the presence of cisterns/cerebrospinal fluid surrounding the vessel and define its outer surface. The pre-contrast T1-weighted sequence was used as a reference to define the overall thickness of the aneurysmal wall, and avoid including into the ROI areas of pseudo-enhancement secondary to luminal contrast stagnation.

Then, the aneurysm-to-pituitary stalk ratio (CR_{stalk}) was calculated as the contrast ratio of the maximal signal intensity (SI) of the aneurysm wall on the post-contrast T1-weighted sequence over the averaged pituitary stalk enhancement as described elsewhere.[29,30] Briefly, 4 different SI points were randomly sampled throughout the pituitary stalk in the sagittal post-contrast T1-weighted images. The maximal SI of all these points was used as the denominator to calculate the CR_{stalk} as follows: maximal $SI_{wall\ post}$/maximal $SI_{stalk\ post}$. Based on published literature,[30] a cut-off ≥ 0.60 for CR_{stalk} was used to define presence or absence of increased enhancement in the aneurysmal wall.

Statistical Analysis

Data are summarized as mean and standard deviation for continuous variables, and as frequency for categorical variables. Patients on regular use of ASA were compared to those without or inconsistent use of ASA. Aneurysm enhancement on HR-VWI was treated as a binary categorical variable, presence or absence, based on CR_{stalk} results. Univariate analysis was used to test baseline covariates association with aneurysm enhancement. Statistical analyses of categorical variables were performed using the $\chi 2$ and Fisher exact tests; comparison of means was performed using Student t-test. Factors associated with aneurysm enhancement in the univariate analysis ($P < 0.20$) were also entered into an aneurysm-specific multivariate logistic regression analysis, adjusted for aneurysm multiplicity. P-values < 0.05 were considered statistically significant in the multivariate model. Odds ratios (ORs) were estimated for magnitude of effect with 95% confidence intervals (CI). All statistical analyses were performed with SPSS Statistics version 25.0 (IBM, Armonk, New York).

RESULTS

Patient Characteristics

A total of 74 patients with 96 UIAs were included. Mean age was 64.7 ± 12.4 years-old, and 60 (81%) were women. Baseline characteristics of the sample are detailed in Table 1. Among comorbidities, 41 (55.4%) had hypertension, 40 (54.1%) patients had positive smoking status according to our criteria, and 32 (43.2%) had hyperlipidemia. Thirty-nine (52.7%) patients were taking ≥81 mg of ASA daily during the last 6 months or longer. At diagnosis, no patients were on dual antiplatelet therapy. Seven (9.5%) patients had family history of intracranial aneurysms and 4 (5.4%) had history of previous SAH. Additionally, no patients with aneurysmal wall enhancement in this cohort went on to have SAH since they were treated promptly.

Aneurysms Characteristics

Mean aneurysm diameter was 8.1 mm (range 3-27 mm). Twenty-six (27.1%) aneurysms were located in the middle cerebral artery (21 MCA bifurcation, 2 M1 segment, 3 M2 segment), 25 (26%) in the internal carotid artery (7 ophthalmic/paraophthalmic, 6 supraclinoid, 4 T-terminus, 6 cavernous, and 2 paraclinoid), 15 (14.6%) in the basilar artery (11 BA tip, 2 mid-BA, 2 vertebrobasilar junction), 16 anterior communicating artery (ACOM), 5 posterior communicating artery (PCOM), 5 anterior cerebral artery (2 A1 segment, 3 A2/pericallosal), 3 superior cerebellar artery and 1 vertebral artery. Correlation

statistics demonstrated high agreement for areas covered by ROIs in the axial, coronal and sagittal projections for co-registered pre- and post-contrast T1-weighted images (Pearson coefficients > 0.93, $P<0.001$).

Factors Associated With Aneurysmal Wall Enhancement

Results from univariate and multivariate analyses using $CR_{stalk} \geq 0.60$ as cutoff to define aneurysm enhancement are presented in Table 2. Although ORs for sex, hypertension, hyperlipidemia, smoking status and history of previous SAH favored presence of wall enhancement on HR-VWI, such associations were statistically non-significant ($P > 0.20$) and were not included in the multivariate analysis. Based on the univariate analysis, age, aneurysm location in the ACOM/PCOM/BA and aneurysm size ≥ 7 mm were associated with increased wall enhancement (age OR = 1.05, $P = 0.007$; location OR = 2.22, $P = 0.07$; size OR = 6.15, $P = <0.001$), while aspirin use was associated with a lower chance of aneurysmal wall enhancement (OR = 0.46, $P = 0.17$).

When multivariate analysis was applied, independent factors significantly associated with increased wall enhancement on HR-VWI were: age (OR = 1.12, 95% CI = 1.05-1.19, $P = 0.001$), location in the ACOM, PCOM and BA arteries (OR = 10.7, 95% CI = 2.45-46.5, $P = 0.002$) and size ≥ 7 mm (OR = 21.3, 95% CI = 4.88-92.8, $P = <0.001$). On the other hand, daily intake of ASA was significantly protective (OR 0.22, 95% CI 0.06-0.83, P = 0.026), reducing the odds of aneurysmal wall enhancement by an average of 78%.

DISCUSSION

Aneurysm Enhancement on HR-VWI and Instability

This is the first study to establish a significant correlation between ASA intake and decreased wall enhancement of UIAs. Several studies have evaluated the relationship between wall enhancement on HR-VWI and classic risk factors of aneurysm rupture. Backes et al[3] showed that the strongest determinant of wall enhancement in 89 predominantly small UIAs (84% <7 mm) was aneurysm size (OR 14.8, 95% CI 2.1–a104.6 for ≥7.0 mm), followed by location in the PCOM (OR 3.6, 95% CI: 1.1-11.4) or MCA (OR 3.0, 95% CI: 1.0-8.6). No association was found between aneurysm wall enhancement and smoking status, use of statins, hypertension and irregular shape.[3] Liu et al[27] also found that aneurysm size was independently associated with aneurysm wall enhancement in 48 patients with 61 predominantly large UIAs (59% ≥7 mm). Lv et al[28] demonstrated a significant association between HR-VWI enhancement, aneurysm size ≥7 mm and location in the anterior cerebral, PCOM and posterior circulation arteries ($P<0.001$). Wang and colleagues[36] analyzed 88 UIAs and demonstrated that irregular shape and high depth/neck width aspect ratio were significantly associated with wall enhancement (OR 12.5, $P=0.02$ and OR 32.9, $P=0.01$, respectively). Hartman et al compared wall enhancement of 65 UIAs and their PHASES scores, showing that aneurysms with PHASES score > 3 were more likely to demonstrate wall enhancement (42.1% vs. 14.8%, $P=0.022$).[14] Recently, Vergouwen and colleagues prospectively followed 57 patients with 65 UIAs to assess the association between aneurysmal wall enhancement and instability. After median follow-up of 27 months, 4/19 enhancing aneurysms showed instability (growth = 2, rupture =2), whereas none of 46 non-

enhancing UIAs demonstrated significant changes (risk difference, 21%; 95% CI, 3%-39%).[34] This suggested that gadolinium wall enhancement of UIAs is associated with increased risk of instability and might be used as an independent predictor of aneurysm growth and rupture.

Although interesting findings, all these studies relied on subjective assessments and arbitrary scales to determine presence or absence of aneurysm enhancement on HR-VWI. In 2016, Omodaka et al proposed the CR_{stalk} on post-contrast T1-weighted imaging as a standardized tool to objectively quantify contrast enhancement in the wall of UIAs on HR-VWI. Using *maximal* SI values, the authors reported that a cut-off for $CR_{stalk} \geq 0.64$ achieved sensitivity = 75% and specificity = 83% to distinguish ruptured (n=28) from UIAs (n=76).[30] Later on, the same group compared CR_{stalk} in 69 stable UIAs, 26 evolving UIAs and 67 ruptured aneurysms, reporting significantly higher CR_{stalk} values in evolving UIAs compared to stable UIAs (0.54 vs 0.34, $P<0.0001$), but lower compared to ruptured aneurysms (0.54 vs 0.83, $P<0.0002$).[29] An internal validation study performed by our group compared several objective methodologies to quantify SI in the wall of UIAs using HR-VWI. This analysis showed that CR_{stalk} using *maximal* SI achieved the best area under the curve among all contrast ratios, and a cut-off ≥ 0.60 reached optimal sensitivity = 81.5% and specificity = 60.1%. Consequently, we used *maximal* SI values to calculate CR_{stalk} as determinant of aneurysmal wall enhancement in this cohort.

HR-VWI and Aneurysm Inflammation

Previous studies have demonstrated that it is possible to image active wall inflammation of UIAs in-vivo.[15,17] Our group has investigated the potential use of targeted imaging with ferumoxytol-enhanced magnetic resonance imaging (Fe-MRI) to assess the effects of ASA on inflammation in the vessel wall of UIAs. Since ferumoxytol is a superparamagnetic iron oxide agent phagocytized by macrophages and cleared 24 to 72 h after injection, it can be used as a contrast agent to target active inflammatory cells in MRI. In a prospective study of 11 patients with UIAs randomized into an ASA-treated (n=6) or no-ASA (n=5) group, we found a significant decrease in the SI of the aneurysmal wall of patients on ASA after 3 months.[17] Moreover, immunostaining of histological samples following microsurgical aneurysm clipping showed a significant decrease in the number of inflammatory cells and expression of cytokines in the aneurysmal wall.[17] These findings indicated that ASA effectively reduces inflammation in the aneurysmal wall and Fe-MRI detects these changes in an early phase.

Gadolinium-enhanced HR-VWI studies have also suggested a significant correlation between aneurysmal wall enhancement, inflammatory changes and instability. After analyzing 10 post-clipping wall specimens from UIAs with pre-surgical HR-VWI available, our group demonstrated that aneurysms with avid enhancement had higher average atherosclerotic wall thickness ($P=0.003$), macrophage infiltration and cellularity ($P=0.048$) in comparison to aneurysms with mild- or no-enhancing wall.[22] Similarly, Shimonaga et al found a significant association between aneurysmal wall enhancement and presence of vasa vasorum disease, neovascularization and macrophage infiltration on histological analysis of

9 UIAs.[32] A critical review of the current evidence of vessel wall inflammation in enhancing UIAs can be found elsewhere.[31]

ASA and Aneurysm Inflammation

Several pre-clinical studies suggested that ASA beneficially attenuates the aberrant inflammatory microenvironment within the aneurysm wall, ultimately preventing rupture. Aoki et al[1,2] hypothesized that the COX-2 (cyclooxygenase)/mPGES (microsomal prostaglandin E2 synthase-1)/PGE-2/E2,4 pathway could be involved in aneurysm pathogenesis and progression. A mice study comparing mPGES-deleted vs wild-type animals conducted by our group[16] suggested that ASA, via its inhibitory effect over COX-2 activity, effectively attenuates the proinflammatory environment in mPGES-1 deficient mice by decreasing the concentration of upstream mPGES-1 substrates. Furthermore, anti-inflammatory response to ASA may differ in males versus females. Chalouhi et al.[8] observed that male mice on ASA exhibit higher levels of 15-hydroxyprostaglandin dehydrogenase (15-PGDH, which catalyzes formation of anti-inflammatory 15-Keto-PGE-2) compared to female mice receiving ASA. After administering a 15-PGDH activator to female mice on ASA, the rate of aneurysm rupture was similar to male mice receiving ASA only.[7] Thus, decreased concentrations of 15-PGDH in females might not only explain their higher propensity to aneurysm formation and rupture, but may also account for a decreased anti-inflammatory effect of ASA in the wall of UIAs harbored by these patients. We validated these findings in a human study quantifying levels of 15-PGDH in the aneurysmal lumen.[7]

Clinical studies in humans have also shown significant associations between ASA use and reduced risk of aSAH.[21] Our group performed a nested case-control study by selecting individuals from the prospective cohort of 1691 patients with untreated UIAs from ISUIA. After categorizing patients into ASA usage frequency groups, we found that patients who used ASA at least 3 times per week had decreased odds of aneurysmal hemorrhage when compared with those who reported no ASA usage (OR 0.27, 95% CI 0.11-0.67).[18] These findings were later confirmed by Garcia-Rodriguez et al.[11] in a large, rigorous European study (1797 patients with ICH, 1340 cases of SAH and 10 000 controls) in which long-term (> 3 years) intake of ASA was associated with a decreased odds of SAH (OR 0.63, 95% CI 0.45-0.90). ASA use was not significantly associated with an increased risk of ICH (OR, 0.89; 95% CI, 0.73-1.09).[11] More recently, a case-control study by Hostettler et al.[19] of 2334 patients (1729 with aneurysm rupture, 605 with UIAs) showed a significant protective effect of ASA over aneurysm rupture status (OR 0.28, 95% CI 0.20-0.40).

ASA and Aneurysm Enhancement on HR-VWI

Our findings of increased wall enhancement in UIAs ≥ 7 mm located in the ACOM, PCOM and BA arteries are consistent with the presented literature. However, the association between ASA and decreased wall enhancement in patients with UIA has not been reported before. Although previous evidence failed to find such correlation, most existing studies using HR-VWI did not establish clear criteria to define ASA use, or simply excluded these patients.[14,27,29,34,37] It has been widely demonstrated that the anti-inflammatory effect of ASA is dependent on the dose, frequency and duration of the regimen. Can et al.[4] performed

a case-control study with 4701 patients (1284 with ruptured aneurysms, 3404 with UIAs). This study not only found that ASA was associated with decreased odds of SAH (OR 0.60, 95% CI 0.53-0.81), but also showed a significant inverse dose-response relationship between ASA use and SAH (OR, 0.65; 95% CI, 0.53-0.81).[4] In the studies by Edjlali et al[9] and Lv et al,[28] ASA use was only assessed for frequency (daily intake), without considering dose or duration. Although Backes et al[3] considered patients with a daily intake ≥80 mg of ASA, the minimum duration criterion was only 3 months, which might not be long enough to establish a substantial ASA-mediated anti-inflammatory response in the aneurysm wall detectable using gadolinium-enhanced MRI. Our study used a strict criterion to define ASA use as daily intake of ≥81 mg during the last 6 months or longer.

Limitations

Our study is limited by its retrospective design, which did not allow us to accurately estimate a dose-response relationship between ASA and aneurysmal wall enhancement. Statistically, the small sample size also decreases the power of the study, with wide 95% confidence intervals for some of the associated variables. However, imaging data in this cohort was collected systematically with prospective follow-up. Our findings result from a homogenous sample of Caucasian patients with UIAs, and thus may not be generalizable to populations with a different racial background. Although ASA compliance was documented in the medical chart, this may not reflect true compliance. At our institution, patients who have already had an intracranial aneurysm found incidentally are put on aspirin. Other indications for aspirin included coronary and peripheral vascular disease. Our multivariable analysis was adjusted for most of these comorbidities (hypertension, hyperlipidemia, history of previous SAH). Thus, the risk of confounding bias for aspirin use in this cohort is very low. However, patients with hypertension and hyperlipidemia could not be stratified into controlled and uncontrolled categories due to heterogeneous information in the medical charts.

Despite the co-registration protocol applied for HR-VWI analysis, some locations preclude easy demarcation of the contour of the aneurysm wall due to surrounding SI artifacts. This is especially difficult for aneurysms located in the paraclinoid, paraophthalmic and cavernous segments of the ICA (close proximity to the cavernous/sphenoid sinuses and the dural folds of the skull base), and for those located in the distal MCA (M2-M3 segments) surrounded by brain parenchyma. Additionally, our logistic regression analyses assumed a cutoff of CR_{stalk} ≥ 0.60 using maximal SI to objectively define significant contrast enhancement in the aneurysm. Although such assumption is well supported by previous studies and provides a reliable method for objective assessment of HR-VWI,[30] the gold standard would be longitudinal follow-up of possible growth and/or rupture of UIA based on follow-up MRI and clinical assessments.

CONCLUSION

UIAs ≥7 mm located in the ACOM, PCOM and BA arteries demonstrate significantly increased wall enhancement. ASA is associated with a decreased rate of aneurysmal wall

enhancement, suggesting that HR-MRI might be used as a non-invasive biomarker of aneurysm wall inflammation and UIA instability.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Baseline characteristics of the sample.

Variable	Patients = 74 Aneurysms = 96
Age (in years, mean ± SD)	64.7 ± 12.4
Women (%)	60 (81)
Smoking (%)	40 (54.1)
Hypertension (%)	41 (55.4)
Diabetes (%)	12 (16.2)
Hyperlipidemia (%)	32 (43.2)
Family history of intracranial aneurysms (%)	7 (9.5)
History of previous SAH (%)	4 (5.4)
Aspirin *	39 (52.7)
Size (in mm, mean, range)	8.1 (3-27)
- ≥7 mm (%)	48 (50.0)
- <7 mm (%)	48 (50.0)
Location	
- Internal carotid artery (%)	25 (26.0)
- Anterior communicating artery (%)	16 (16.7)
- Anterior cerebral artery (%)	5 (5.2)
- Middle cerebral artery (%)	26 (27.1)
- Posterior communicating artery (%)	5 (5.2)
- Basilar artery (%)	15 (15.6)
- Superior cerebellar (%)	3 (3.1)
- Vertebral artery (%)	1 (1.0)
Aneurysmal wall enhancement †	
- Positive	59 (61.5%)
- Negative	37 (38.5%)

mm: millimeters; SD: standard deviation

*Refers to daily intake of ≥81 mg of aspirin during the last 6 months.

†Defined as positive if aneurysm-to-pituitary stalk contrast ratio (CR_{stalk}) > 0.60.

Table 2.

Univariate and multivariate analyses using $CR_{stalk} \geq 0.60$ as cut-off for aneurysm enhancement.

Variable	Univariate		Multivariate	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***
Age	1.05 (1.01-1.10)	0.007	1.12 (1.05-1.19)	0.001
Sex (women)	1.67 (0.48-5.78)	0.42	-	-
Hypertension	1.27 (0.55-2.98)	0.57	-	-
Hyperlipidemia	1.22 (0.53-2.83)	0.65	-	-
Smoking	1.36 (0.59-3.19	0.47	-	-
History of previous SAH	2.54 (0.40-16.03)	0.32	-	-
Aspirin*	0.46 (0.15-1.36)	0.17	0.22 (0.06-0.83)	0.026
Size (≥7 mm)	6.15 (2.42-15.65)	<0.001	21.3 (4.88-92.8)	<0.001
Location†	2.22 (0.94-5.24)	0.07	10.7 (2.45-46.5)	0.002

CI: confidence interval; ER: enhancement ratio; OR: odds ratio; *P*: p-value; SAH: subarachnoid hemorrhage.

*Refers to daily intake of ≥81 mg of aspirin during the last 6 months.

†Refers to location in the anterior communicating, posterior communicating and basilar arteries.