Original Contribution

Lipid-Lowering Agents and High HDL (High-Density Lipoprotein) Are Inversely Associated With Intracranial Aneurysm Rupture

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Background and Purpose—Growing evidence from experimental animal models and clinical studies suggests the protective effect of statin use against rupture of intracranial aneurysms; however, results from large studies detailing the relationship between intracranial aneurysm rupture and total cholesterol, HDL (high-density lipoprotein), LDL (low-density lipoprotein), and lipid-lowering agent use are lacking.

Methods—The medical records of 4701 patients with 6411 intracranial aneurysms diagnosed at the Massachusetts General Hospital and the Brigham and Women's Hospital between 1990 and 2016 were reviewed and analyzed. Patients were separated into ruptured and nonruptured groups. Univariable and multivariable logistic regression analyses were performed to determine the effects of lipids (total cholesterol, LDL, and HDL) and lipid-lowering medications on intracranial aneurysm rupture risk. Propensity score weighting was used to account for differences in baseline characteristics of the cohorts.

Results—Lipid-lowering agent use was significantly inversely associated with rupture status (odds ratio, 0.58; 95% confidence interval, 0.47–0.71). In a subgroup analysis of complete cases that includes both lipid-lowering agent use and lipid values, higher HDL levels (odds ratio, 0.95; 95% confidence interval, 0.93–0.98) and lipid-lowering agent use (odds ratio, 0.41; 95% confidence interval, 0.23–0.73) were both significantly and inversely associated with rupture status, whereas total cholesterol and LDL levels were not significant. A monotonic exposure–response curve between HDL levels and risk of aneurysmal rupture was obtained.

Conclusions—Higher HDL values and the use of lipid-lowering agents are significantly inversely associated with ruptured intracranial aneurysms. **(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.117.019972.)**

Key Words: aneurysm ■ cholesterol ■ intracranial aneurysms ■ lipids ■ subarachnoid hemorrhage

Although the correlation between serum total cholesterol and risk of coronary heart disease has been well established, the relation with aneurysmal subarachnoid hemorrhage (aSAH) remains controversial with studies reporting both increased and decreased associations. A recent systematic review of 21 studies investigating the association between cholesterol and risk of SAH showed that elevated total cholesterol level increases the risk for SAH in men.[1] However, study sizes of included studies were small, ranging from 55 to 858 patients with ruptured intracranial aneurysms.[1] Moreover, only 4 studies included HDL (high-density lipoprotein) values, whereas none of the studies assessed LDL (low-density lipoprotein) values.[1] In addition, growing evidence from various experimental animal models and smaller clinical studies supports the inverse relationship between statin use and intracranial aneurysm rupture.[2–4] Here, we present the largest case–control study to date, to investigate the role of total cholesterol, HDL, LDL, and use of lipid-lowering agents on the risk of SAH in 4701 patients with 6411 intracranial aneurysms.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request. We included 4701 patients who were diagnosed with an intracranial aneurysm

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between 1990 and 2016 at the Brigham and Women's Hospital and Massachusetts General Hospital. This study has been approved by our institutional review board and considered minimal risk. Patient consent was, therefore, waived by the board. We used a combination of machine learning algorithms and manual medical chart review to identify patients both prospectively on clinical presentation (2007–2016) and retrospectively using natural language processing in conjunction with the Partners Healthcare Research Patients Data Registry.[5] This Registry includes 4.2 million patients who have received care from Brigham and Women's Hospital and Massachusetts General Hospital (1990–2013). We obtained an initial set of potential aneurysm patients from the Research Patients Data Registry with the use of ICD-9 *(International Classification of Diseases, 9th Revision, Clinical Modification)* and CPT (Current Procedural Terminology) codes, and we then used natural language processing to train a classification algorithm with a sensitivity of 0.78 and specificity of 0.95, which yielded 5589 patients.[5] Seven hundred twenty-seven of these patients were also seen on clinical presentation from 2007 to 2013 with prospectively collected data. In addition, we included 474 additional patients with prospectively collected data who were seen on clinical presentation from 2013 to 2016. We ultimately identified 4701 patients with definite saccular aneurysms after review of the medical records and imaging studies of all patients (A.C., R.D.). We recorded the results of the imaging studies, including intracranial aneurysm site and size and excluded patients with possible infundibula or nondefinitive diagnoses of aneurysms, feeding artery aneurysms associated with arteriovenous malformations, fusiform or dissecting aneurysms, and those lacking clinical notes or radiographic images. Patients who received treatment of their aneurysm(s) before presentation were also excluded from this study, and we categorized patients who presented with an aSAH as harboring a ruptured aneurysm.

Information on patient characteristics, including age, sex, and race, and comorbidities, including hypertension, coronary artery disease, and atrial fibrillation, was obtained. We also noted the number and maximum size of intracranial aneurysms, antihypertensive medication use, family history of aneurysms or family history of SAH, and information on current tobacco and alcohol use. The diagnosis of aSAH was confirmed with a computed tomographic scan, cerebrospinal fluid analysis, or intraoperatively by a neurosurgeon. We also collected detailed data on lipid-lowering agent use at diagnosis (including types and dose), and HDL, LDL, and total cholesterol levels within 30 days and 1 year of diagnosis and included the values closest to the diagnosis date. A risk factor was assumed to be absent if we found no documentation of its presence. We obtained clinical notes by using the following search terms: high cholesterol, hypercholesterolemia, dyslipidemia, statin, statins, altoprev, lovastatin, crestor, rosuvastatin, lescol, fluvastatin, lipitor, atorvastatin, livalo, pitavastatin, pravachol, pravastatin, zocor, simvastatin, colestid, colestipol, prevalite, cholestyramine, welchol, colesevelam, zetia, ezetimibe, vytorin, ezetimibe/simvastatin, fibrates, antara, tricor, fenofibrate, lopid, gemfibrozil, niacin, niaspan, niacor, advicor, lovaza, omtryg, omega-3, omega, vascepa, icosapent, caduet, pralulent, alirocumab, repatha, evolocumab, lomitapide, mipomersen,

Table 1. Patient Characteristics Stratified by Lipid-Lowering Agent Use

Variables	All (n=4701)	Missing	Lipid-Lowering Agent User (n=1129)*	Nonlipid-Lowering Agent User (n=3572)	*P* Value
Female (%)	3666 (78.0)	0	842 (74.6)	2824 (79.1)	<0.01
White race (%)	3738 (79.5)	0	920 (81.5)	2818 (78.9)	0.06
Black race (%)	291 (6.2)	0	53 (4.7)	238 (6.7)	0.02
Hispanic race (%)	270 (5.7)	0	53 (4.7)	217 (6.1)	0.08
Asian race (%)	107 (2.3)	0	80 (7.1)	84 (2.4)	<0.01
Other race (%)	295 (6.3)	0	23 (2.0)	215 (6.0)	<0.01
Age at diagnosis (SD)	55.6 (13.7)	0	63.0 (11.0)	53.2 (13.6)	<0.01
Hypertension (%)	2152 (45.8)	0	724 (64.1)	1428 (40.0)	<0.01
Coronary artery disease (%)	252 (5.4)	0	153 (13.6)	99 (2.8)	<0.01
Myocardial infarction (%)	193 (4.1)	0	101 (8.9)	92 (2.6)	<0.01
Atrial fibrillation (%)	142 (3.0)	0	52 (4.6)	90 (2.5)	<0.01
Size of largest aneurysm (SD)	6.9 (4.8)	92	6.8 (4.6)	6.9 (4.8)	0.31
No. of aneurysms (SD)	1.4 (0.8)	0	1.3 (0.7)	1.4 (0.8)	0.44
Family history of aneurysms (%)	788 (16.8)	0	183 (16.2)	605 (16.9)	0.57
Family history of SAH (%)	456 (9.7)	0	100 (8.9)	356 (10.0)	0.27
Antihypertensive agent use (%)	2240 (47.6)	0	770 (68.2)	1470 (41.2)	<0.01
Current tobacco use (%)	1397 (30.4)	105	298 (26.6)	1099 (31.6)	<0.01
Current alcohol use (%)	2033 (46.7)	347	475 (43.0)	1558 (48.0)	<0.01
HDL (SD)	50.1 (18.3)	3578	50.7 (18.1)	49.8 (18.5)	0.41
LDL (SD)	102.3 (36.6)	4112	92.3 (30.9)	106 (38.0)	<0.01
Total cholesterol (SD)	182.9 (45.3)	3498	176.4 (43.5)	186.0 (45.8)	<0.01

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; and SAH, subarachnoid hemorrhage.

*HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase inhibitors only (n=937); vitamin B3 only (n=8); fibrates only (n=19); 2-azetidinones only (n=21); bile acid sequestrants only (n=8); omega-3 acids only (n=59); HMG-CoA reductase inhibitor combination therapy with vitamin B3 (n=4), fibrates (n=19), 2-azetidinones (n=30), bile acid sequestrants (n=4), omega-3 acids (n=12); 2-azetidinone combination therapy with fibrates (n=1), omega-3 acids (n=1); and combination therapy of ≥3 agents (n=6).

colesevelam, and colestipol. These clinical notes were subsequently manually reviewed.

Differences in baseline characteristics between lipid-lowering agent and nonlipid-lowering agent groups were evaluated using *t* tests for continuous variables and Pearson χ^2 test for categorical variables. As the fasting status was not available for most of the data, a comparison of known fasting versus unknown fasting lipid values within 1 year of diagnosis was performed in patients with known fasting lipid values using a mixed model with subject as the random-effects variable. Univariable and multivariable logistic regression models were implemented to test for effects caused by lipid-lowering agent use, HDL, LDL, and total cholesterol, with a backward elimination procedure to identify significant confounders. Cutoff *P* values of 0.1 were used to select the initial set of variables to be included in the initial multivariable model for backward elimination. The same set of covariates was used in all subsequent multivariable analyses. Adjusted odds ratios (OR) with 95% confidence intervals (CIs) were calculated, and $P<0.05$ was considered significant. To control for differences in baseline characteristics, propensity score weighting was applied. Missing values were accounted for by using multiple imputation with chained equations, and inferential statistics were obtained from 40 imputed data sets. Sensitivity analysis using a subgroup consisting of complete cases only was also performed, including HDL, LDL, and total cholesterol within 30 days and 1 year from diagnosis. All statistical analyses were performed using the Stata statistical software package (version 14; StataCorp, College Station, TX).

Results

Patient demographics and characteristics stratified by lipid-lowering agent use, including HDL, LDL, and total cholesterol are shown in Table 1. A total of 4701 patients with 6411 aneurysms were included, of which 1302 (27.7%) were ruptured and 1129 were taking a lipid-lowering agent at the time of diagnosis (24.0%). In general, patients taking lipid-lowering agents were significantly less frequently female, black, smokers, and alcohol users, while significantly more frequently Asian, diagnosed with hypertension, coronary artery disease, myocardial infarction, atrial fibrillation, and on antihypertensive agents. In addition, patients on lipid-lowering agent therapy were significantly older than nonusers. The median number of days from aneurysm diagnosis to lipid level measurements was not significantly different between unruptured and ruptured aneurysms (median days [interquartile range], unruptured versus ruptured: total cholesterol 38 [2–120] versus 11 [2–83], $P=0.86$; HDL 42 [3–130] versus 17 [4–112], $P=0.91$; LDL 37 [2–125] versus 10 [3–73], $P=0.80$). Comparison of cholesterol and HDL levels with known and unknown fasting status showed no significant difference. There were no direct measurements of LDL with known fasting status. To assess for potential differences in lipid values before and after aneurysmal rupture, we compared lipid levels obtained within 1 year before versus at/after rupture and found no significant differences (before versus at/after rupture, mean±SD: total cholesterol 168±46 versus 163±46, $P=0.25$; HDL 39.0±16.2 versus 38.4±16.0, $P=0.68$; LDL 92.8±38.2 versus 91.8±39.4, $P=0.84$).

Table 2 shows the results of the unweighted and weighted multivariable analyses. In weighted multivariable analysis, younger age (OR, 0.99; 95% CI, 0.98–<1.00), black race

Table 2. Univariable and Multivariable Logistic Regression for Rupture Status in All Patients (n=4701)

	Unweighted Univariable		Unweighted Multivariable		Weighted Multivariable	
Characteristics	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Female	0.64 (0.55–0.74)	<0.01	0.68 (0.58–0.79)	<0.01	0.75 (0.60–0.92)	<0.01
Black race (vs white race)	1.93 (1.51–2.47)	<0.01	1.98 (1.53–2.57)	<0.01	1.79 (1.20–2.67)	<0.01
Hispanic race (vs white race)	1.32 (1.01–1.72)	0.04	1.38 (1.05–1.83)	0.02	1.83 (1.20–2.78)	<0.01
Asian race (vs white race)	1.86 (1.25–2.76)	<0.01	2.04 (1.35–3.07)	<0.01	2.19 (1.27–3.78)	<0.01
Other race (vs white race)	1.32 (1.02–1.71)	0.03	1.48 (1.13–1.93)	<0.01	1.58 (1.15–2.17)	<0.01
Age at diagnosis	0.98 (0.97–0.98)	<0.01	0.99 (0.98–0.99)	<0.01	0.99 (0.98–1.00)	0.01
Hypertension	1.11 (0.98–1.26)	0.10	…	…	…	…
Coronary artery disease	0.70 (0.51–0.95)	0.02	0.88 (0.63–1.22)	0.45	0.93 (0.65–1.33)	0.70
Myocardial infarction	0.86 (0.62–1.20)	0.37	…	…	…	…
Atrial fibrillation	1.02 (0.71–1.49)	0.90	…	…	…	…
Size of largest aneurysm	1.01 (0.99–1.02)	0.36	…	…	…	…
No. of aneurysms	1.02 (0.94–1.11)	0.61	…	…	…	…
Family history of aneurysms	0.60 (0.50–0.73)	<0.01	0.54 (0.45–0.66)	<0.01	0.64 (0.49–0.83)	0.01
Family history of SAH	0.60 (0.47–0.76)	<0.01	…	…	…	…
Antihypertensive agent use	0.89 (0.78–1.01)	0.06	1.07 (0.93–1.23)	0.36	1.01 (0.84–1.21)	0.94
Current tobacco use (vs not current)	1.99 (1.73–2.27)	<0.01	1.86 (1.61–2.14)	<0.01	1.70 (1.40–2.08)	<0.01
Current alcohol use (vs not current)	1.17 (1.09–1.25)	<0.01	1.14 (1.06–1.22)	<0.01	1.21 (1.09–1.33)	<0.01
Lipid-lowering agent use*	0.50 (0.43–0.60)	<0.01	0.56 (0.47–0.68)	<0.01	0.58 (0.47–0.71)	<0.01

Multiple imputation (40 imputations) with chained equations was used for missing data. CI indicates confidence interval; OR, odds ratio; and SAH, subarachnoid hemorrhage.

*HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase inhibitors (statins), vitamin B3 (niacin, nicotinic acid), fibrates, 2-azetidinones, bile acid sequestrants, and omega-3 acids.

Table 3. Multivariable Logistic Regression for Rupture Status With Cholesterol Levels in Complete Cases Only (n=550)

	Unweighted Multivariable		Weighted Multivariable	
Characteristics	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Female	0.95 (0.58–1.58)	0.86	1.33 (0.75–2.37)	0.33
Black race (vs white race)	0.99 (0.40–2.45)	0.98	0.66 (0.19–2.33)	0.52
Hispanic race (vs white race)	1.27 (0.58–2.75)	0.55	2.29 (0.94–5.57)	0.07
Asian race (vs white race)	1.13 (0.36–3.50)	0.84	1.69 (0.43–6.69)	0.45
Other race (vs white race)	2.70 (0.89–8.10)	0.08	1.40 (0.38–5.08)	0.61
Age at diagnosis	0.97 (0.95–0.99)	<0.01	0.97 (0.95–0.99)	<0.01
Coronary artery disease	0.34 (0.10–1.09)	0.07	0.35 (0.10–1.19)	0.09
Family history aneurysms	0.37 (0.17–0.82)	0.01	0.33 (0.11–0.99)	<0.05
Antihypertensive agent use	0.91 (0.57–1.47)	0.70	0.82 (0.46–1.46)	0.50
Current tobacco use (vs not current)	1.45 (0.89–2.38)	0.14	1.58 (0.87–2.84)	0.13
Current alcohol use (vs not current)	1.41 (1.10–1.82)	<0.01	1.56 (1.15–2.10)	<0.01
Lipid-lowering agent use*	0.35 (0.20–0.63)	<0.01	0.41 (0.23–0.73)	<0.01
HDL	0.97 (0.95–0.98)	<0.01	0.95 (0.93–0.98)	<0.01
LDL	1.00 (0.99–1.02)	0.69	1.00 (0.97–1.02)	0.76
Total cholesterol	0.99 (0.97–1.00)	0.06	1.00 (0.97–1.02)	0.80

CI indicates confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and OR, odds ratio.

*HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase inhibitors (statins), vitamin B3 (niacin, nicotinic acid), fibrates, 2-azetidinones, bile acid sequestrants, and omega-3 acids.

(OR, 1.79; 95% CI, 1.20–2.67), Hispanic race (OR, 1.83; 95% CI, 1.20–2.78), Asian race (OR, 2.19; 95% CI, 1.27–3.78), other race (OR, 1.58; 95% CI, 1.15–2.17), current alcohol use (OR, 1.21; 95% CI, 1.09–1.33), and current tobacco use (OR, 1.70; 95% CI, 1.40–2.08) were significantly associated with aSAH. In contrast, female sex (OR, 0.75; 95% CI, 0.60–0.92), family history of aneurysms (OR, 0.64; 95% CI, 0.49–0.83), and lipid-lowering agent use (OR, 0.58; 95% CI, 0.47–0.71) were significantly associated with a lower rupture risk. Lipid-lowering agent use was also significant in the analysis of complete cases only (Table I in the online-only Data Supplement). In a weighted subgroup analysis of cholesterol values in complete cases only, lipid-lowering agent use (OR, 0.41; 95% CI, 0.23–0.73) and HDL (OR, 0.95; 95% CI, 0.93–0.98) were significantly inversely associated with rupture (Table 3). Lipid-lowering agent use and HDL values were also significant in the sensitivity analysis of short-term measurements (within 30 days of diagnosis of aneurysms; Table II in the online-only Data Supplement). Figure 1 shows the proportion of ruptured aneurysms stratified by lipid-lowering agents and doses, and Figure 2 shows a monotonic exposure–response curve between the proportion of ruptured aneurysms and HDL levels.

Discussion

The present case–control study examined the association between aSAH and total cholesterol, LDL, HDL, and the use of lipid-lowering agents. We demonstrated that HDL and the use of lipid-lowering agents are associated with a significantly lower risk of aSAH.

In contrast to the results of a recent systematic review, which showed that elevated total cholesterol was associated with increased risk of SAH in men, we demonstrated no significant association between total cholesterol and SAH risk when controlled for a variety of confounders, including sex, smoking, and alcohol intake.[1] However, previous meta-analyses and reports on the association between total cholesterol levels and risk of aSAH are inconsistent, with studies reporting positive,[6–10] negative,[11–16] or no significant associations.[17–26] Although some authors attribute a positive correlation between increased total cholesterol levels and aSAH to atherosclerotic changes found in aneurysm walls, others explain inverse correlations, caused by weakened endothelium of intracerebral arteries, and altered cell membrane integrity, caused by reduced cholesterol.[11] However, according to Lindbohm et al,[1] the internal quality of previous studies varied considerably with most studies having methodological shortcomings and only 2 with a low risk of bias.

Only 4 previous studies investigated the association between HDL and risk of SAH.[9,10,18,25] Sandvei et al[18] diagnosed aSAH in 122 patients during an 11-year follow-up in a prospective cohort study and found that HDL was inversely associated with the risk of aSAH in a subgroup of patients younger than 50 years of age (hazard ratio per SD increase, 0.6; 95% CI, 0.4–0.9). However, the presence of ruptured aneurysms was not verified in all patients and in some patients SAH occurred many years after baseline measurements. In another prospective cohort study with 331 patients with aSAH, the authors demonstrated no significant association after controlling for lipid-lowering medication use.[9] Leppälä et al[25] investigated

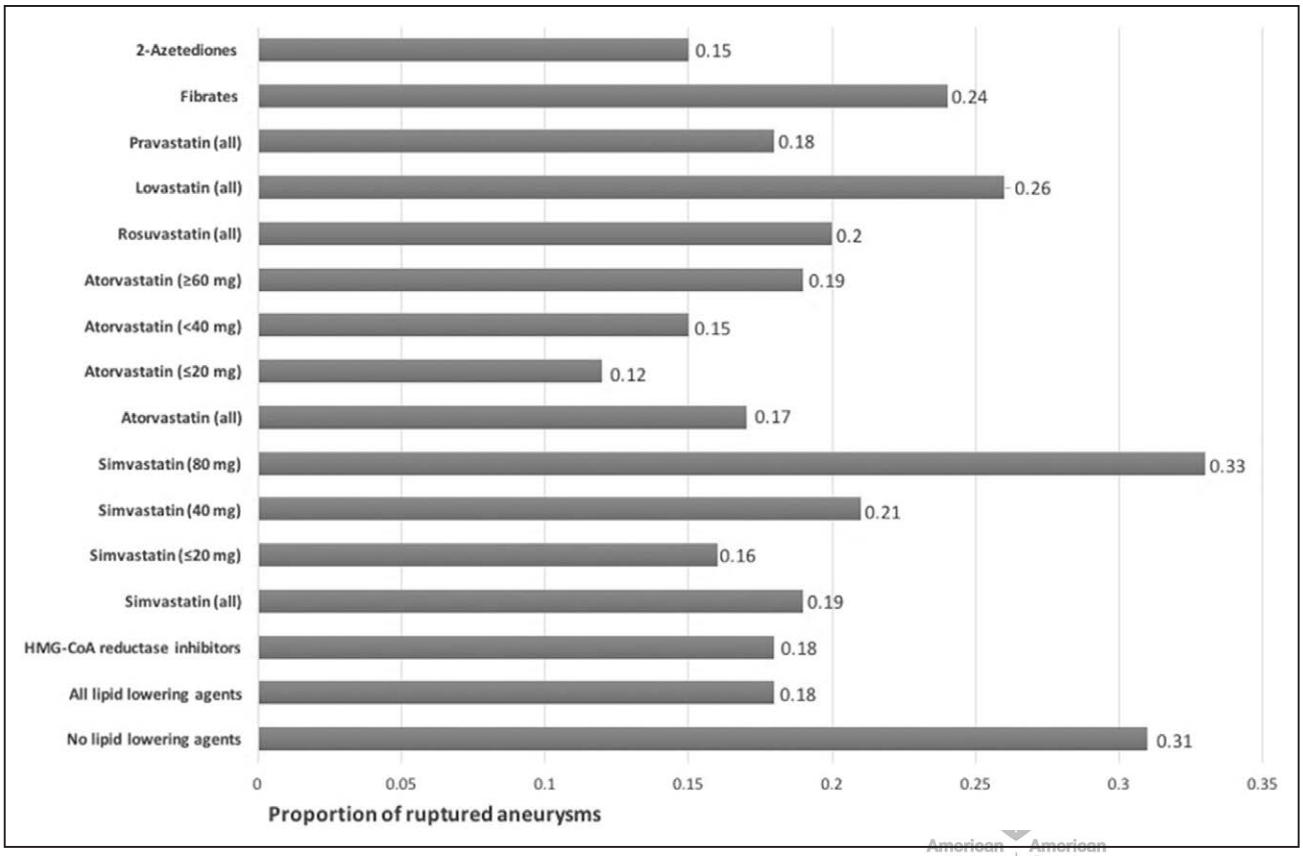

Figure 1. Proportion of ruptured aneurysms stratified according to lipid-lowering agents and dose.

different risk factors for aSAH in a subgroup of male smokers and found that HDL levels ≥0.85 mmol/L were associated with lower aSAH risk. In contrast, in a smaller retrospective case–control study, this association was not confirmed.[10] The inverse association between HDL levels and risk of aSAH is in line with results from previous studies on ischemic heart disease and stroke. HDL, 1 of the 5 major groups of lipoproteins, is thought to play an important role in reverse cholesterol transport, a multi-step process resulting in the net movement of cholesterol from peripheral tissues back to the liver. Moreover, anti-inflammatory, antiapoptotic, antioxidative, and antithrombotic properties have been attributed to HDL activity, demonstrating its beneficial effects in atherosclerosis and other complex conditions.[4,27] Accordingly, Torsney et al[28] recently demonstrated that increasing plasma HDLs inhibit experimental abdominal aortic aneurysm formation. Although increased LDL is a well-known causative risk factor for atherosclerosis and other cardiovascular diseases, it was not significantly associated with an increased risk of aSAH in our study.

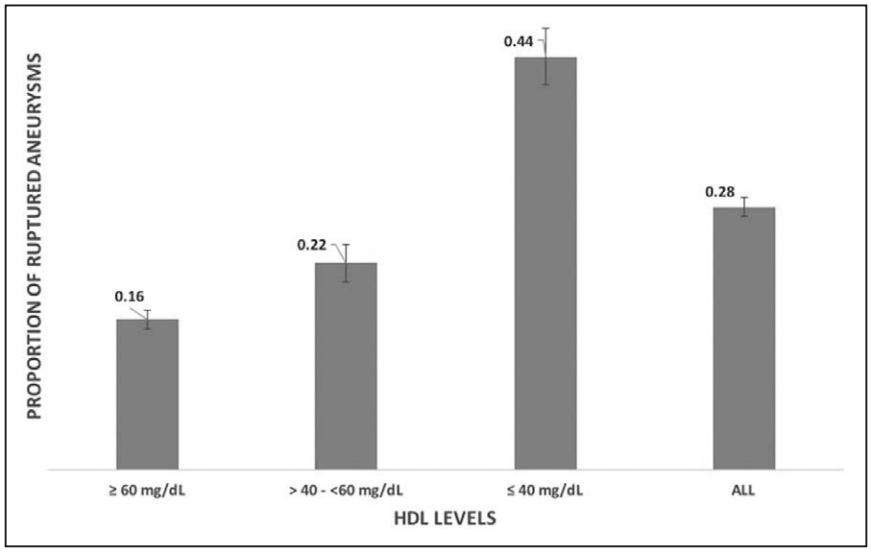

Figure 2. Proportion of ruptured aneurysms stratified by HDL (high-density lipoprotein) levels. Error bars are SEs.

Although there is growing evidence that statin use may reduce the incidence of delayed ischemic neurological deficits after aSAH, the effect on intracranial aneurysm rupture risk remains to be elucidated. In a Dutch population-based case–control study, current use of statins was not significantly associated with reduced risk of SAH.[29] However, statin withdrawal was associated with a significantly increased risk of aSAH (OR, 2.34; 95% CI, 1.35–4.05).[29] In contrast, Yoshimura et al[4] showed a significantly lower rate of statin use in 117 SAH patients compared with 304 controls. In a subsequent retrospective cohort study among 28 931 Medicare patients, Bekelis et al[27] showed that statin use by patients with unruptured cerebral aneurysms was not associated with increased SAH risk during follow-up (OR, 1.03; 95% CI, 0.86–1.23). However, this study was based on an administrative database, and the diagnosis of aneurysm could not be confirmed. The results of our study, the largest case–control study on the effect of lipid-lowering agents on aSAH risk to date, showed a significantly inverse association and is in line with results from various experimental animal models demonstrating that statin use in rodents with intracranial aneurysms was associated with a decreased risk of aneurysm formation, growth, and rupture. Statins may enhance endothelial function and attenuate oxidative stress and inflammation in the vascular wall.[2] In addition, our results are in accordance with recent studies showing that statin use is associated with reduced risk of abdominal aortic aneurysm rupture.[30] Although larger prospective studies and mechanistic studies on lipid-lowering agent use and aSAH risk are needed, including detailed analysis of different lipid-lowering agents, our results support the continuation of therapy in patients with incidentally found aneurysms and suggest that lipid-lowering agents may be a promising candidate for prophylactic treatment of patients not already on lipid-lowering therapy who are diagnosed with unruptured aneurysms.

The major strengths of our study are the high-quality database with confirmed ruptured and unruptured aneurysms, the large sample size, and the detailed records on lipid-lowering agent use and cholesterol levels including LDL levels, which were largely missing in previous reports. The main limitation of our study includes the retrospective design for the majority of patients, the inclusion of only tertiary care centers, and the lack of information on duration of lipid-lowering agent use. Another possible bias in our study could be because of the fact that the use of certain confounders, such as smoking and alcohol use, was based on self-reports. In some cases of aSAH, past medical history was obtained from relatives of patients in poor clinical conditions, which could have led to information bias. However, propensity score weighting was used to control for selection bias. In addition, fasting status was unknown for the vast majority of the lipid levels which may introduce some heterogeneity in the data although we did not find any significant difference in fasting versus unknown fasting lipid levels within subjects. Finally, it is possible that lipid levels may be different before versus at/after rupture of an aneurysm. However, we did not find any significant differences in lipid levels in those 2 time periods.

Summary

We showed that higher HDL values and the use of lipid-lowering agents were significantly inversely associated with intracranial aneurysm rupture. Our results confirm evidence from previous experimental animal studies that statins may prevent aneurysm rupture and pave the way for larger prospective studies and ultimately guidelines for prophylactic treatment of patients with unruptured intracranial aneurysms with lipid-lowering agents.

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Disclosures

None.

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Lipid-Lowering Agents and High HDL (High-Density Lipoprotein) Are Inversely Associated With Intracranial Aneurysm Rupture

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Supplemental Table I: Univariable and multivariable logistic regression for rupture status in complete cases only (N= 4,335).

	Unweighted Multivariable		**Weighted Multivariable**	
Characteristics	**OR (95% CI)**	**P-val.**	**OR (95% CI)**	**P-val.**
Female	0.68 (0.58-0.80)	<0.01	0.77 (0.64-0.92)	<0.01
Black race (vs. white race)	2.03 (1.56-2.65)	<0.01	2.12 (1.56-2.88)	<0.01
Hispanic race (vs. white race)	1.32 (0.98-1.77)	0.07	1.43 (1.03-1.99)	0.03
Asian race (vs. white race)	2·13 (1.39-3.27)	<0.01	2.30 (1.39-3.81)	<0.01
Other race (vs. white race)	1.54 (1.15-2.07)	<0.01	1.56 (1.12-2.19)	<0.01
Age at diagnosis	0.99 (0.99-1.00)	<0.01	0.99 (0.99-1.00)	0.04
Coronary artery disease	0.85 (0.61-1.19)	0.35	0.93 (0.64-1.35)	0.69
Family history of aneurysms	0.60 (0.49-0.73)	<0.01	0.67 (0.53-0.84)	<0.01
Antihypertensive agent use	1.08 (0.93-1.25)	0.31	1.02 (0.86-1.20)	0.85
Current tobacco use (vs. not current)	1.96 (1.69-2.27)	<0.01	1.86 (1.57-2.19)	<0.01
Current alcohol use (vs. not current)	1.17 (1.08-1.26)	<0.01	1.15 (1.06-1.25)	<0.01
Lipid-lowering agent use*	0.55 (0.46-0.67)	<0.01	0.55 (0.45-0.67)	<0.01

* including HMG-CoA reductase inhibitors (statins), vitamin B3 (niacin, nicotinic acid), fibrates, 2-azetidiones, bile acid sequestrants, omega-3 acids.