ARTICLE CLASS OF EVIDENCE

Safety of Aspirin Use in Patients With Stroke and Small Unruptured Aneurysms

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Abstract

Objective
We initiated a multicenter, prospective cohort study to test the hypothesis that aspirin is safe for patients with ischemic cerebrovascular disease (ICVD) harboring unruptured intracranial aneurysms (UIAs) <7 mm.

Methods
This prospective, multicenter cohort study consecutively enrolled 1,866 eligible patients with ICVD harboring UIAs <7 mm in diameter from 4 hospitals between January 2016 and August 2019. Baseline and follow-up patient information, including the use of aspirin, was recorded. The primary endpoint was aneurysm rupture.

Results
After a total of 4,411.4 person-years, 643 (37.2%) patients continuously received aspirin treatment. Of all included patients, rupture occurred in 12 (0.7%). The incidence rate for rupture (IRR) was 0.27 (95% confidence interval [CI] 0.15–0.48) per 100 person-years. The IRRs were 0.39 (95% CI 0.21–0.72) and 0.06 (95% CI 0.010–0.45) per 100 person-years for the nonaspirin and aspirin groups, respectively. In the multivariate analysis, uncontrolled hypertension and UIAs 5 to <7 mm were associated with a high rate of aneurysm rupture, whereas aspirin use was associated with a low rate of aneurysm rupture. Compared with other groups, the high-risk group (UIAs 5 to <7 mm with concurrent uncontrolled hypertension) without aspirin had higher IRRs.

Conclusion
Aspirin is a safe treatment for patients with concurrent small UIAs and ICVD. Patients who are not taking aspirin in the high-risk group warrant intensive surveillance.

ClinicalTrials.gov Identifier
NCT02846259.

Classification of Evidence
This study provides Class III evidence that for patients harboring UIAs <7 mm with ICVD, aspirin does not increase the risk of aneurysm rupture.

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Coinvestigators are listed in appendi ›2.

Glossary

CI = confidence interval; **DBP** = diastolic blood pressure; **HR** = hazard ratio; **ICVD** = ischemic cerebrovascular disease; **IRR** = incidence rate for rupture; **PROTECT-U** = Prospective Randomized Open-Label Trial to Evaluate Risk Factor Management in Patients With Unruptured Intracranial Aneurysms; **SAH** = subarachnoid hemorrhage; **SBP** = systolic blood pressure; **UIA** = unruptured intracranial aneurysm.

The management of small unruptured intracranial aneurysms (UIAs) has been a very controversial topic in neurosurgery.[1] The standard of care has been to observe these lesions.[2,3] However, aneurysms <7 mm accounted for 69.6% to 71.8% of all ruptured aneurysms.[4,5] The determination of the high rupture risk of a small aneurysm is critical to prevent fatal and disabling intracranial hemorrhage.

Currently, high-resolution MRI simultaneously detects UIAs and ischemic cerebrovascular disease (ICVD) more frequently.[6,7] Aspirin is the standard secondary preventive agent prescribed to patients with ICVD.[8] Researchers have not clearly determined whether aspirin is safe for patients with ICVD harboring small aneurysms. Short-term (<3 months) use of aspirin was associated with an increased risk of aneurysm rupture.[9,10] However, aspirin was recently described as a potential therapeutic modality in preventing aneurysm rupture by exerting an anti-inflammatory effect on the wall of the aneurysm.[11,12]

Thus, we initiated a multicenter, prospective cohort study to elucidate the risk of small UIA rupture and to test the hypothesis that aspirin is safe for patients with ICVD harboring small UIAs.

Methods

Classification of Evidence

The primary research question was to investigate whether aspirin use was safe in patients harboring UIAs <7 mm with concurrent ICVD. This study provides Class III evidence that for patients harboring UIAs <7 mm with ICVD, aspirin does not increase the risk of aneurysm rupture.

Standard Protocol Approvals, Registrations, and Patient Consents

We performed this study (clinicaltrials.gov identifier NCT02846259) according to an institutional review board–approved protocol in compliance with local and institutional regulations for studies of human participants. Written informed consent was obtained from all patients (or guardians of patients) participating in the study, and a signed patient consent-to-disclosure form was obtained for the use of any recognizable patient photos.

Study Design and Participants

This multicenter cohort study consecutively enrolled eligible patients in 4 hospitals from January 2016 to August 2019. Previous articles have analyzed the risk factors predicting UIA rupture, which included a history of subarachnoid hemorrhage (SAH), a familial history of aneurysms, multiple aneurysms, a multilobulated morphology, and modifiable risk factors (previous and current cigarette smoking, alcohol consumption, and antihypertensive treatment).[13–25] Preventive management strategies (endovascular or surgical aneurysm repair) may be more appropriate for patients with the aforementioned risk factors. In our study, we excluded patients with these unmodifiable rupture risk factors. Patients included in our study must fulfill all the following inclusion criteria: (1) UIAs <7 and ≥2 mm in the greatest diameter confirmed by magnetic resonance angiography, CT angiography, or digital subtraction angiography; (2) either symptomatic ICVD (ischemic stroke or TIA) or asymptomatic ICVD (clinically silent lacunar infarction identified on brain CT/MRI)[6,26,27]; (3) age >18 years; and (4) provision of written informed consent.

The exclusion criteria were as follows: (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, etc), intracranial tumor, hydrocephalus, and hypertensive cerebral hemorrhage; (4) allergy to contrast medium; (5) severe neurologic disability (modified Rankin Scale score ≥3); and (6) fusiform or daughter sac UIAs.

Procedures

Two radiologists who were blinded to the participants' information identified the location, size, and number of UIAs and whether cerebral ischemic changes were present in images to reduce the measurement bias. Disagreements over the diagnostic results between radiologists were resolved by discussion, with the involvement of senior radiologists when necessary. The determination of the aneurysm size was based on the greatest dimension of the aneurysmal sac on the image. Then, neurologists and neurosurgeons simultaneously confirmed the diagnoses of all patients with UIAs accompanied by cerebral ischemic stroke or ischemic changes on images. The aneurysm size, location, and number were detected with the picture archiving and communications system. Then, on the basis of the Malhotra and Population, Hypertension, Age, Size of Aneurysm, Earlier SAH from Another Aneurysm, Site of Aneurysm (PHASES) studies, we categorized the size of the UIAs into 3 groups: <3, 3 to <5, and 5 to <7 mm.[13,28] After this screening process, our study included 1866 patients harboring UIAs accompanied by ICVD. On the basis of the presence of

3 groups according to the history of hypertension and actual blood pressure data: nonhypertension, controlled hypertension, and uncontrolled hypertension groups. Controlled hypertension referred to the receipt of standard hypertension treatment (daily targeted mean systolic blood pressure [SBP]/diastolic blood pressure [DBP] <140/90 mm Hg with a home SBP measuring device), and uncontrolled hypertension was defined as SBP/DBP ≥40/90 mm Hg (even when the patient was taking antihypertensive medications).[32]

From January 2016 through December 2019, a subset of patients agreed to undergo follow-up imaging at 3 and 12 months and then annually after recruitment, and researchers required them to image subsequently with the same imaging modality. Aneurysm growth was defined as (1) growth ≥1.0 mm in at least 1 direction determined with identical imaging modalities; (2) growth ≥0.5 mm in 2 directions determined with identical imaging modalities; and (3) an indisputable change in aneurysm shape (i.e., change from a regular shape to an irregular shape).[33,34]

When patients refused to participate in further follow-up visits or failed to return due to other medical conditions (death due to causes other than aneurysmal SAH), the follow-up period was recorded as the time from their inclusion to the last day of follow-up.

Outcomes

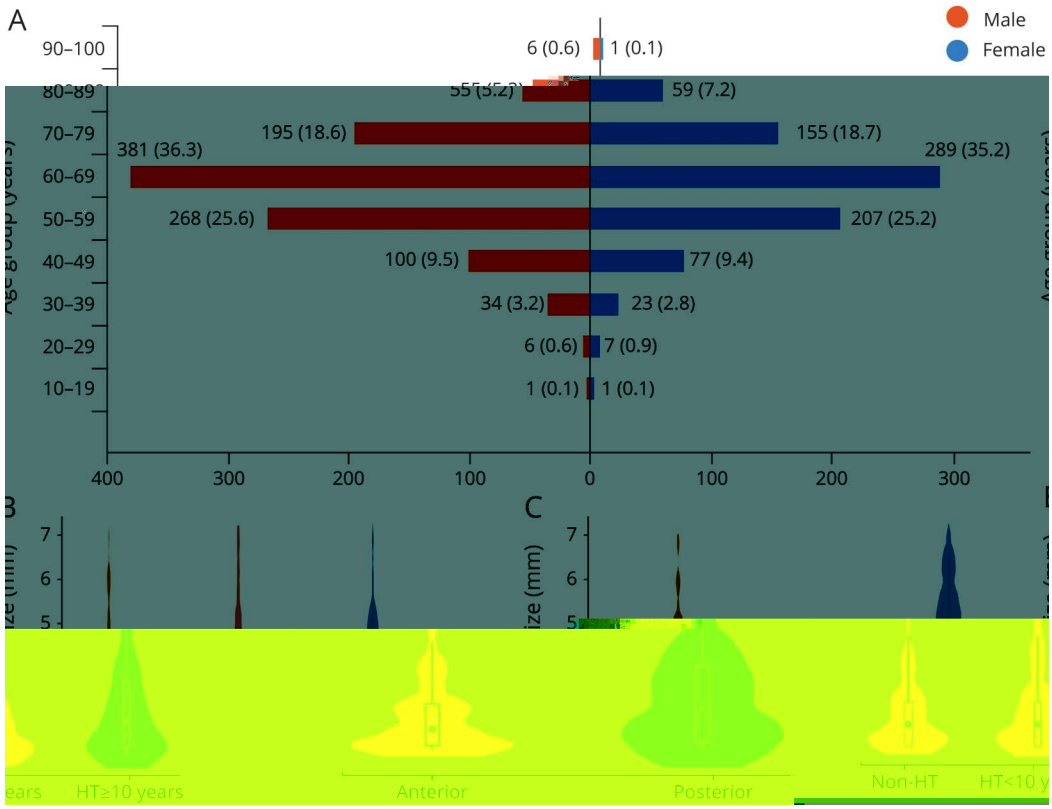
The primary endpoint was UIA rupture. Preoperative CT or MRI, CSF analysis, or a neurosurgeon during the operation confirmed the diagnosis of aneurysm rupture. The patients who presented only with suspected symptoms of hemorrhage but not hemorrhagic changes on CT, MRI, or the CSF analysis were not recorded as having ruptured UIAs in our study.

The secondary outcomes included (1) recurrent or new ischemic events (symptoms suggestive of ischemic stroke or TIA and confirmed by neurologists in the town/village clinic of their choice)[8]; (2) hemorrhagic stroke, defined as the acute extravasation of blood into the brain parenchyma or subarachnoid space with associated neurologic symptoms and a bleeding area far from the aneurysm location[8]; (3) death during the follow-up period; and (4) UIA growth.

Statistical Analysis

Continuous variables are presented as mean ± SD, and categorical variables are presented as number and percentage. An unpaired *t* test was used to compare continuous variables

Figure 2 Distribution of UIAs Among Age Groups and Aneurysm Size in Different Groups



(A) Unruptured intracranial aneurysms (UIAs) were more common in the seventh and sixth decades of life in both the male and female groups. (B) Violin plot shows the significant differences in aneurysm sizes among patients with a hypertension (HT) duration ≥10 years, a hypertension duration <10 years, and no hypertension. (C) Violin plot shows the significant difference in aneurysm sizes between posterior circulation and anterior circulation arteries.

(normality was proven with Q-Q plots). The incidence rate of the primary outcome event was calculated by dividing the number of events by person-years at risk, with the 95% confidence interval (CI) estimated by a Poisson model. The cumulative incidence of outcome events was presented in Kaplan-Meier curves. Univariate Cox proportional hazards analyses were performed to evaluate pertinent risk factors associated with UIA rupture and secondary outcomes. Covariates, including smoking and those covariates with values of $p < 0.10$ in the univariate analysis, were entered into the multivariate Cox regression analysis with the backward stepwise selection method. Analyses were performed with the

Table 1 Baseline Characteristics of the Patients

Characteristic	Overall (n = 1866)	ASA (n = 643)[a]	Non-ASA (n = 1,087)[a]
Age, mean, y	61.9 11.7	64.4 9.7	60.3 12.4
Age ≥60 y, n (%)	1,144 (61.3)	461 (71.7)	592 (54.5)
Female, n (%)	820 (43.9)	249 (38.7)	508 (46.7)
BMI ≥24 kg/m^2,[b] n (%)	1,154 (61.8)	428 (66.6)	641 (59.0)
Current smoking,[b] n (%)	446 (23.9)	184 (28.6)	233 (21.4)
Regular alcohol drinkers, n (%)	634 (34.0)	244 (37.9)	346 (31.8)
Medical history, n (%)			
Hypertension	1,115 (59.8)	457 (71.1)	580 (53.4)
Previous TIA or ischemic stroke	391 (21.0)	168 (26.1)	192 (17.7)
Hyperlipidemia[b]	479 (25.7)	205 (31.9)	236 (21.7)
Diabetes mellitus[b]	433 (23.2)	181 (28.1)	216 (19.9)
Coronary heart disease	219 (11.7)	91 (14.2)	113 (10.4)
Medications, n (%)			
Antihypertensive drug[b]	968 (51.9)	398 (61.2)	505 (46.5)
Lipid-lowering drug	944 (50.6)	388 (60.3)	489 (45.0)
Location, n (%)			
Middle cerebral artery	170 (9.1)	64 (10.0)	92 (8.5)
ACoA	115 (6.2)	32 (5.0)	78 (7.2)
Internal carotid artery	1,209 (64.8)	404 (62.8)	713 (65.6)
PCoA	73 (3.9)	23 (3.6)	43 (4.0)
Anterior cerebral artery	61 (3.3)	23 (3.6)	34 (3.1)
BA tip or BA-SCA	84 (4.5)	36 (5.6)	47 (4.3)
VA-PICA or VB junction	76 (4.1)	35 (5.4)	36 (3.3)
Posterior cerebral artery	42 (2.3)	16 (2.5)	23 (2.1)
Other	36 (1.9)	10 (1.6)	21 (1.9)
Size, mean ±SD, mm	2.9 1.0	2.9 1.1	2.9 1.1
<3, n (%)	1,085 (58.1)	367 (57.1)	633 (58.2)
3–<5, n (%)	647 (34.7)	228 (35.5)	375 (34.5)
5–<7, n (%)	134 (7.2)	48 (7.5)	79 (7.3)

Abbreviations: ACoA = anterior communicating arter ; ASA = aspirin; BA = basilar arter ; BMI = bod mass inde ; ICVD = ischemic cerebrovascular disease (ischemic stroke or TIA); PCoA = posterior communicating arter ; PICA = posterior inferior cerebellar arter ; SCA = superior cerebellar arter ; VA = vertebral arter ; VB = vertebrobasilar.
[a] One hundred t ent -eight patients ere lost to follo -up, and 8 patients could not provide details on medication use.
[b] There are 3, 6, 7, 13, 29, and 43 individuals ith missing information on alcoholic consumption, BMI, h perlipidemia, diabetes, histor of smoking, and use of antih pertensive drugs, respectivel .

statistical software STATA 14.0 (StataCorp, College Station, TX). All p values are based on 2-tailed statistical tests, with the significance level set at $p < 0.05$.

Data Availability

Deidentified data that are not published within this article will be made available to any qualified investigator on request. Researchers requesting access to the data must sign the data access and use agreement before obtaining access. Data will be shared via a secure portal.

Results

Patient Characteristics

After screening for eligibility (figure 1), we prospectively enrolled 1866 consecutive eligible patients during the study period, and all participants were Chinese. The ratio of asymptomatic ICVD group to symptomatic ICVD group was nearly 3.8:1. UIAs were more common in the seventh and sixth decades of life in both the male and female groups (figure 2 and table 1).

Size and Location of UIAs <7 mm

The most common size and location of UIAs <7 mm were 2.0 to 3.0 mm and the internal carotid artery, respectively (table 1). The mean sizes were 3.3 ± 1.3 and 2.8 ± 1.0 mm in posterior and anterior circulation arteries, respectively ($p < 0.001$). The mean sizes were 2.8 ± 0.9, 2.8 ± 1.0, and 3.0 ± 1.3 mm in patients without hypertension, patients with a hypertension duration <10 years, and patients with a hypertension duration ≥10 years, respectively ($p < 0.001$). Significant differences in size were not observed among the other subgroups (figure 2).

Outcomes

After a mean follow-up duration of 30.5 ± 12.3 months (range 1.0–45.6 months), 128 (6.9%) patients were lost to follow-up, and we excluded these patients from further analysis. During the follow-up period, 9 (0.5%) patients underwent an operation due to morphologic changes in 5 patients and fear of aneurysm rupture in 4 patients. The details of aspirin use are listed below. Six hundred forty-three (37.2%) patients used aspirin to prevent recurrent or new ischemic events; 624 patients took aspirin at a dose of 100 mg daily, 10 at a dose of 100 mg at least 3 times a week, and 9 at a dose of 75 mg daily. In addition, patients used the following other antithrombotic agents: 61 (3.5%) patients received clopidogrel with aspirin, and 30 (1.7%), 5 (0.3%), 5 (0.3%), and 4 (0.2%) patients took clopidogrel, dabigatran, warfarin, and rivaroxaban alone, respectively. All other antithrombotic agents were used for <3 months (mean time of use 1.2 months, range 0.3–3.0 months), and the mean follow-up time in these patients was 30.5 months (range 7.1–45.4 months). The mean interval between the discontinuation of medication and the end of follow-up was 30.2 months (range 6.1–44.4 months).

The primary outcome is shown in table 2. UIA rupture occurred in 12 (0.7%) patients, with a median rupture-free survival time of 14.6 months (range, 2.2–35.7 months). After a total of 4,411.4 person-years, the incidence rate for rupture (IRR) was 0.27 (95% CI 0.15–0.48) per 100 person-years. The rupture occurred in 11 of 1,087 (1.01%) and 1 of 643 (0.16%) in the nonaspirin and aspirin groups, respectively (hazard ratio [HR] 0.11, 95% CI 0.01–0.86, $p = 0.035$). Therefore, the absolute risk reduction was 0.9% (95% CI 0.2%–1.5%), and the number needed to treat was 117 (95% CI 66–532). In patients taking aspirin, aneurysm rupture occurred in 1 of 394 male (HR 0.25, 95% CI 0.03–2.05, $p = 0.195$) and 0 of 249 female (HR 0.03, 95% CI 0–70.37, $p = 0.368$) patients, respectively. In the multivariate analyses, UIAs with diameters of 5 to <7 mm and uncontrolled hypertension were associated with a high rate of UIA rupture, whereas aspirin was associated with a low rate of UIA rupture (table 3). There were no statistical differences among current smokers, former smokers, and nonsmokers (HR 1.22, 95% CI 0.55–2.72, $p = 0.621$). We stratified the patients into 3 groups according to the presence of 2 risk factors: the low-risk group has no risk factors; the intermediate-risk group only has 1 risk factor; and the high-risk group has 2 risk factors. Compared with other groups, the IRR was higher in the patients in the high-risk group who were not taking aspirin (table 4).

Table 2 Incidence Rates of Aneur sm Rupture, Cerebral Ischemic Stroke or TIA, and Cerebral Hemorrhagic Stroke in the Aspirin and Nonaspirin Groups

	Overall		Nonaspirin		Aspirin	
Event	**No. of events**	**IR (95% CI)**	**No. of events**	**IR (95% CI)**	**No. of events**	**IR (95% CI)**
Aneurysm rupture	12	0.27 (0.15–0.48)	11	0.39 (0.21–0.72)	1	0.06 (0.01–0.45)
Recurrent or new IE[a]	45	5.36 (4.00–7.18)	37	8.58 (6.22–11.84)	8	1.96 (0.98–3.92)
New IE[b]	48	1.42 (1.08–1.89)	31	1.38 (0.97–1.97)	17	1.51 (0.94–2.43)
Hemorrhagic stroke	6	0.14 (0.06–0.30)	4	0.14 (0.05–0.38)	2	0.13 (0.03–0.51)

Abbreviations: CI = confidence interval; IE = ischemic event; IR = incidence rates per 100 person- ears.
[a] S mptomatic ischemic cerebrovascular disease group.
[b] As mptomatic ischemic cerebrovascular disease group.

Table 3 Univariate and Multivariate Co »Regression for Risk Factors Associated With UIA Rupture[a]

		Univariate analysis		Multivariate analysis	
Variables	**No. of events**	**HR (95% CI)**	***p* Value**	**HR (95% CI)**	***p* Value**
Female	5	0.89 (0.28–2.82)	0.848		
Age ≥60 y	9	2.02 (0.55–7.47)	0.291		
Aneurysm size, mm					
<3 (R)	5				
3–<5	2	0.64 (0.12–3.23)	0.588	0.61 (0.12–3.13)	0.551
5–<7	5	7.66 (2.22–26.49)	0.001[b]	7.45 (2.15–25.79)	0.002[b]
Posterior circulation artery	2	1.48 (0.32–6.75)	0.627		
Previous TIA or ischemic stroke	3	1.28 (0.35–4.74)	0.710		
Diabetes mellitus[c]	1	0.32 (0.04–2.46)	0.272		
Hypertension[c]					
Nonhypertension (R)	1				
Controlled hypertension	2	3.20 (0.29–35.26)	0.343	3.48 (0.32–38.52)	0.309
Uncontrolled hypertension	9	13.59 (1.72–107.26)	0.013[b]	16.66 (2.10–132.09)	0.008[b]
Hyperlipidemia[c]	2	0.59 (0.13–2.67)	0.489		
Aspirin[c]	1	0.16 (0.02–1.23)	0.078	0.11 (0.01–0.86)	0.035[b]
Antihypertensive drug[c]	8	0.38 (0.08–1.81)	0.227		
BMI ≥24 kg/m^2[c]	7	0.88 (0.28–2.79)	0.833		
Regular alcohol drinkers	7	2.64 (0.86–8.06)	0.089		
Smoking[c]					
Nonsmoker (R)	5				
Former smoker	2	1.67 (0.32–8.60)	0.541		
Current smoker	5	2.54 (0.73–8.77)	0.141		

Abbreviations: BMI = bod mass inde ; CI = confidence interval; HR = ha ard ratio; R = reference; UIA = unruptured intracranial aneur sm.
[a] One hundred t ent -eight patients ho ere lost to follo -up ere e cluded from the rupture-free survival anal sis.
[b] $p < 0.05$.
[c] There are 3, 6, 7, 8, 13, 29, and 43 individuals ith missing information on alcoholic consumption, BMI, h perlipidemia, medication use of aspirin, diabetes, histor of smoking, and use of antih pertensive drug, respectivel .

Table 2 summarizes the secondary outcomes. In symptomatic patients with ICVD, a significant difference in the incidence rate of ischemic events was observed between the nonaspirin and aspirin groups. In contrast, in asymptomatic patients with ICVD, no significant difference was observed between the nonaspirin and aspirin groups (figure 3). A significant difference in the incidence of hemorrhagic stroke was not observed between the aspirin and nonaspirin groups (HR 0.93, 95% CI 0.17–5.06). Fifty-two (3.0%) patients died: 9 (0.5%), 16 (0.9%), and 27 (1.6%) patients died of aneurysm rupture, cerebral ischemic events, and other causes, including pneumonia, cerebral hemorrhagic stroke, prostate cancer, and coronary heart disease, respectively.

Of all participants, only 272 patients underwent follow-up imaging. After a total follow-up time of 443.3 patient-years, 113 patients were continuously treated with aspirin, and 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). The incidence rate for aneurysm growth was 6.99 (95% CI 4.92–9.94) per 100 person-years. No aneurysm rupture occurred in the patients with aneurysm growth (n = 31): 5 received preventive treatment, and the remaining patients were still undergoing follow-up. Patients without changes in aneurysm morphology (n = 241) did not experience aneurysm rupture. In the multivariate Cox analysis, aspirin was associated with a low rate of UIA growth (HR 0.29, 95% CI 0.11–0.77).

Table 4 Aneur sm IRR in Different Risk Groups

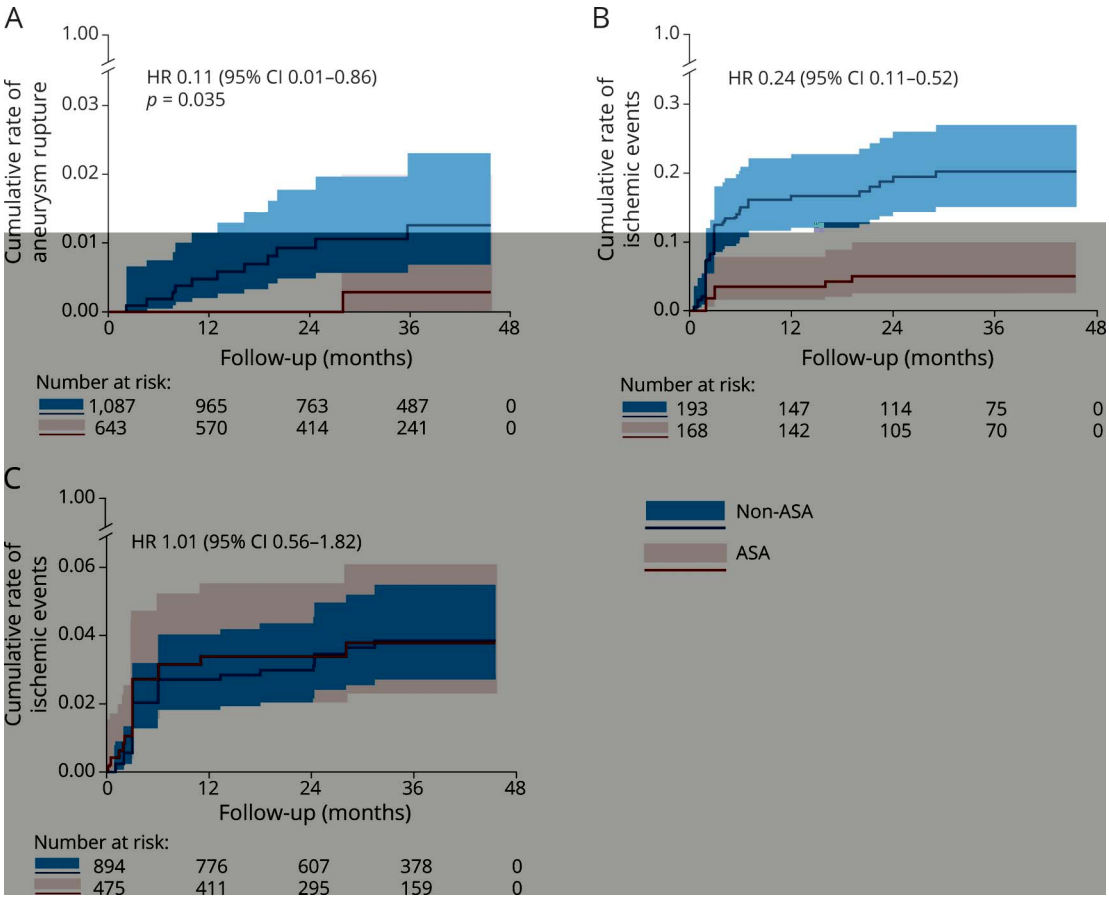
	Aspirin (583)		Nonaspirin (1,026)	
Group (n)[a]	**n/N**	**IRR (95% CI)**	**n/N**	**IRR (95% CI)**
Low risk (1,059)[b]	0/348	0	1/711	0.04 (0.01–0.31)
Intermediate risk (512)[b]	1/217	0.18 (0.03–1.29)	7/295	0.93 (0.44–1.95)
High risk (38)[b]	0/18	0	3/20	6.56 (2.12–20.34)

Abbreviations: IRR = incidence rate for rupture per 100 person- ears; n = number of events; N = total number in the corresponding group.
[a] There are 8 and 121 individuals missing information on medication use of aspirin and dail blood pressure, respectivel .
[b] The patients ere stratified into 3 groups according to the presence of 2 risk factors (uncontrolled h pertension and unruptured intracranial aneur sms ith diameters of 5 to <7 mm): the lo -risk group has no risk factors; the intermediate-risk group onl has 1 risk factor; and the high-risk group has 2 risk factors.

Discussion

Patients harboring small UIAs accompanied by ICVD are facing the composite risk of both hemorrhagic and ischemic events, particularly when using aspirin.[35,36] Our current multicenter, prospective cohort study showed that the IRR of patients with UIAs <7 mm and concomitant ICVD was 0.27 per 100 person-years. Patients who were not taking aspirin harboring UIAs measuring 5 to <7 mm in diameter with concurrent uncontrolled hypertension present a higher rate of UIA rupture. Aspirin use was associated with lower rates of UIA rupture and growth. Therefore, aspirin use is considered to be safe for this specific population.

Figure 3 Kaplan-Meier Curve Sho ing the Cumulative Rate of Aneur sm Rupture and Ischemic Events



(A) There as a significant difference in the rate of aneur sm rupture bet een the aspirin (ASA) and non-ASA groups. (B) In patients ith s mptomatic ischemic cerebrovascular disease (ICVD), there as a significant difference in the rate of ischemic events bet een the ASA and non-ASA groups. (C) In patients ith as mptomatic ICVD, there as no statistical difference in the rate of ischemic events bet een the ASA and non-ASA groups. CI = confidence interval; HR = ha ard ratio.

Controversy exists regarding whether conservative treatment is appropriate for patients with UIAs 5 to <7 mm in diameter. Because of the relatively low rupture risk of patients with UIAs <7 mm, conservative management (routine, periodic imaging surveillance) would be appropriate for these patients.[2] Moreover, the Collaborative Unruptured Endovascular Versus Surgery (CURES) study reported the morbidity and mortality rates for UIA treatment of 3.6%–4.2%, indicating that the risk of preventive treatment outweighs the rupture risk of UIA sized 5 to <7 mm.[37] However, a prospective study showed that in the UIAs <7 mm, aneurysms 5 to 6 mm in size were associated with a significantly increased risk of rupture compared with aneurysms 2 to 4 mm in size; therefore, the authors recommended preventive treatment for UIAs with diameters of 5 to 6 mm or larger.[4] In our study, compared with other groups, patients harboring UIAs 5 to <7 mm in diameter with concurrent uncontrolled hypertension who were not taking aspirin had a higher rate of rupture. Considering the fairly high morbidity and mortality rates associated with the preventive treatment of UIA, we suggest that patients in this subgroup warrant intensive surveillance at least.

Aspirin as an antiplatelet drug is also a powerful inhibitor of inflammation. The previous studies reported that inflammation plays a key role in the pathogenesis of intracranial aneurysm rupture. Blood flow leading to high wall shear stress activates proinflammatory signaling in endothelial cells, resulting in the infiltration of macrophages into the local site exposed to high wall shear stress. The inflammatory reaction predisposed the individual to UIA initiation, growth, and eventual rupture.[38] According to another study, aspirin is able to decrease inflammatory activities after 3 months in the aspirin treatment group.[39] Therefore, aspirin has emerged as a candidate for the noninvasive treatment of intracranial aneurysms.[12,39–41] However, several population-based studies have explored the association between antiplatelet therapy and SAH, with conflicting results.[9,10] In the present study, an oral aspirin treatment was associated with low rates of UIA rupture and growth. Meanwhile, consistent with previous studies, patients in the symptomatic ICVD group who were taking aspirin showed a lower incidence of ischemic events than patients who were not taking aspirin.[8,42] Overall, aspirin use is safe for patients in this specific population, according to our results.

Our study has several limitations. First, the history of other occlusive vascular diseases (myocardial infarction, mesenteric ischemia, peripheral arterial occlusion, etc) in the recruited patients was not recorded because the benefits of antiplatelet medications for these ischemic diseases have been well recognized and are not the focus of our study.[36] Second, the median follow-up duration was 32.1 months, and 12 ruptures occurred during our study. The low rupture rate was quite different from our estimated number and may be attributed to the fact that the current study excluded patients with risk factors associated with a high risk of aneurysm rupture (SAH history, multiple aneurysms, irregular aneurysm shape, etc). Longer follow-up is needed to further strengthen the results of the current study. Owing to the low rupture rate, we were unable to identify any interaction between sex and the aspirin effect; in the multivariate analysis, significant differences in the risk of UIA rupture were not observed among current smokers, former smokers, and nonsmokers. Due to the limited number of patients in the high-risk subgroup, the rate of UIA rupture in this group was much higher than that in previous studies. Third, medication adherence was assessed with the self-reported data, which may be biased measures as with all observational studies, although we recorded the use of aspirin every 3 to 6 months during the follow-up period to increase the quality of the self-report adherence measures.[43] Fourth, because patients in our study were all Chinese, we do not know whether the results are applicable to other ethnic groups. Fifth, there might be some unknown confounding factors we did not add into analysis that could also influence our results. Finally, we found that controlled hypertension and oral aspirin are associated with lower UIA rupture. The Prospective Randomized Open-Label Trial to Evaluate Risk Factor Management in Patients With Unruptured Intracranial Aneurysms (PROTECT-U) trial, which will compare a treatment strategy of aspirin plus intensive blood pressure control (targeted office SBP <120 mm Hg) and a strategy of nonaspirin plus routine blood pressure control (targeted office SBP <140 mm Hg), is very relevant to our study.[44]

Physicians are now often faced with the dilemma of whether to treat small unruptured aneurysms <7 mm in diameter in patients with ICVD. On the basis of the results of our study, patients who were not taking aspirin in this specific population harboring UIAs 5 to <7 mm with concurrent uncontrolled hypertension warrant intensive surveillance. Oral aspirin use is associated with low rates of aneurysm rupture and growth; therefore, aspirin use is safe for patients with concurrent UIAs and ICVD.

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Disclosures

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Appendix 1 Authors

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Jie Wang, MD	Capital Medical Universit , Beijing Tiantan Hospital, China	Acquisition and interpretation of data, critical revision of the manuscript for intellectual content
Xin Du, MD	Capital Medical Universit , Beijing An hen Hospital, China	Anal sis and interpretation of data, critical revision of the manuscript for intellectual content
Hao Li, MD	Capital Medical Universit , Beijing Tiantan Hospital, China	Anal sis and interpretation of data, critical revision of the manuscript for intellectual content
Yu-Ming Jiao, MD	Capital Medical Universit , Beijing Tiantan Hospital, China	Anal sis and interpretation of data, statistical anal sis, critical revision of the manuscript for intellectual content
Wei-Lun Fu, MD	Capital Medical Universit , Beijing Tiantan Hospital, China	Acquisition of data, critical revision of the manuscript for intellectual content
Ran Huo, MD	Capital Medical Universit , Beijing Tiantan Hospital, China	Acquisition of data, critical revision of the manuscript for intellectual content
Zi-Han Yan, MD	Capital Medical Universit , Beijing Tiantan Hospital, China	Acquisition of data, critical revision of the manuscript for intellectual content
Hong-Yuan Xu, MD	Capital Medical Universit , Beijing Tiantan Hospital, China	Acquisition of data, critical revision of the manuscript for intellectual content
Shuo Wang, MD	Capital Medical Universit , Beijing Tiantan Hospital, China	Anal sis and interpretation of data, critical revision of the manuscript for intellectual content
Yong Cao, MD	Capital Medical Universit , Beijing Tiantan Hospital, China	Design and conceptuali ed stud , revised the manuscript for intellectual content
Ji-Zong Zhao, MD	Capital Medical Universit , Beijing Tiantan Hospital, China	Design and conceptuali ed stud , revised the manuscript for intellectual content

Appendix 2 Coinvestigators

Name	Location	Role	Contribution
Zang Liu, MD	Capital Medical Universit , Affiliated Friendship Hospital	Coinvestigator	Major role in the acquisition of data
Hong-Rui Ma, MD	Capital Medical Universit , Beijing Xuan u Hospital	Coinvestigator	Major role in the acquisition of data
Chao Liang, MD	Capital Medical Universit , Beijing Chao ang Hospital	Coinvestigator	Major role in the acquisition of data

References

1. Zanaty M, Daou B, Chalouhi N, Starke RM, Jabbour P, Hasan D. Evidence that a subset of aneurysms less than 7 mm warrant treatment. J Am Heart Assoc 2016;5:e003936.
2. Wiebers DO, Whisnant JP, Huston J III, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet 2003;362:103–110.
3. Morita A, Kirino T, Hashi K, et al. The natural course of unruptured cerebral aneurysms in a Japanese cohort. N Engl J Med 2012;366:2474–2482.
4. Murayama Y, Takao H, Ishibashi T, et al. Risk analysis of unruptured intracranial aneurysms: prospective 10-year cohort study. Stroke 2016;47:365–371.
5. Joo SW, Lee SI, Noh SJ, Jeong YG, Kim MS, Jeong YT. What is the significance of a large number of ruptured aneurysms smaller than 7 mm in diameter? J Korean Neurosurg Soc 2009;45:85–89.
6. Wang W, Jiang B, Sun H, et al. Prevalence, incidence, and mortality of stroke in China: results from a nationwide population-based survey of 480 687 adults. Circulation 2017;135:759–771.
7. 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;159:514–521.
8. Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med 2013;369:11–19.
9. Phan K, Moore JM, Griessenauer CJ, Ogilvy CS, Thomas AJ. Aspirin and risk of subarachnoid hemorrhage: systematic review and meta-analysis. Stroke 2017;48:1210–1217.
10. Pottegard A, Garcia Rodriguez LA, Poulsen FR, Hallas J, Gaist D. Antithrombotic drugs and subarachnoid haemorrhage risk: a nationwide case-control study in Denmark. Thromb Haemost 2015;114:1064–1075.
11. Zanaty M, Roa JA, Nakagawa D, et al. Aspirin associated with decreased rate of intracranial aneurysm growth. J Neurosurg Epub 2019 Oct 29.
12. Hasan DM, Mahaney KB, Brown RD Jr, et al. Aspirin as a promising agent for decreasing incidence of cerebral aneurysm rupture. Stroke 2011;42:3156–3162.
13. Greving JP, Wermer MJH, Brown 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;13:59–66.
14. Kissela BM, Sauerbeck L, Woo D, et al. Subarachnoid hemorrhage: a preventable disease with a heritable component. Stroke 2002;33:1321–1326.
15. Etminan N, Buchholz BA, Dreier R, et al. Cerebral aneurysms: formation, progression, and developmental chronology. Transl Stroke Res 2014;5:167–173.
16. Etminan N, Rinkel GJ. Unruptured intracranial aneurysms: development, rupture and preventive management. Nat Rev Neurol 2016;12:699–713.
17. Feigin V, Parag V, Lawes CM, et al. Smoking and elevated blood pressure are the most important risk factors for subarachnoid hemorrhage in the Asia-Pacific region: an overview of 26 cohorts involving 306,620 participants. Stroke 2005;36:1360–1365.
18. Nahed BV, DiLuna ML, Morgan T, et al. Hypertension, age, and location predict rupture of small intracranial aneurysms. Neurosurgery 2005;57:676–683.
19. Juvela S, Porras M, Poussa K. Natural history of unruptured intracranial aneurysms: probability of and risk factors for aneurysm rupture. J Neurosurg 2000;93:379–387.
20. Wiebers DO. Unruptured intracranial aneurysms: risk of rupture and risks of surgical intervention. N Engl J Med 1998;339:1725–1733.
21. 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.
22. Guresir E, Vatter H, Schuss P, et al. Natural history of small unruptured anterior circulation aneurysms: a prospective cohort study. Stroke 2013;44:3027–3031.
23. Can A, Castro VM, Ozdemir YH, et al. Alcohol consumption and aneurysmal subarachnoid hemorrhage. Transl Stroke Res 2018;9:13–19.
24. Juvela S. Growth and rupture of unruptured intracranial aneurysms. J Neurosurg 2018;131:843–851.
25. Sonobe M, Yamazaki T, Yonekura M, Kikuchi H. Small unruptured intracranial aneurysm verification study: SUAVe study, Japan. Stroke 2010;41:1969–1977.
26. Leary MC, Saver JL. Annual incidence of first silent stroke in the United States: a preliminary estimate. Cerebrovasc Dis 2003;16:280–285.
27. Wu S, Wu B, Liu M, et al. Stroke in China: advances and challenges in epidemiology, prevention, and management. Lancet Neurol 2019;18:394–405.
28. Malhotra A, Wu X, Forman HP, et al. Growth and rupture risk of small unruptured intracranial aneurysms: a systematic review. Ann Intern Med 2017;167:26–33.
29. Chien A, Liang F, Sayre J, Salamon N, Villablanca P, Vinuela F. Enlargement of small, asymptomatic, unruptured intracranial aneurysms in patients with no history of subarachnoid hemorrhage: the different factors related to the growth of single and multiple aneurysms. J Neurosurg 2013;119:190–197.
30. Cao Y, Nishihara R, Wu K, et al. Population-wide impact of long-term use of aspirin and the risk for cancer. Jama Oncol 2016;2:762–769.
31. Cochrane J, Chen H, Conigrave KM, Hao W. Alcohol use in China. Alcohol 2003;38:537–542.
32. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;71:e127–e248.
33. Backes D, Vergouwen MD, Tiel Groenestege AT, et al. PHASES score for prediction of intracranial aneurysm growth. Stroke 2015;46:1221–1226.
34. 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.
35. Al-Shahi Salman R, Dennis MS, Sandercock PAG, et al. Effects of antiplatelet therapy after stroke due to intracerebral haemorrhage (RESTART): a randomised, open-label trial. Lancet 2019;393:2613–2623.
36. Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet 2018; 392:1036–1046.
37. Darsaut TE, Findlay JM, Magro E, et al. Surgical clipping or endovascular coiling for unruptured intracranial aneurysms: a pragmatic randomised trial. J Neurol Neurosurg Psychiatry 2017;88:663–668.
38. Frosen J, Cebral J, Robertson AM, Aoki T. Flow-induced, inflammation-mediated arterial wall remodeling in the formation and progression of intracranial aneurysms. Neurosurg Focus 2019;47:E21.
39. 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:e000019.
40. Hasan D, Hashimoto T, Kung D, Macdonald RL, Winn HR, Heistad D. Upregulation of cyclooxygenase-2 (COX-2) and microsomal prostaglandin E2 synthase-1 (mPGES-1) in wall of ruptured human cerebral aneurysms: preliminary results. Stroke 2012;43:1964–1967.
41. Can A, Rudy RF, Castro VM, et al. Association between aspirin dose and subarachnoid hemorrhage from saccular aneurysms: a case-control study. Neurology 2018;91:e1175-e1181.
42. Johnston SC, Easton JD, Farrant M, et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. N Engl J Med 2018;379:215–225.
43. Stirratt MJ, Dunbar-Jacob J, Crane HM, et al. Self-report measures of medication adherence behavior: recommendations on optimal use. Transl Behav Med 2015;5:470–482.
44. Vergouwen MD, Rinkel GJ, Algra A, et al. Prospective Randomized Open-label Trial to evaluate risk faCTor management in patients with Unruptured intracranial aneurysms: study protocol. Int J Stroke 2018;13:992–998.