Stroke

ORIGINAL CONTRIBUTION

Aspirin and Growth of Small Unruptured Intracranial Aneurysm

Results of a Prospective Cohort Study

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BACKGROUND AND PURPOSE: The role of aspirin in unruptured intracranial aneurysm (UIA) growth remains largely unknown. We aim to identify whether aspirin is associated with a lower rate of UIA growth in patients with UIA <7 mm.

METHODS: This prospective cohort study consecutively enrolled patients with UIAs <7 mm with ischemic cerebrovascular disease between January 2016 and December 2019. Baseline and follow-up patient information, including the use of aspirin and blood pressure level, were recorded. Patients were considered aspirin users if they took aspirin, including standard- and low-dose aspirin, ≥3× per week. The primary end point was aneurysm growth in any direction or an indisputable change in aneurysm shape.

RESULTS: Among the 315 enrolled patients, 272 patients (86.3%) underwent imaging examinations during follow-up (mean follow-up time, 19.6±12.7 months). A total of 113 patients were continuously treated with aspirin. UIA growth occurred in 31 (11.4%) patients. In the multivariate Cox analysis, specific aneurysm locations (anterior communicating artery, posterior communicating artery, or middle cerebral artery; hazard ratio, 2.89 [95% CI, 1.22–6.88]; P=0.016) and a UIA size of 5 to <7 mm (hazard ratio, 7.61 [95% CI, 3.02–19.22]; P<0.001) were associated with a high risk of UIA growth, whereas aspirin and well-controlled blood pressure were associated with a low risk of UIA growth (hazard ratio, 0.29 [95% CI, 0.11–0.77]; P=0.013 and hazard ratio, 0.25 [95% CI, 0.10–0.66]; P=0.005, respectively). The cumulative annual growth rates were as high as 40.0 and 53.3 per 100 person-years in the high-risk patients (>1 risk factor) with and without aspirin, respectively.

CONCLUSIONS: Aspirin therapy and well-controlled blood pressure are associated with a low risk of UIA growth; the incidence of UIA growth in high-risk patients in the first year is high, warranting intensive surveillance in this patient group.

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Key Words: aneurysm ■ aspirin ■ blood pressure ■ incidence ■ risk factors

Approximately 2.0% to 4.0% of the adult population has unruptured intracranial aneurysms (UIAs).[1–3] The International Study of Unruptured Intracranial Aneurysms and Unruptured Cerebral Aneurysm Study of Japan showed that of all the UIAs, small unruptured aneurysms <7 mm accounted for 62.0% and 74.5%, respectively.[4,5] Because the risk of morbidity and mortality from preventive treatment outweighs the risk of rupture, UIAs <7 mm are often left untreated, and radiographic follow-up at regular intervals is indicated.[2,4] A prospective study reported that aneurysm growth was observed in all patients before aneurysm rupture.[5] Therefore, aneurysm growth has been used as a surrogate outcome measure of aneurysm rupture, with the aim of reducing the risk of rupture. However, there is no clear consensus at present on the optimal

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Nonstandard Abbreviations and Acronyms

CT	computed tomography
HR	hazard ratio
ICVD	ischemic cerebrovascular disease
IR	incidence rate
MR	magnetic resonance
UIA	unruptured intracranial aneurysm

interval for repeated imaging and risk factors associated with aneurysm growth.

Currently, no medical treatment has proven to be effective in preventing aneurysm growth and subsequent rupture. Aspirin is a representative nonsteroidal anti-inflammatory drug used as an anti-inflammatory and antiplatelet drug. Previous studies suggest that aspirin is associated with a lower risk of aneurysm growth and rupture, possibly because of its anti-inflammatory effect on the aneurysm wall.[6–11] However, because of the lack of prospective studies, there is insufficient evidence to determine the role of aspirin in UIA growth.

Aspirin has been widely used for the prevention of recurrent ischemic events.[12,13] Additionally, with the wide use of high-resolution magnetic resonance (MR) imaging, ischemic cerebrovascular disease (ICVD) and UIAs are now simultaneously detected frequently.[1,14] In our cohort study, we aim to determine the risk factors associated with aneurysm growth and whether aspirin is associated with a lower rate of aneurysm growth in patients harboring UIAs <7 mm with concurrent ICVD.

METHODS

Data Availability Disclosure

Deidentified data not published within this article will be made available to any qualified investigator upon request. To gain access, those requesting access to data will need to sign data access and use agreement. Data will be shared via a secure portal.

Study Design

This prospective cohort study consecutively enrolled eligible patients with UIAs <7 mm and concurrent ICVD. All patients consented to follow-up imaging in Beijing Tiantan Hospital between January 2016 and December 2019. This study was performed according to an institutional review board–approved protocol in compliance with local and institutional regulations for the study of human subjects. Written informed consent was obtained from all participating patients (or guardians of patients), and a signed patient consent-to-disclosure form was obtained for photos of any recognizable patient.

Participants

The study inclusion criteria were as follows: (1) patients with UIAs <7 and ≥2 mm in the greatest diameter confirmed by MR angiography, computed tomography (CT) angiography, or digital subtraction angiography; (2) patients with either symptomatic ICVD (ischemic stroke or transient ischemic attack) or asymptomatic ICVD (clinically silent lacunar infarction identified on brain CT/MR imaging)[14]; (3) patients aged 18 to ≤80 years; (4) patients who provided written informed consent; (5) patients who consented to follow-up imaging with MR angiography or CT angiography.

According to the 2015 American Heart Association/American Stroke Association guidelines for the management of patients with UIAs, patients with some well-accepted unmodifiable risk factors (family history of intracranial aneurysms, history of subarachnoid hemorrhage, and multiple aneurysms) are considered to have high risk of aneurysm rupture and growth.[15] In our hospital, these patients received preventive aneurysm treatment or intensive surveillance. So, these patients were not included in this observational study. Patients with some modifiable risk factors (hypertension, smoking, etc) were not excluded from our study. Patients were ineligible if they met the following exclusion criteria: (1) a history of intracranial aneurysm rupture–related hemorrhage or multiple aneurysms; (2) a family history of intracranial aneurysm; (3) a history of vascular malformation (arteriovenous malformation, Moyamoya disease, and so on), intracranial tumor, hydrocephalus, or hypertensive cerebral hemorrhage; (4) an allergy to contrast medium; (5) a modified Rankin Scale score ≥2; (6) fusiform or daughter sac UIAs; (7) residence in a rural area that prevented regular follow-up (Figure 1).[16]

Data Collection

All participants were asked to complete a standard questionnaire to provide demographic data (age, sex, main complaint, personal medical history, body weight, body height, medication history, alcohol consumption, previous or current cigarette smoking, and performance status according to the modified Rankin Scale). A history of hypertension was diagnosed by local cardiovascular physicians as systolic blood pressure repeatedly ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or both.[17] Taking aspirin for patients with small aneurysms is controversial yet. Pottegard et al[18] demonstrated that the short-term (<3 months) use of aspirin was associated with an increased risk of aneurysm rupture, whereas other literature reported that aspirin was able to reduce the risk of aneurysm rupture.[6,9] Therefore, concerning the possibility of risk of aneurysm rupture, less than half of patients with ICVD took aspirin, and they selected it according to their personal intention. Aspirin users were defined as those who reported aspirin use at least 3× per week, including standard- and low-dose aspirin. Nonaspirin users were those who used no aspirin.[6] Based on values in China, we categorized the patients as regular alcohol drinkers (drink once or more than once per week) and occasional alcohol drinkers (drink less than once per week) according to their alcohol consumption.[19] In addition, patients were stratified into nonsmoker, former smoker, and current smoker groups.[4]

Aneurysm characteristics (aneurysm size, location, and shape) were detected by neuroradiologists in picture archiving and communications systems. Based on previous studies, we

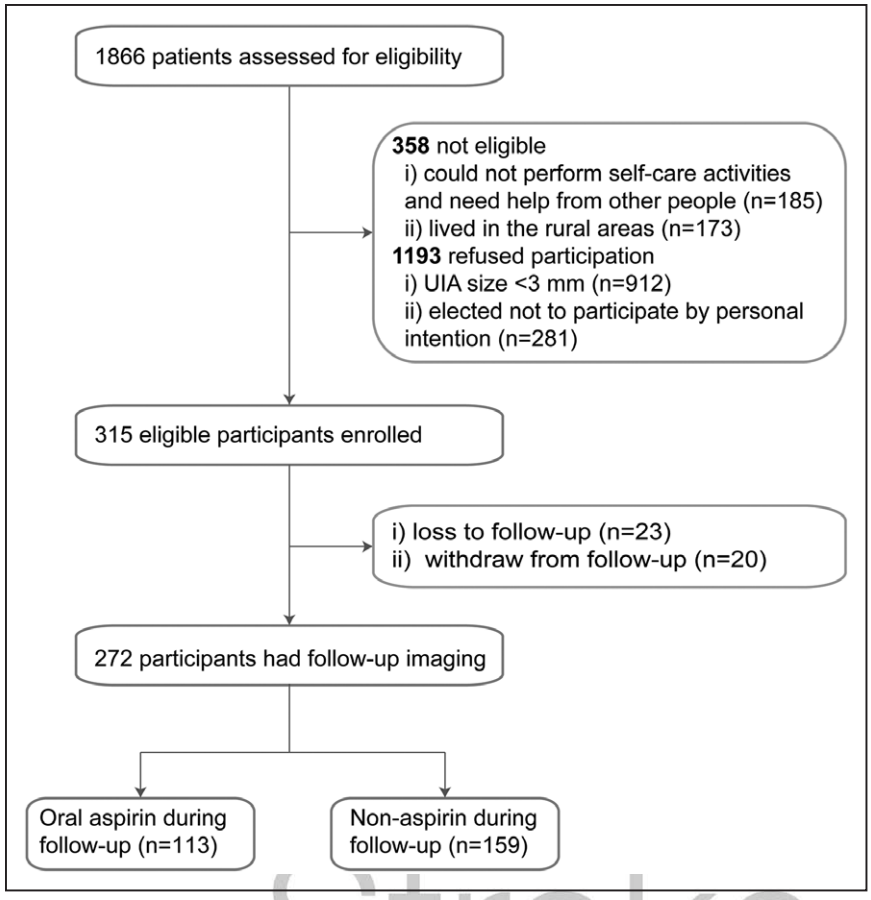

Figure 1. Flowchart of the study patients.
UIA indicates unruptured intracranial aneurysm.

categorized the size of UIAs into 3 size groups: <3 mm, 3 to <5 mm, and 5 to <7 mm.[1,20]

Follow-Up

Telephone follow-up was performed for all participants, and daily blood pressure level, alcohol consumption, cigarette smoking, medication use (antihypertensive drugs, aspirin, and lipid-lowering drugs), etc, were recorded every 3 to 6 months from January 2016 to December 2019. Patients with hypertension receiving standard hypertension treatment (defined as daily targeted mean systolic blood pressure/diastolic blood pressure below 140/90 mm Hg with a home blood pressure measuring device) were considered to have controlled hypertension.[21]

Follow-up imaging for UIAs without surgical or endovascular treatment was performed at 3 and 12 months and then annually for 48 months after registration. In the case of patients refusing further follow-up or failing to return due to another medical condition (death due to causes other than aneurysmal subarachnoid hemorrhage), discontinued use of aspirin, non-aspirin users starting aspirin treatment, or undergoing surgical or endovascular treatment, the follow-up period was defined as the time from inclusion to the last day of follow-up.

Outcome and Aneurysm Measurements

To perform a more accurate assessment of aneurysm growth, all patients enrolled in our study were required to image subsequently with the same imaging modality. The primary outcome was aneurysm growth, which was defined as (1) growth ≥1.0 mm in at least 1 direction by identical imaging modalities, (2) growth ≥0.5 mm in 2 directions by identical imaging modalities, and (3) an indisputable change in aneurysm shape (ie, change from a regular shape to an irregular shape; Figure 2).[1,2] The secondary outcome was UIA rupture. The diagnosis of aneurysm rupture was confirmed by preoperative CT, MR imaging, cerebrospinal fluid analysis, or a neurosurgeon during operation.[22]

All first-visit and follow-up CT angiography and MR angiography findings were examined by 2 neurosurgeons (H.L. and Y.-M.J.) who were blinded to the patients' clinical data and patient- and aneurysm-specific risk factors. Discrepancies were resolved by a senior neuroradiologist (J.Z.). Aneurysm height (h) and width (d) together with the neck width (n) were measured to assess the growth of a UIA.[1,5] If a consensus on aneurysm growth was reached on the basis of the first and last follow-up images, all follow-up MR angiography, CT angiography, or digital subtraction angiography imaging results were evaluated for aneurysm growth. The time between baseline imaging and the first follow-up image that showed aneurysm growth was used for further analysis. In aneurysms without growth, the time between the first and last imaging was used. For aneurysms that ruptured, the last follow-up image before the rupture was considered end point imaging.[1] We used picture archiving and communications systems to evaluate all the images.

Statistical Analysis

Continuous variables were presented as means±SDs or as medians and interquartile ranges, and categorical variables were expressed as percentages. Wilcoxon rank-sum tests, *t* tests, and

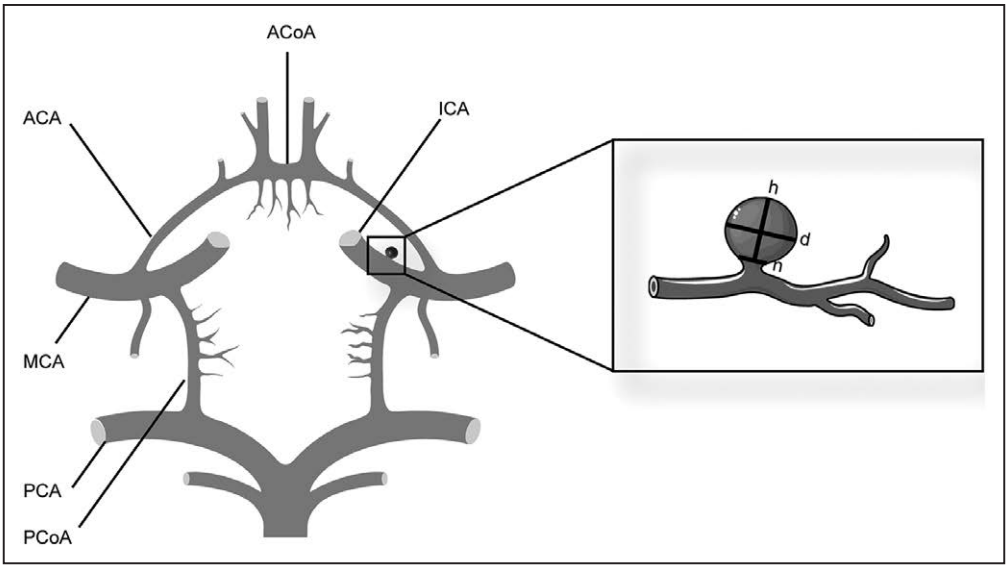

Figure 2. Aneurysm measurements.
Aneurysm height (h) was measured from the center of the aneurysm neck (n) to the aneurysm dome, and aneurysm width (d) was the maximum width measured perpendicular to the aneurysm height. ACA indicates anterior cerebral artery; ACoA, anterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; and PcoA, posterior communicating artery.

χ^2 tests were used accordingly. The associations between aneurysm growth and pertinent risk factors were evaluated by univariate Cox regression analysis. Covariates including age, female sex, hyperlipidemia, pretransient ischemic attack, or ischemic stroke, as well as those covariates with $P<0.10$ in the univariate analysis, were entered into the multivariate Cox regression analysis. Multivariate Cox analysis using forward stepwise selection method was used. The incidence rates (IRs) for primary outcome events were calculated by dividing the numbers of events by person-years at risk, with 95% CIs estimated using a Poisson model. The cumulative incidence of outcome events is presented with Kaplan-Meier curves. Analyses were performed with the statistical software STATA 14.0 (StataCorp, College Station, TX). All P values were based on 2-tailed statistical tests, with a significance level set at $P<0.05$.

RESULTS

Patient Population

A total of 1866 patients from Beijing Tiantan Hospital were assessed for eligibility. All patients with tiny UIAs (sized <3 mm) assessed for eligibility were informed in advance of the low risk of rupture (0.23% annually) and growth (1.22% annually).[23,24] Therefore, of 1012 patients harboring tiny UIAs, only 100 patients agreed to perform follow-up imaging. Moreover, a total of 281 of 596 eligible patients personally refused to perform follow-up imaging, and the proportion of patients personally refusing was consistent with the study of Chien et al.[25] As a result, 315 patients were consecutively enrolled between January 2016 and December 2019. There were 23 (7.3%) patients lost to follow-up, 20 (6.3%) patients who withdrew from follow-up, and 272 (86.3%) patients who complied with follow-up imaging (Figure 1).

The mean age at aneurysm detection was 58.9±11.2 years (range, 26–80 years), and 141 (51.8%) patients were women. The comorbid diseases were hypertension in 141 (51.8%) patients, previous ischemic stroke or transient ischemic attack in 34 (12.5%) patients, hyperlipidemia in 59 (21.7%) patients, diabetes mellitus in 50 (18.4%) patients, and coronary heart disease in 35 (12.9%) patients. To prevent recurrent or new cerebral ischemic events (transient ischemic attack or ischemic stroke), 111 (40.8%) patients received low-dose aspirin treatment alone (100 mg at least 3× a week), 2 (0.7%) patients received clopidogrel with aspirin; 9 (3.3%) patients took clopidogrel alone, and 2 (0.7%) patients took dabigatran alone. Overall, 123 (45.2%) and 107 (39.3%) patients took antihypertensive drugs and lipid-lowering drugs, respectively (Table 1).

Size and Location of UIAs <7 mm

Table 1 summarizes the distributions of UIAs <7 mm in diameter according to the size and location. The most common location of UIAs <7 mm in our study was the internal carotid artery (n=195, 71.7%), followed by the anterior communicating artery (n=25, 9.2%) and the middle cerebral artery (n=18, 6.6%). The mean UIA size was 3.4±1.0 mm, and 151 UIAs (55.5%) were 3 to <5 mm.

Outcomes

After a total follow-up time of 443.3 patient-years, aneurysm growth occurred in 31 (11.4%) patients, with a median growth-free survival time of 19.0 months (range, 3.0–48.0 months). In patients taking aspirin,

Table 1. Baseline Characteristics of the Patients*

Variables	Overall (n=272)	Aspirin (n=113)	Nonaspirin (n=159)	*P* Value
Age, y; mean	58.9±11.2	62.4±9.9	56.4±11.4	<0.001†‡
≥60 y, n (%)	138 (50.7)	73 (64.6)	65 (40.9)	<0.001‡§
Women, n (%)	141 (51.8)	49 (43.4)	92 (57.9)	0.018‡§
BMI ≥24 kg/m^2, n (%)	157 (57.7)	69 (61.1)	88 (55.3)	0.347§
Current smoker, n (%)	38 (14.0)	17 (15.0)	21 (13.2)	0.292§
Regular alcohol drinkers, n (%)	88 (32.4)	41 (36.3)	47 (29.6)	0.243§
Medical history, n (%)				
Hypertension	141 (51.8)	71 (62.8)	70 (44.0)	0.002‡§
Hyperlipidemia	59 (21.7)	37 (33.0)	22 (13.8)	<0.001‡§
Diabetes mellitus	50 (18.4)	27 (23.9)	23 (14.5)	0.048‡§
Coronary heart disease	35 (12.9)	19 (16.8)	16 (10.1)	0.101§
Previous TIA or ischemic stroke	34 (12.5)	21 (18.6)	13 (8.2)	0.011‡§
Medications, n (%)				
Antihypertensive	123 (45.2)	64 (56.6)	59 (37.1)	0.001‡§
Lipid lowering	107 (39.3)	73 (64.6)	34 (21.4)	<0.001‡§
Location, n (%)				
ICA	195 (71.7)	87 (77.0)	108 (67.9)	0.557§
MCA	18 (6.6)	9 (8.0)	9 (5.7)	
ACA	6 (2.2)	2 (1.8)	4 (2.5)	
ACoA	25 (9.2)	6 (5.3)	19 (11.9)	
PCoA	13 (4.8)	4 (3.5)	9 (5.7)	
BA tip or BA-SCA	6 (2.2)	2 (1.8)	4 (2.5)	
VA-PICA or VB junction	3 (1.1)	1 (0.9)	2 (1.3)	
PCA	6 (2.2)	2 (1.8)	4 (2.5)	
Size, mm; mean±SD	3.4±1.0	3.5±1.0	3.3±1.1	0.376†
2 to <3	100 (36.8)	35 (31.0)	65 (40.9)	0.241§
3 to <5	151 (55.5)	69 (61.1)	82 (51.6)	
5 to <7	21 (7.7)	9 (8.0)	12 (7.5)	

ACA indicates anterior cerebral artery; ACoA, anterior communicating artery; BA, basilar artery; BMI, body mass index; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; PCoA, posterior communicating artery; PICA, posterior inferior cerebellar artery; SCA, superior cerebellar artery; TIA, transient ischemic attack; VA, vertebral artery; and VB, vertebrobasilar.

*There were 23 (7.3%) patients lost to follow-up; 20 (6.3%) patients withdrew from follow-up imaging.

†*t* test.

‡*P*<0.05.

§χ^2 test.

aneurysm growth occurred in 2 of 64 men (hazard ratio [HR], 0.27 [95% CI, 0.06–1.26]; *P*=0.095) and 3 of 49 women (HR, 0.40 [95% CI, 0.12–1.38]; *P*=0.147), respectively. The mean durations of follow-up for patients with growing and nongrowing UIAs were 21.9±16.0 and 19.3±12.3 months (*P*=0.655), respectively. The IR for aneurysm growth was 6.99 (95% CI, 4.92–9.94) per 100 person-years. Owing to aneurysm growth, 3 (1.1%) and 2 (0.7%) patients received surgical and endovascular treatment, respectively. There was no aneurysm rupture during follow-up.

The univariate Cox analysis found that oral aspirin, UIAs with a size of 5 to <7 mm, uncontrolled hypertension, and specific aneurysm locations (anterior communicating artery, posterior communicating artery, or middle cerebral artery) had *P*<0.1. In the multivariate Cox analysis, uncontrolled hypertension (HR, 6.11 [95% CI, 2.42–15.38]; *P*<0.001), specific aneurysm locations (HR, 2.89 [95% CI, 1.22–6.88]; *P*=0.016), and UIAs sized 5 to <7 mm (HR, 7.61 [95% CI, 3.02–19.22]; *P*<0.001) were associated with a high growth rate. Oral aspirin was associated with a low growth rate (HR, 0.29 [95% CI, 0.11–0.77]; *P*=0.013; Table 2; Figure 3). The patients were stratified into 3 groups according to the presence of 3 risk factors (uncontrolled hypertension, specific aneurysm locations, and UIAs sized 5 to <7 mm): the low-risk group is without any of the 3 risk factors, intermediate-risk group only has 1 risk factor, and high-risk group has >1 risk factor.

The IRs for aneurysm growth per 100 person-years in the aspirin and nonaspirin groups were 2.85 (95% CI, 1.19–6.85) and 9.70 (95% CI, 6.61–14.25), respectively;

Table 2. Univariate and Multivariate Cox Analyses of Risk Factors Associated With Aneurysm Growth

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age ≥60 y	0.87 (0.46–1.94)	0.866		
Women	1.71 (0.80–3.63)	0.165		
BMI ≥24 kg/m^2	1.08 (0.53–2.22)	0.912		
Hyperlipidemia	0.53 (0.19–1.53)	0.241		
Previous TIA or ischemic stroke	1.38 (0.59–3.22)	0.460		
Diabetes mellitus	1.41 (0.61–3.27)	0.428		
Antihypertensive	0.63 (0.14–2.78)	0.541		
Lipid lowering	0.54 (0.25–1.16)	0.115		
Aspirin	0.31 (0.12–0.81)	0.016*	0.29 (0.11–0.77)	0.013*
Smoker				
Nonsmoker (R)				
Former smoker	0.35 (0.08–1.51)	0.160		
Current smoker	1.13 (0.46–2.81)	0.785		
Regular alcohol drinkers	1.11 (0.51–2.43)	0.789		
Hypertension				
Nonhypertension (R)				
Uncontrolled hypertension†	3.76 (1.55–9.11)	0.003*	6.11 (2.42–15.38)	<0.001*
Controlled hypertension†	1.40 (0.59–3.33)	0.447	1.55 (0.63–3.80)	0.340
Location				
ICA (R)				
ACoA, PCoA, or MCA	2.51 (1.10–5.75)	0.029*	2.89 (1.22–6.88)	0.016*
Others	1.64 (0.56–4.86)	0.370	1.23 (0.40–3.85)	0.718
Size				
2 to <5 mm (R)				
5 to <7 mm	5.79 (2.42–13.85)	<0.001*	7.61 (3.02–19.22)	<0.001*

AcoA indicates anterior communicating artery; BMI, body mass index; HR, hazard ratio; ICA, internal carotid artery; MCA, middle cerebral artery; PCoA, posterior communicating artery; R, reference; and TIA, transient ischemic attack.

*P<0.05.

†Patients with hypertension receiving standard hypertension treatment (defined as daily targeted mean systolic blood pressure/diastolic blood pressure below 140/90 mm Hg with a home blood pressure measuring device) were defined as controlled hypertension, otherwise, defined as uncontrolled hypertension.

the annual cumulative IR for growth of UIAs in the low-risk group ranged from 0 to 18.05 (95% CI, 4.51–72.15) per 100 person-years in the first 4 years, whereas the cumulative IRs for UIA growth in the high-risk group were 53.33 (95% CI, 13.34–213.25) and 40.00 (95% CI, 5.64–283.96) per 100 person-years in the first follow-up year in the nonaspirin and aspirin groups, respectively (Table 3).

DISCUSSION

Aneurysm growth has been used as a clinical surrogate for rupture.[1,2,15,25–28] There is a disconnect between current doctrine stating that incidental UIAs <7 mm ought to be left untreated and clinical practice, in which a majority of enlarged intracranial aneurysms are <7 mm.[4,5] Therefore, patients with high-risk factors for aneurysm growth need to undergo follow-up imaging at optimal intervals. However, the optimal interval for imaging and risk factors associated with aneurysm growth still need to be determined. Our current cohort study showed that the risk factors associated with a high rate of aneurysm growth were uncontrolled hypertension, specific aneurysm locations (anterior communicating artery, posterior communicating artery, or middle cerebral artery), and UIAs sized 5 to <7 mm. The cumulative IRs for UIA growth in the high-risk group were 53.33 and 40.00 per 100 person-years in the first follow-up year in the nonaspirin and aspirin groups, respectively; therefore, first-year imaging examinations are mandatory for patients in the high-risk group. Oral aspirin was associated with a decreased growth rate, indicating that aspirin might be a candidate prophylactic treatment for the prevention of the growth of UIAs <7 mm.

Previously published reports demonstrated that risk factors for UIA growth were female sex, cigarette smoking, initial UIA size, aneurysm location, multiple

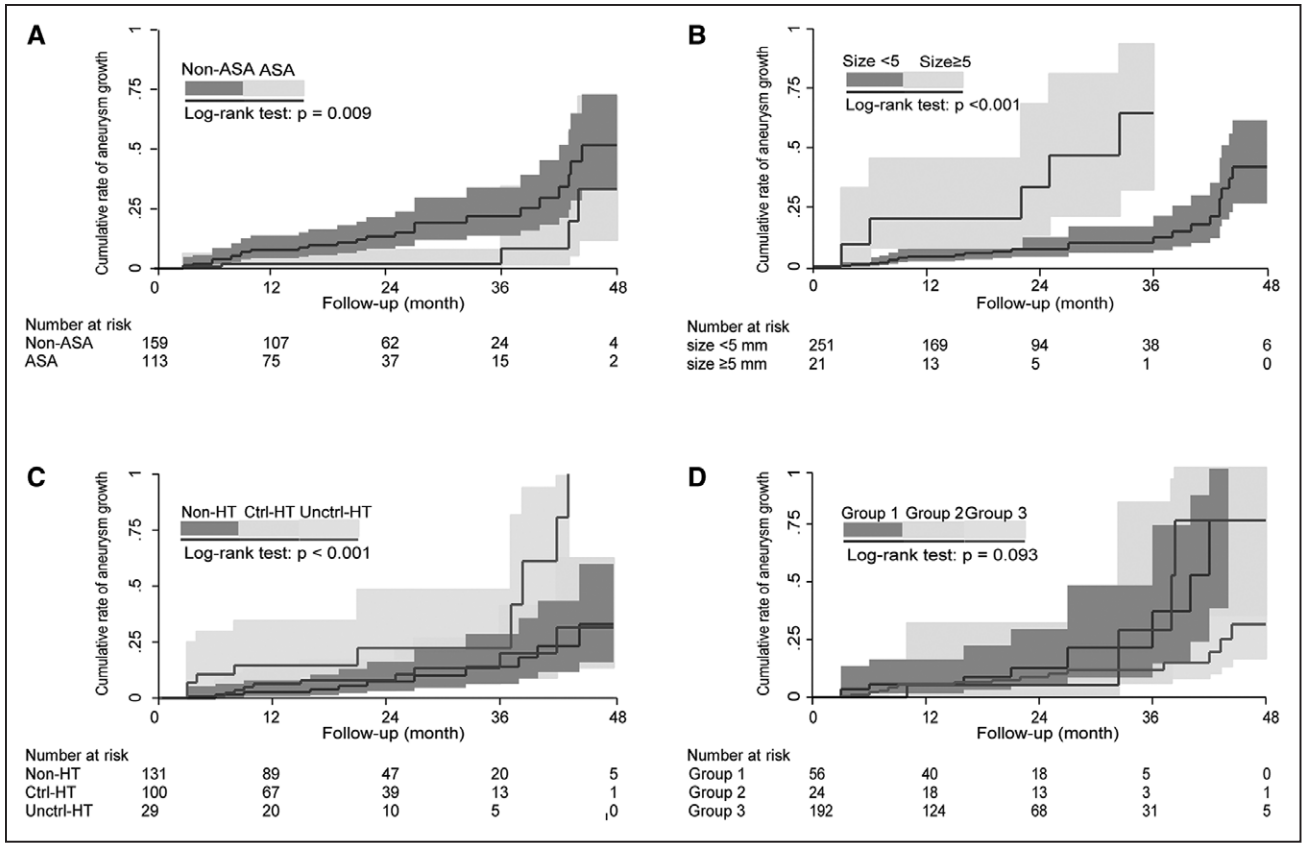

Figure 3. Kaplan-Meier curves showing the aneurysm growth rates in different subgroups.
Kaplan-Meier curve analysis (log-rank test) showing the different unruptured intracranial aneurysm (UIA) growth rates between the aspirin (ASA) and non-ASA groups (**A**); between UIAs sized 5 to <7 mm and UIAs sized <5 mm groups (**B**); among the nonhypertension (non-HT), controlled-hypertension (Ctrl-HT), and uncontrolled-hypertension (Unctrl-HT) groups (**C**); among specific aneurysm locations (group 1), other aneurysm locations (group 2), and the internal carotid artery (ICA; group 3; **D**). Patients with UIAs sized 5 to <7 mm, uncontrolled hypertension, and specific aneurysm locations had a higher rate of UIA growth than those without such factors; oral ASA was associated with a low rate of UIA growth. Specific aneurysm locations included the middle cerebral artery, anterior communicating artery, and posterior communicating artery. Other locations were defined as all aneurysm locations except for the ICA and specific aneurysm locations.

aneurysms, etc.[1,2,5,11,15,23,25,27,29] However, there is still no consensus regarding risk factors for UIA growth. The current study indicated that the initial size of the UIA (5 to <7 mm), specific aneurysm locations, and uncontrolled hypertension were risk factors for UIA growth; these findings were in line with the studies of Backes et al[2] and Miyazawa et al.[30] Moreover, we identified that the timing for follow-up might vary across different subgroups. The first-year cumulative IR of growth in the high-risk group (53.33–40.00 per 100 person-years) was much higher than that in the low-risk group (1.68–6.72 per 100 person-years) and intermediate-risk group (0–7.00 per 100 person-years). Therefore, we suggest that follow-up imaging in the first year is mandatory for patients in the high-risk group, and it is safe for patients in the low- and intermediate-risk groups to undergo follow-up imaging in the third or fourth year.

Previous studies have shown that chronic hypertension plays a major role in UIA growth.[1,15,31,32] However, whether blood pressure control reduces the risk of UIA growth is still unclear. In our study, patients were stratified into nonhypertension, controlled-hypertension, and uncontrolled-hypertension groups. For the comparison of UIA growth, there was no significant difference between the nonhypertension and controlled-hypertension groups. However, compared with the nonhypertension patients and controlled-hypertension patients, patients in the uncontrolled-hypertension group had 6.1-fold and 3.9-fold increases in aneurysm growth, respectively. Therefore, the findings of our study emphasize the important role of blood pressure control, which does matter in ameliorating the risk of UIA growth.

At present, no medical treatment to arrest aneurysm growth is applied in the clinic.[15] Both animal models and human specimen data indicate that chronic inflammation is key in the formation, progression, and rupture of intracranial aneurysms.[32,33] Aspirin is known as an anti-inflammatory drug. However, its role in UIA growth remains largely unknown. The study of Zanaty et al[11] showed that aspirin significantly decreased the growth rate of multiple UIAs ≤5 mm. Multiple aneurysms are a risk factor associated with a high rate of UIA growth. Therefore, their results

Table 3. Cumulative Annual Growth Rate According to Risk Stratification

		Nonaspirin		Aspirin	
		N	IR	N	IR
Low risk*	First year	6	6.72 (3.02–14.96)	1	1.68 (0.24–11.92)
	Second year	2	3.72 (0.93–14.86)	0	0
	Third year	1	3.97 (0.56–28.21)	0	0
	Fourth year	2	18.05 (4.51–72.15)	0	0
	Overall†	11	6.13 (3.40–11.08)	1	0.88 (0.12–6.21)
Intermediate risk*	First year	3	7.00 (2.26–21.72)	0	0
	Second year	2	7.30 (1.83–29.17)	0	0
	Third year	2	20.17 (5.04–80.64)	1	13.04 (1.84–92.60)
	Fourth year	5	140.85 (58.62–338.39)	2	126.32 (31.59–505.07)
	Overall†	12	14.34 (8.14–25.24)	3	5.16 (1.66–15.99)
High risk*	First year	2	53.33 (13.34–213.25)	1	40.00 (5.64–283.96)
	Second year	1	85.71 (12.07–608.49)	0	0
	Overall†	3	61.02 (19.68–189.19)	1	35.30 (4.97–250.56)
Total		26	9.70 (6.61–14.25)	5	2.85 (1.19–6.85)

In our study, uncontrolled hypertension, specific aneurysm locations (ACoA, PCoA, or MCA), and UIAs sized 5 to <7 mm were associated with a high growth rate. AcoA indicates anterior communicating artery; IR, incidence rate per 100 person-years; MCA, middle cerebral artery; N, number of aneurysm growth; PCoA, posterior communicating artery; and UIA, unruptured intracranial aneurysm.

*The patients were stratified into 3 groups according to the presence of 3 risk factors: the low-risk group is without any of the 3 risk factors, intermediate-risk group only has 1 risk factor, and high-risk group has >1 risk factor.

†Overall IRs in corresponding group.

could not be generalized to patients with a single UIA. Prospective studies are also needed to strengthen their findings. In the current prospective cohort study, the included patients had concurrent ICVD. Consequently, our patients represent a more compliant group of patients than those with UIA alone regarding aspirin use and may be better suited to comprehensively assess the effects of aspirin. Compared with nonaspirin use patients, patients who used aspirin experienced a decreased risk of aneurysm growth. Our study implies that aspirin might be a candidate prophylactic treatment for small UIA enlargement. The PROTECT-U trial (Prospective Randomized Open-Label Trial to Evaluate Risk Factor Management in Patients With Unruptured Intracranial Aneurysms) is investigating whether a treatment strategy of aspirin plus targeted systolic blood pressure <120 mm Hg reduces the risk of aneurysm growth compared with nonaspirin plus targeted office systolic blood pressure <140 mm Hg.[21] The results of this study will provide more robust evidence.

There are several limitations to our study. First, the exact time of aneurysm growth is difficult to determine because aneurysm growth is likely to be an irregular process. The date of aneurysm growth was defined as the first imaging study showing aneurysm growth, but the actual growth time was likely shorter than the growth time we used, which was only an approximate value of the actual growth time.[1] Second, UIAs located in the posterior circulation arteries were not a risk factor for UIA growth in our study; this result was inconsistent with those in previous studies.[1,26,31] Our study comprised only a limited number of enrolled patients with UIAs located in posterior circulation arteries, thereby limiting the statistical power. Because UIAs sized 5 to <7 mm in the posterior circulation were regarded as a risk factor for UIA growth, the majority of these patients chose preventive treatment. Third, current smoker was not a risk factor for UIA growth in our study, which was inconsistent with previous studies.[23,34] This lack of association may due to the lower event rate in this study. Finally, the finding of our study requires further prospective randomized controlled trials.

CONCLUSIONS

Our results have implications for clinical practice. First, the incidence of UIA growth in high-risk patients in the first year is high, warranting intensive surveillance in this patient group. Second, for patients with concurrent hypertension, blood pressure control has an effect on ameliorating the risk of UIA growth. Finally, oral aspirin is associated with a decreased risk of aneurysm growth and could be a candidate prophylactic treatment for the prevention of the growth of UIAs <7 mm. Determining whether aspirin plays a preventive role in aneurysm growth requires further prospective randomized controlled trials.

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Disclosures

None.

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