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Atorvastatin and growth, rupture of small unruptured intracranial aneurysm: results of a prospective cohort study

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On behalf of the Small Unruptured Aneurysms Study Group

Abstract

Background and aims: The role of statins in unruptured intracranial aneurysm (UIA) growth and rupture remains ambiguous. This study sought to determine whether atorvastatin is associated with aneurysm growth and rupture in patients harboring UIA <7 mm.

Methods: This prospective, multicenter cohort study consecutively enrolled patients with concurrent UIA <7 mm and ischemic cerebrovascular disease from four hospitals between 2016 and 2019. Baseline and follow-up patient information was recorded. Because of the strong anti-inflammatory effect of aspirin, patients using aspirin were excluded. Patients taking atorvastatin 20 mg daily were atorvastatin users. The primary and exploratory endpoints were aneurysm rupture and growth, respectively.

Results: Among the 1087 enrolled patients, 489 (45.0%) took atorvastatin, and 598 (55%) took no atorvastatin. After a mean follow-up duration of 33.0 ± 12.5 months, six (1.2%) and five (0.8%) aneurysms ruptured in atorvastatin and non-atorvastatin groups, respectively. In the adjusted multivariate Cox analysis, UIA sized 5 to <7 mm, current smoker, and uncontrolled hypertension were associated with aneurysm rupture, whereas atorvastatin [adjusted hazard ratio (HR) 1.495, 95% confidence interval (CI) 0.417–5.356, $p = 0.537$] was not. Of 159 patients who had follow-up imaging, 34 (21.4%) took atorvastatin and 125 (78.6%) took no atorvastatin. Aneurysm growth occurred in five (14.7%) and 21 (16.8%) patients in atorvastatin and non-atorvastatin groups (mean follow-up: 20.2 ± 12.9 months), respectively. In the adjusted multivariate Cox analysis, UIAs sized 5 to <7 mm and uncontrolled hypertension were associated with a high growth rate; atorvastatin (adjusted HR 0.151, 95% CI 0.031–0.729, $p = 0.019$) was associated with a reduced growth rate.

Conclusions: We conclude atorvastatin use is associated with a reduced risk of UIA growth, whereas atorvastatin is not associated with UIA rupture.

The trial registry name: The Clinic Benefit and Risk of Oral Aspirin for Unruptured Intracranial Aneurysm Combined With Cerebral Ischemia

Clinical Trial Registration-URL: http://www.clinicaltrials.gov

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Introduction

Unruptured intracranial aneurysm (UIA) is a cerebrovascular disease affecting 2.0–4.0% of the adult population.[1–3] The Unruptured Cerebral Aneurysm Study of Japan and International Study of Unruptured Intracranial Aneurysms showed that of all UIAs, small unruptured intracranial aneurysms sized <7 mm accounted for 62.0% and 74.5%, respectively.[4,5] The annual rupture rate of small UIAs is less than 1.0%[6] and the risk

of morbidity and mortality from surgical clipping or endovascular treatment outweighs aneurysm rupture; therefore, a conservative treatment strategy might be recommended for patients with UIAs <7 mm.[2,4] However, 69.6% to 71.8% of ruptured aneurysms are <7 mm.[7,8] No drug treatment to prevent small aneurysm growth and subsequent rupture has been established.

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are widely used as lipid-lowering drugs. In addition to their lipid-lowering effect, statins can also exert pleiotropic effects to protect the vasculature via their anti-inflammatory effects and ability to stimulate the production of extracellular matrix and chemotactic migration of mesenchymal progenitor cells.[9–12] Researchers suggested that statin use can reduce abdominal aortic aneurysm growth rates and rupture risk by its pleiotropic effects.[13–15] Currently, the role of statins in UIA rupture and growth is still unclear and controversial. Prior studies suggested that statins have protective effects in experimental cerebral aneurysm models and can protect against aneurysm rupture in humans.[16–18] However, several studies also suggested that oral administration of statins is not associated with cerebral aneurysm rupture.[19,20]

Statins have been widely used for ischemic cerebrovascular disease (ICVD).[21] With the wide use of high-resolution magnetic resonance (MR) imaging, ICVD and UIAs are now simultaneously detected frequently.[1,22] In our cohort study, we aim to evaluate whether oral administration of atorvastatin is associated with a reduced risk of UIA rupture and growth in patients harboring small UIAs with concurrent ICVD.

Methods

Study design

This prospective, multicenter cohort study consecutively enrolled eligible patients in four hospitals between 2016 and 2019 (clinical trial registration number: NCT02846259, http://www.clinicaltrials.gov). The study protocol was approved by the Ethics Committee for Human Research at the Beijing Tiantan Hospital (approval number KY2016-033-02) and was in accordance with the principles of the Helsinki Declaration and the ICH-GCP guidelines. 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

We included adults (≥18 years) who had UIAs sized 2 to <7 mm in greatest diameter confirmed by MR angiography, computed tomography (CT) angiography, or digital subtraction angiography, and these patients with concurrent either symptomatic ICVD or asymptomatic ICVD. All participants provided written informed consent. Aneurysm neck, height (measured from the center of the aneurysm neck to the aneurysm dome), and width (maximum width measured perpendicular to the aneurysm height) were measured to assess the greatest diameter of aneurysm.[1] Patients with a history of ischemic stroke or transient ischemic stroke were categorized into symptomatic ICVD group. Clinical asymptomatic patients whose CT/MR imaging showed lacunar infarction on the brain were categorized into the asymptomatic ICVD group.[22,23]

According to the 2015 American Heart Association/American Stroke Association guidelines for the management of patients with UIAs,[24] patients with some well-accepted unmodifiable risk factors (family history of intracranial aneurysms, history of subarachnoid hemorrhage, multiple aneurysms, etc.) are considered to be associated with a high rate of aneurysm rupture and growth. Therefore, these patients were excluded from this observational study. Patients were ineligible if they met one or more of 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 ≥3; (6) fusiform or daughter sac UIAs; (7) infundibular dilatation of cerebral arteries; (8) aspirin use or incomplete information on medication use.

Recruited patients who simultaneously fulfilled the aforementioned criteria and all following inclusion criteria participated in imaging follow-up: (1) patients aged 18 to ≤80 years; (2) patients who provided written informed consent; and (3) patients who consented to follow-up imaging with MR angiography or CT angiography. Patients

were excluded if they met the following exclusion criteria: (1) patients could not perform self-care activities (a modified Rankin Scale score ⩾2); (2) residence in a rural area that prevented regular follow-up.[25]

In addition to the lipid-lowering effect, statins can also exert pleiotropic effects to protect the vasculature. Previous studies suggested that the dose of 20 mg of atorvastatin could reduce key inflammatory factors in human vascular wall.[26,27] Therefore, in our study patients took atorvastatin with a dose of 20 mg daily.

Data collection

All patients were required to complete a standard questionnaire to provide demographic data. The demographic and clinical information of the UIA patients included age, sex, main complaint, medical history, body weight, body height, medication history (dosage, frequency, and duration), alcohol consumption, cigarette smoking history, performance status according to the modified Rankin Scale, and aneurysm location, size, and shape.

Any medical record of systolic blood pressure repeatedly ⩾140 mmHg, diastolic blood pressure ⩾90 mmHg, or both were considered a positive history of hypertension.[28] We divided patients into three groups according to the history of hypertension and actual blood pressure data: non-hypertension, controlled hypertension, and uncontrolled hypertension groups. Patients with hypertension receiving standard hypertension treatment (daily targeted mean systolic blood pressure/diastolic blood pressure <140/90 mmHg with a home blood pressure measuring device) were considered to have controlled hypertension.[29] We grouped the patients as regular alcohol drinkers (drinking once or more than once per week) and occasional alcohol drinkers (drinking less than once per week).[30] Additionally, smoking was grouped as follows: nonsmoker, former smoker, and current smoker.[4] Neuroradiologists used picture archiving and communications systems to detect aneurysm characteristics (aneurysm size, location, and shape). Based on previous studies, we categorized the size of UIAs into two size groups: <5 mm, 5 to <7 mm.[6,31]

Follow-up

Telephone follow-up was performed for all participants, and daily blood pressure level, alcohol consumption, cigarette smoking, and medication use (antihypertensive drugs, aspirin, and atorvastatin), etc. were recorded every 3 to 6 months from January 2016 to December 2019. The follow-up imaging 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 atorvastatin, non-atorvastatin users starting atorvastatin 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 radiological assessment

The primary endpoint was aneurysm rupture. The diagnosis of aneurysm rupture was confirmed by preoperative CT or MR imaging, cerebrospinal fluid analysis, or a neurosurgeon during the operation.[32] The last follow-up image before the rupture was considered endpoint imaging.[1] The exploratory endpoint was UIA growth. To perform a more accurate assessment of aneurysm growth, patients who participated in imaging follow-up were required to image subsequently with the same imaging modality. Aneurysm growth was defined as (1) growth ⩾1.0 mm in at least one direction by identical imaging modalities; (2) growth ⩾0.5 mm in two directions by identical imaging modalities; and (3) an indisputable change in aneurysm shape (i.e., change from a regular shape to an irregular shape).[33] 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 first and last imaging was used.

First imaging and all follow-up imaging were assessed by two neurosurgeons (H.L & Y.M.J) who were blinded to the patients' clinical data, rupture-related and growth-related 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.[33] 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.

Statistical analysis

Continuous variables were presented as the means ± SDs or as medians and interquartile ranges, and categorical variables were expressed as percentages. Wilcoxon rank-sum tests, *t*-tests, and chi-squared (χ^2) tests were used as appropriate. The associations of pertinent risk factors with aneurysm rupture and growth were evaluated by univariate Cox regression analysis. Covariates with *p*-values less than 0.10 and covariates having clinical significance in the univariate analysis were entered into the multivariate Cox regression analysis. In order to avoid selection bias and comorbidities between atorvastatin and non-atorvastatin groups, baseline characteristics with *p*-values less than 0.05 between them were also entered into the multivariate Cox regression analysis. Multivariate Cox analysis using the enter selection method was used. The incidence rates for primary and exploratory endpoint events were calculated by dividing the numbers of events by person-years at risk, with 95% confidence intervals (CIs) estimated using a Poisson model. Analyses were performed with the statistical software SPSS 24.0 (IBM Corp, Armonk, NY, USA). A 2-tailed *p*-value <0.05 was considered statistically significant.

Results

Patient population

A total of 1866 patients were assessed for eligibility. Of all patients, 128 (6.9%) were lost to follow-up. Besides being an antiplatelet drug, aspirin also has anti-inflammatory effects, which is similar to atorvastatin;[26,27,34,35] therefore 643 patients taking aspirin were excluded from our study and eight were excluded because of incomplete information on medication use. Therefore, 1087 patients were consecutively enrolled in our study between January 2016 and December 2019.

The clinical information of 1087 patients is presented in Table 1. Of all patients, 489 (45%) patients took atorvastatin 20 mg daily and 598 (55%) patients took no atorvastatin. Eligible patients were informed in advance that the antithrombotic agents might be associated with a high rate of aneurysm rupture.[36,37] Patients did not select these agents according to their personal intention. As a result, only 44 (4.0%) patients took other antithrombotic drugs, including 30 (2.8%), five (0.46%), five (0.46%), and four (0.37%) patients taking clopidogrel, dabigatran, warfarin, and rivaroxaban, respectively. All antithrombotic drugs were used for less than 3 months (mean time of use of 1.6 months, range 0.5–3.0 months), and the mean follow-up time in these patients was 31.3 months (range 7.1–45.4 months). The mean interval between the discontinuation of medication and the end of follow-up was 29.3 months (range 6.1–44.4 months).

A total of 159 patients were recruited for imaging follow-up. Of 1087 patients, 568 patients harboring tiny aneurysms (sized <3 mm) refused to perform imaging follow-up because all patients with tiny UIAs were informed in advance of the low risk of rupture (0.23% annually) and growth (1.22% annually);[31] 115 patients who could not perform self-care activities and need help from other people were ineligible for follow-up imaging; 123 patients in rural areas were not enrolled; 112 patients refused to perform follow-up imaging; 10 patients withdrew from follow-up (Figure 1). The clinical information of 159 patients is shown in Table 2. Among 159 patients, 34 (21.4%) patients took atorvastatin 20 mg daily and 125 (78.6%) patients took no atorvastatin.

Size and location of UIAs

Among 1087 patients, the most common location was the internal carotid artery ($n = 713$, 65.6%), followed by the middle cerebral artery ($n = 92$, 8.5%) and anterior communicating artery ($n = 78$, 7.2%). The mean UIA size was 2.9 ± 1.1 mm and the median (interquartile range) was 2.5 (2.1–3.3) (Table 1).

Among 159 patients, the most common location was the internal carotid artery ($n = 108$, 67.9%), followed by the anterior communicating artery ($n = 19$, 11.9%), the posterior communicating artery ($n = 9$, 5.7%) and middle cerebral artery ($n = 9$, 5.7%). The mean UIA size was 3.3 ± 1.1 mm and the median (interquartile range) was 3.2 (2.6–3.8) (Table 2).

Outcomes

Among 1087 patients, after a total of 2811.9 person-years, 11 (1.01%) aneurysms ruptured with a mean follow-up duration of 33.0 ± 12.5 months (range, 1.0–46.0 months). Six (1.2%) and five (0.8%) aneurysms ruptured in atorvastatin and non-atorvastatin groups, respectively. The incidence rates for rupture

Table 1. Baseline characteristics of the patients.

Variables	Overall ($n=1087$)	Atorvastatin ($n=489$)	Non-atorvastatin ($n=598$)	p-value
Age-mean-yr	60.3 ± 12.4	62.4 ± 11.7	58.5 ± 12.7	<0.001†§
⩾60 years-no. (%)	592(54.5)	294(60.1)	298(49.8)	<0.001‡§
Female-no. (%)	508(46.7)	199(40.7)	309(51.7)	<0.001‡§
BMI ⩾24 kg/m^2-no. (%)	641(59.0)	313(64.0)	328(54.8)	0.002‡§
Current smoker-no. (%)	233(21.4)	124(25.4)	109(18.2)	0.003‡§
Regular alc drinkers-no. (%)	346(31.8)	173(35.4)	173(28.9)	0.016‡§
Medical history-no. (%)				
Hypertension	580(53.4)	286(58.5)	294(49.2)	0.001‡§
Diabetes mellitus	216(19.9)	116(23.7)	100(16.7)	0.004‡§
Hyperlipidemia	236(21.7)	120(24.5)	116(19.4)	0.034‡§
Coronary heart disease	113(10.4)	48(9.8)	65(10.9)	0.239‡
Pre-TIA or stroke	192(17.7)	88(17.9)	104(17.4)	0.828‡
Antihypertensive drug-no. (%)	505(46.5)	259(53.0)	246(41.1)	0.357‡
Location-no.(%)				0.313‡
ICA	713(65.6)	326(66.7)	387(64.7)	
MCA	92(8.5)	45(9.2)	47(7.9)	
ACA	34(3.1)	16(3.3)	18(3.0)	
ACoA	78(7.2)	31(6.3)	47(7.9)	
PCoA	43(4.0)	14(2.9)	29(4.8)	
BA tip or BA-SCA	47(4.3)	22(4.5)	25(4.2)	
VA-PICA or VB junction	36(3.3)	14 (2.9)	22(3.7)	
PCA	23(2.1)	12(2.4)	11(1.8)	
Other	21(1.9)	9(1.8)	12(2.0)	
Size				
Mean ± SD, mm	2.9 ± 1.1	2.8 ± 1.0	2.9 ± 1.1	
Median (IQR)	2.5(2.1–3.3)	2.5(2.1–3.3)	2.5(2.1–3.3)	0.792*
Size group				0.077‡
2 to <5 mm	1008(92.7)	461(94.3)	547(91.5)	
5 to <7 mm	79(7.3)	28(5.7)	51(8.5)	-

Abbreviations: Alc, alcohol; ACA, anterior cerebral artery; ACoA, anterior communicating artery; BA, basilar artery; BMI, body mass index; ICA, internal carotid artery; IQR, Interquartile range; MCA, middle cerebral artery; PCA, posterior cerebral vascular; PCoA, posterior communicating artery; PICA, posterior inferior cerebellar artery; Pre, previous; SCA, superior cerebellar artery; TIA, transient ischemic attack; VA, vertebral artery; VB, vertebrobasilar. † t-test; ‡ Chi-square test; * Wilcoxon rank-sum test; § $p<0.05$.

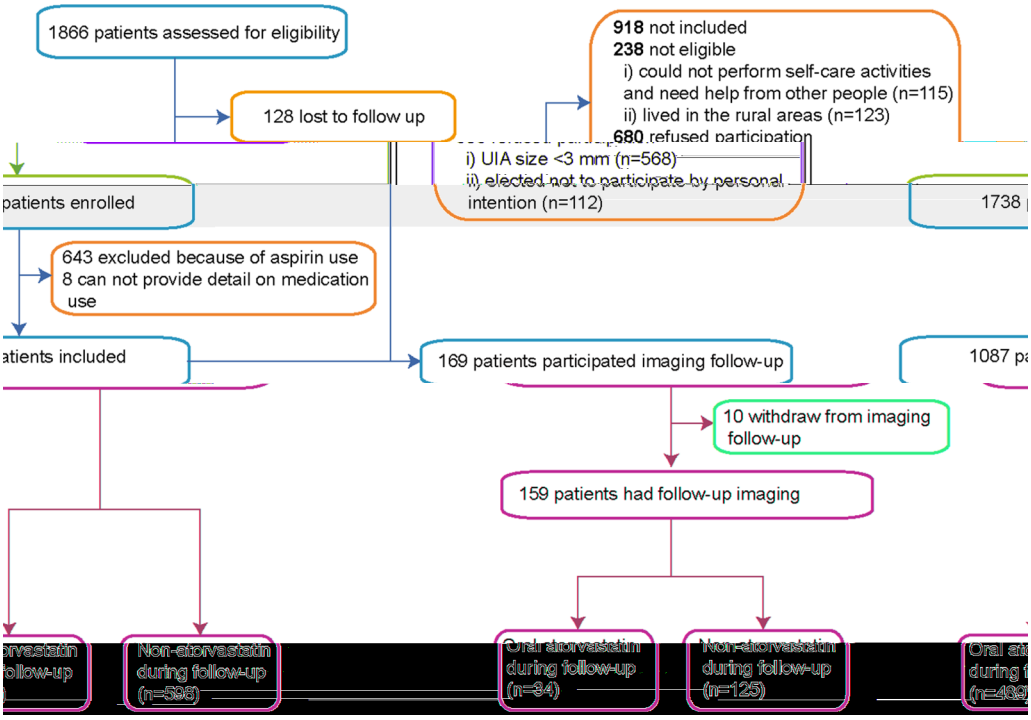

Figure 1. The flow chart of the study patients. UIA, unruptured intracranial aneurysm.

were 0.32 (95% CI 0.13–0.77) and 0.48 (95% CI 0.22–1.07) per 100 person-years for the non-atorvastatin and atorvastatin groups, respectively. Owing to the aneurysm rupture, 11 patients received surgical or endovascular treatment. The univariate Cox analysis found that UIAs with a size of 5 to <7 mm, uncontrolled hypertension, current smoker, and specific aneurysm locations (anterior communicating artery, posterior communicating artery, or middle cerebral artery) had p-values <0.1. On adjusted multivariate Cox analysis, uncontrolled hypertension [adjusted hazard ratio (HR) 15.898, 95% CI 1.868–135.301, $p = 0.011$], UIAs sized 5 to <7 mm (adjusted HR 12.316, 95% CI 3.239–46.822, $p < 0.001$) and current smoker (adjusted HR 13.410, 95% CI 1.176–152.977, $p = 0.037$) were associated with a high rupture rate, whereas oral administration of atorvastatin (adjusted HR 1.495, 95% CI 0.417–5.356, $p = 0.537$) was not associated with UIA rupture (Table 3).

Among 159 patients, after a total of 257.4 person-years, 26 (16.4%) aneurysms enlarged with a mean follow-up duration of 20.2 ± 12.9 months (range, 3.0–48.0 months). Aneurysm growth occurred in five (14.7%) and 21 (16.8%) patients in atorvastatin and non-atorvastatin groups, respectively. The incidence rates for growth were 10.7 (95% CI 7.0–16.4) and 8.2 (95% CI 6.9–14.8) per 100 person-years for the non-atorvastatin and atorvastatin groups, respectively. Owing to the aneurysm growth, three patients received surgical or endovascular treatment. *De novo* aneurysm was not found during follow-up. The univariate Cox analysis found that UIAs with a size of 5 to <7 mm and uncontrolled hypertension had p-values <0.1. On adjusted multivariate Cox analysis, uncontrolled hypertension (adjusted HR 6.445, 95% CI 1.389–29.895, $p = 0.017$) and UIAs sized 5 to <7 mm (adjusted HR 7.919, 95% CI 2.459–25.505, $p = 0.001$) were associated with a high growth rate. Oral administration of atorvastatin was associated with a low growth rate (adjusted HR 0.151, 95% CI 0.031–0.729, $p = 0.019$) (Table 4).

Discussion

Statins have recently gained traction as a possible therapeutic agent due to their pleiotropic effects on the aneurysm wall.[38] In our cohort study, oral atorvastatin is not associated with small UIA rupture, whereas oral atorvastatin is associated with a decreased growth rate. Uncontrolled hypertension and UIAs sized 5 to <7 mm are associated with UIA growth and rupture.

Table 2. Baseline characteristics of the patients had follow-up imaging.

variables	Overall (*n* = 159)	Atorvastatin (*n* = 34)	Non-atorvastatin (*n* = 125)	*p*-value
Age-mean-yr	56.4 ± 11.4	61.9 ± 10.6	54.5 ± 11.0	<0.001†§
⩾60 years-no. (%)	65(40.9)	24(70.6)	41(32.8)	<0.001‡§
Female-no. (%)	92(57.9)	20(58.8)	72(57.6)	0.898‡
BMI ⩾24 kg/m^2-no. (%)	88(55.3)	31(91.2)	57(45.6)	<0.001‡§
Current smoker-no. (%)	21(13.2)	6(17.6)	15(12.0)	0.388‡
Regular alc drinkers-no. (%)	47(29.6)	14(41.2)	33(26.4)	0.094‡
Medical history-no. (%)				
Hypertension	70(44.0)	26(76.5)	44(35.2)	0.001‡§
Hyperlipidemia	22(13.8)	6(17.6)	16(12.8)	0.468‡
Diabetes mellitus	23(14.5)	13(38.2)	10(8.0)	<0.001‡§
Coronary heart disease	16(10.1)	6(17.6)	10(8.0)	0.097‡
Pre-TIA or ischemic stroke	13(8.2)	7(20.6)	6(4.8)	0.003‡§
Antihypertensive drug-no. (%)	59(37.1)	21(61.8)	38(30.4)	<0.001‡
Location-no. (%)				0.418‡
ICA	108(67.9)	25(73.5)	83(66.4)	
MCA	9(5.7)	2(5.9)	7(5.6)	
ACA	4(2.5)	0(0)	4(3.2)	
ACoA	19(11.9)	4(11.8)	15(12.0)	
PCoA	9(5.7)	0(0)	9(7.2)	
BA tip or BA-SCA	4(2.5)	2(5.9)	2(1.6)	
VA-PICA or VB junction	2(1.3)	0(0)	2(1.6)	
PCA	4(2.5)	1(2.9)	3(2.4)	
Size				
Mean ± SD, mm	3.3 ± 1.1	3.2 ± 1.3	3.4 ± 1.0	
Median (IQR)	3.2(2.6–3.8)	2.8(2.3–3.5)	3.2(2.7–3.9)	0.059*
Size group				0.294‡
2 to <5 mm	147(92.5)	30(88.2)	117(93.6)	
5 to <7 mm	12(7.5)	4(11.8)	8(6.4)	

Abbreviations: ACA, anterior cerebral artery; ACoA, anterior communicating artery; alc, alcohol; BA, basilar artery; BMI, body mass index; ICA, internal carotid artery; IQR, interquartile range; MCA, middle cerebral artery; PCA, posterior cerebral vascular; PCoA, posterior communicating artery; PICA, posterior inferior cerebellar artery; Pre, previous; SCA, superior cerebellar artery; TIA, transient ischemic attack; VA, vertebral artery; VB, vertebrobasilar. †*t*-test; ‡Chi-square test; *Wilcoxon rank-sum test; §$p < 0.05$.

Table 3. Univariate and multivariate Cox analyses of risk factors associated with aneurysm rupture.

Variable	*n*	Univariate analysis		Multivariate analysis		Adjusted multivariate analysis ‡	
		HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Age ⩾60 years	8	2.248(0.596–8.473)	0.232				
Female	5	0.916(0.279–3.003)	0.885				
BMI ⩾24 kg/m^{2}†	6	0.855(0.261–2.803)	0.796				
Hyperlipidemia†	2	0.799(0.173–3.698)	0.774				
Pre-TIA or ischemic stroke	3	1.759(0.467–6.633)	0.404	0.935(0.230–3.796)	0.926	0.878(0.204–3.783)	0.861
Diabetes mellitus†	1	0.420(0.054–3.279)	0.408				
Antihypertensive†	7	0.368(0.076–1.777)	0.214				
Atorvastatin	6	1.515(0.462–4.963)	0.493	1.189(0.351–4.028)	0.781	1.495(0.417–5.356)	0.537
Smoker†							
Nonsmoker (*R*)	4						
Former smoker	2	2.150(0.394–11.741)	0.377	2.361(0.381–14.640)	0.356	6.722(0.520–86.888)	0.145
Current smoker	5	3.755(1.008–13.987)	0.049*	3.500(0.884–13.861)	0.074	13.410(1.176–152.977)	0.037*
Regular alc drinkers	6	2.636(0.804–8.640)	0.110				
Hypertension							
Non-hypertension (*R*)	1						
Uncontrolled hypertension§	2	16.299(2.038–130.328)	0.009*	12.656(1.536–104.292)	0.018*	15.898(1.868–135.301)	0.011*
Controlled-hypertension§	8	3.961(0.359–43.681)	0.261	2.993(0.265–33.796)	0.375	3.392(0.293–39.302)	0.328
Location							
ICA (R)	4						
ACoA, PCoA, or MCA	4	3.326(0.832–13.298)	0.089	2.909(0.714–11.854)	0.136	3.512(0.775–15.912)	0.103
Others	3	3.436(0.769–15.355)	0.106	3.000(0.647–13.906)	0.160	3.192(0.602–16.923)	0.173
Size							
2 to <5 mm (*R*)	6						
5 to <7 mm	5	10.424(3.180–34.165)	<0.001*	9.781(2.837–33.727)	<0.001*	12.316(3.239–46.822)	<0.001*

Abbreviations: Alc, alcohol; ACoA, anterior communicating artery; BMI, body mass index; CI, confidence interval; HR, hazard ratio; ICA, internal carotid artery; MCA, middle cerebral artery; *n*, number of events; PCoA, posterior communicating artery; Pre, previous; R, reference; TIA, transient ischemic attack; †There are 1,2, 2, 10 and 15 missing information in body mass index (BMI), hyperlipidemia, diabetes, history of smoking, the use of antihypertensive drug, respectively. ‡In order to adjust the difference between atorvastatin and non-atorvastatin groups, baseline characteristics with *p*-values less than 0.05 in Table 1 were entered into the multivariate Cox regression analysis. §Patients with hypertension receiving standard hypertension treatment (defined as daily targeted mean systolic blood pressure/diastolic blood pressure below 140/90 mmHg with a home blood pressure measuring device) were defined as controlled hypertension, otherwise, defined as uncontrolled hypertension. *$p < 0.05$.

Table 4. Univariate and multivariate Cox analyses of risk factors associated with aneurysm growth.

Variable	*n*	Univariate analysis		Multivariate analysis		Adjusted multivariate analysis‡	
		HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Age ⩾60 years	14	1.208(0.555–2.626)	0.634				
Female	18	1.341(0.582–3.090)	0.491				
BMI ⩾24 kg/m^2	13	0.979(0.450–2.128)	0.957				
Hyperlipidemia	3	0.829(0.248–2.772)	0.761				
Pre-TIA or ischemic stroke	4	1.196(0.402–3.558)	0.747	4.119(0.964–17.603)	0.056	3.976(0.897–17.629)	0.069
Diabetes mellitus	7	1.694(0.710–4.044)	0.235				
Antihypertensive	13	0.613(0.135–2.778)	0.525				
Atorvastatin	5	0.620(0.230–1.669)	0.344	0.159(0.035–0.734)	0.018*	0.151(0.031–0.729)	0.019*
Smoker†							
Nonsmoker (*R*)	18						
Former smoker	1	0.266(0.035–1.995)	0.198	0.122(0.011-1.329)	0.084	0.107(0.009–1.286)	0.078
Current smoker	6	1.526(0.604–3.855)	0.371	1.402(0.508–3.867)	0.514	1.435(0.488–4.221)	0.511
Regular alc drinkers	8	1.148(0.498–2.645)	0.746				
Hypertension†							
Non-hypertension (*R*)	11						
Uncontrolled hypertension§	9	3.578(1.314–9.743)	0.013*	5.312(1.644–17.167)	0.005*	6.445(1.389–29.895)	0.017*
Controlled-hypertension§	6	1.523(0.629–3.686)	0.351	1.333(0.482–3.692)	0.580	1.348(0.454–4.007)	0.591
Location							
ICA (R)	16						
ACoA, PCoA, or MCA	7	1.716(0.690–4.268)	0.245	0.405(0.138–1.192)	0.101	0.413(0.140–1.220)	0.110
Others	3	1.036(0.301–3.564)	0.955	1.027(0.230–4.595)	0.972	0.980(0.212–4.540)	0.980
Size							
2 to <5 mm (R)	20						
5 to <7 mm	6	4.737(1.864–12.037)	0.001*	7.514(2.367–23.853)	0.001*	7.919(2.459–25.505)	0.001*

Abbreviations: ACoA, anterior communicating artery; alc, alcohol; BMI, body mass index; CI, confidence interval; HR, hazard ratio; ICA, internal carotid artery; MCA, middle cerebral artery; PCoA, posterior communicating artery; Pre, previous; R, reference; TIA, transient ischemic attack; †There are 2 and 8 missing information in history of smoking and hypertension course, respectively. ‡ In order to adjust the difference between atorvastatin and non-atorvastatin groups, baseline characteristics with *p*-values less than 0.05 in Table 2 were entered into the multivariate Cox regression analysis. §Patients with hypertension receiving standard hypertension treatment (defined as daily targeted mean systolic blood pressure/diastolic blood pressure below 140/90 mmHg with a home blood pressure measuring device) were defined as controlled hypertension, otherwise, defined as uncontrolled hypertension. *$p < 0.05$.

At present, there is no medical treatment to arrest aneurysm rupture. Statins are known as drugs that can exert pleiotropic effects including lipid-lowering effect, anti-inflammation of the vasculature, and ability to stimulate the production of extracellular matrix.[9–12] Their role in UIA rupture remains largely ambiguous and controversial.[16–20] In our prospective cohort study, oral atorvastatin was not associated with UIA rupture. The rate of aneurysm rupture is low in our study and longer follow-up is needed to further strengthen the results of the current study.

In our current study, compared with non-atorvastatin use patients, patients who used atorvastatin had a decreased risk of aneurysm growth. Aneurysm growth has been used as a clinical surrogate for rupture.[24,39,40] Villablanca et al. showed that aneurysms growing 5% in volume had a 12-fold higher risk of rupture over time.[41] Our result indicate that atorvastatin might be a candidate prophylactic treatment for small UIA growth. However, also in our study, oral atorvastatin was not associated with aneurysm rupture. Backes et al. reported that 56% of aneurysms rupture occurred in nongrowth aneurysms;[2] cigarette smoking, posterior circulation location of aneurysm, age, and female sex were also risk factors for UIA rupture.[5,24,42–44] Aneurysm growth is not the only risk factor for aneurysm rupture. Whether or not atorvastatin prevented aneurysm rupture through preventing aneurysm growth needs long-term research.

There are several limitations to our study. First, 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 a high risk of aneurysm rupture (subarachnoid hemorrhage history, multiple aneurysms, irregular aneurysm shape, etc.). In addition, previous studies indicated that cigarette smoking and female were associated with a high rate of aneurysm growth and rupture.[24,43,45] These results differ from our data may be attributed to fairly short follow-up duration (mean follow-up duration of 33.0 ± 12.5 months) and longer follow-up is needed to further strengthen the results of the current study and assure whether smoking and female are associated with a high rate of aneurysm growth. Second, medication adherence was assessed using self-reported data, which may be a biased measure as with all observational studies.[46] Third, the exact time of aneurysm growth was difficult to determine because aneurysm growth was 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] Finally, there was a high selection of atorvastatin use by several prognostic variables in our study. Its use was more common in older patients, men, more obese, smokers, drinkers, and in those with hypertension, diabetes, hyperlipidemia. Randomized controlled trial studies are needed to mitigate this selection bias.

Conclusion

Oral administration of atorvastatin is associated with a decreased risk of aneurysm growth. For patients with concurrent hypertension, blood pressure control has an effect on alleviating the risk of small UIA growth and rupture. Determining whether atorvastatin plays a suppressive role in aneurysm growth and rupture requires further prospective randomized controlled clinical trials.

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Author contributions

Jie Wang and Jiancong Weng designed the study; acquired and analyzed the data; performed statistical analysis and drafted the manuscript for intellectual content. Hao Li, Yuming Jiao, and Weilun Fu analyzed, interpreted the data and revised the manuscript for intellectual content. Ran Huo, Zihan Yan, and Hongyuan Xu collected the data and revised the manuscript for intellectual content. Jiong Zhan resolved the discrepancies of follow-up imaging. Shuo Wang and Jizong Zhao designed the study and revised the manuscript for intellectual. Yong Cao and Xin Du provided overall oversight of the research.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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