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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

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Methods

Study design

Participants

Data collection

Follow-up

Outcome and radiological assessment

Statistical analysis

Results

Patient population

Size and location of UIAs

Outcomes

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; § $p<0.05$.

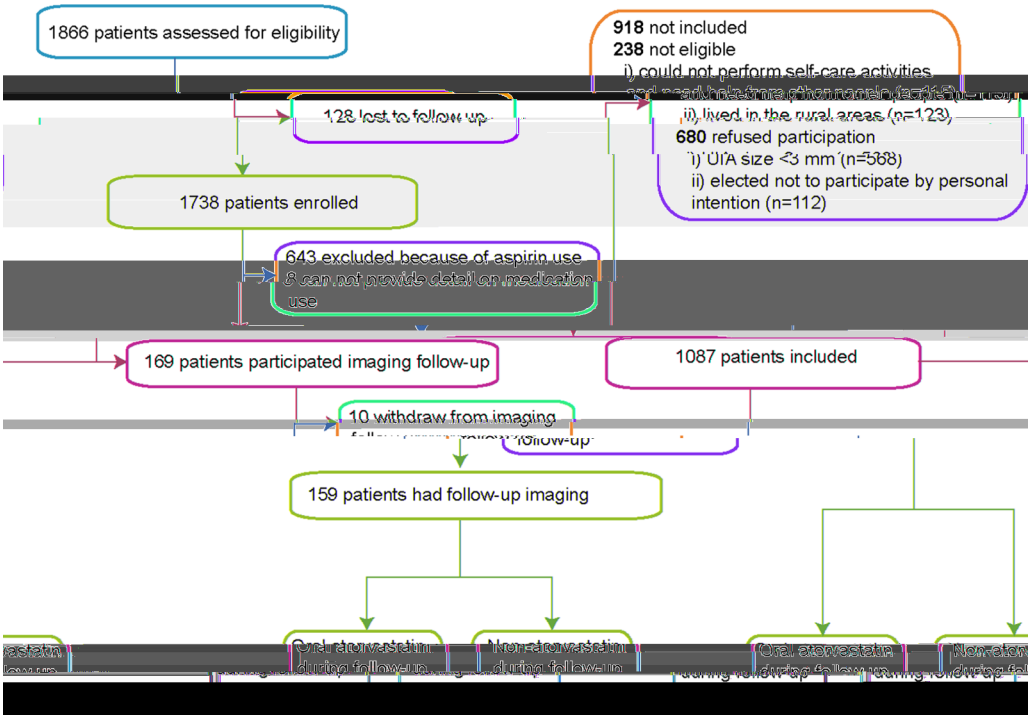

Figure 1. The flow chart of the study patients. UIA, unruptured intracranial aneurysm.

Discussion

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)	4((36–3(61.8)Tj12.667 0 Td(4)–3(2.9))Tj9.764 0 T4((37–39(4.8))Tj10.575 0 Td59*.8)-)Tj43.279 -2.08 Td(group(%))Tj43.757 0 Td2(0			
PCA	9(2.5)	4(11.8)		

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. *$p < 0.05$.

Conclusion

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Author contributions

Conflict of interest statement

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ORCID iDs


References