Published in final edited form as:
Stroke. 2013 November ; 44(11): . doi:10.1161/STROKEAHA.113.001304.

Apolipoprotein E, Statins and Risk of Intracerebral Hemorrhage

Daniel Woo, MD, MS[*], **Ranjan Deka, PhD**[+], **Guido J. Falcone, MD, MPH**[X,φ,Y], **Matthew L. Flaherty, MD**[*], **Mary Haverbusch, RN, BSN**[*], **Sharyl R. Martini, MD, PhD**[*], **Steven M. Greenberg, MD, PhD**[φ], **Alison M. Ayres, BA**[φ], **Laura Sauerbeck, RN, MS**[*], **Brett M. Kissela, MD, MS**[*], **Dawn O. Kleindorfer, MD**[*], **Charles J. Moomaw, PhD**[*], **Christopher D. Anderson, MD**[X,φ,Y], **Joseph P. Broderick, MD**[*], **Jonathan Rosand, MD, MS**[X,φ,Y], **Carl D. Langefeld, PhD**[#], and **Jessica G. Woo, PhD, MHSA**[§]

[*]University of Cincinnati Department of Neurology

[+]University of Cincinnati Department of Environmental Health

[X]Center for Human Genetic Research, Division of Neurocritical Care and Emergency Neurology, Massachusetts General Hospital

[φ]Hemorrhagic Stroke Research Group, Massachusetts General Hospital

[Y]Program in Medical and Population Genetics, Broad Institute

[#]Wake Forest University, Department of Biostatistical Sciences

[§]Cincinnati Children's Hospital Medical Center, Division of Biostatistics and Epidemiology

Abstract

Background and Purpose—*Apolipoprotein E (ApoE)* genotypes have been associated with lobar intracerebral hemorrhage (ICH). Although HMG-CoA reductase inhibitors (statins) have been associated with an increased risk of ICH, meta-analyses have not consistently shown a statin-induced risk of ICH. Here, we test whether hypercholesterolemia and *ApoE* polymorphisms affect the risk with ICH by statin use.

Methods—The Genetic and Environmental Risk Factors for Hemorrhagic Stroke study is a prospective, demographically-matched case-control study of ICH. A similar study of ICH, Genetic Risks for Medication-Related Hemorrhagic Stroke study, was used as a replication cohort. Subjects were classified as normocholesterolemia (NC), hypercholesterolemia without statin (HC-NS), and hypercholesterolemia with statin use (HC-S). Statistical comparisons were performed using Fisher's Exact Test, chi-square tests, and the Breslow-Day test.

Results—The discovery cohort consisted of 558 ICH cases and 1,444 controls, and the replication cohort consisted of 1,020 ICH cases and 382 controls. The association of lower risk for hypercholesterolemia was not attenuated by statin use. Statin use was observed to confer a higher risk for lobar ICH in those carrying *ApoE4/E4* and *ApoE2/E4* genotypes in both discovery and replication cohorts and combined, showed a trend towards significance (p=0.11 for Statin vs. *ApoE4/E4*).

Correspondence: Daniel Woo, M.D., University of Cincinnati, 260 Stetson Street, Suite 2300 Cincinnati, OH 45267. Daniel.woo@uc.edu. Phone: 513 558 5478 Fax: 513 558 4887.

Conclusions—Statin use does not appear to attenuate the association of hypercholesterolemia with decreased risk for non-lobar ICH. Our data support a gene-by-drug effect for lobar ICH, but larger sample sizes are needed to confirm the association before any clinical change is warranted.

Search Terms

Intracerebral hemorrhage [7]; Apolipoprotein E; Hypercholesterolemia; Statins; Case control studies [53]; Risk factors in epidemiology [59]

Introduction

Hemorrhagic stroke occurs in ~100,000 persons in the U.S. each year, of which 40%–50% die within 30 days[1, 2]. In intracerebral hemorrhage (ICH), half of the mortality occurs in the first two days after stroke, and at present there are no proven effective treatments. Thus, prevention is of paramount importance to reducing health care burden related to ICH.

Hypercholesterolemia has been consistently reported to have an inverse relationship with the risk of hemorrhagic stroke[3–9]. However, the relationship between high cholesterol, medications used to lower cholesterol, and risk of ICH is complex. HMG Co-A reductase inhibitors (statins) are commonly used treatments to lower cholesterol levels to prevent ischemic heart disease and stroke. A randomized placebo-controlled trial, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, found a higher risk of hemorrhagic stroke among subjects who had previously had ischemic stroke and were treated with a high-dose statin medication, atorvastatin, compared with placebo (OR 1.68; 95% CI 1.09–2.59),[10] although the absolute number of hemorrhagic events was small and did not correlate with LDL levels. However, in a recent large meta-analysis of statin use and risk of ICH, McKinney et al. did not find this risk. The authors evaluated 31 randomized controlled trials in which active treatment with statins was compared with placebo or low-dose statin use[11]. This meta-analysis, which included 91,588 subjects in the active treatment group and 91,215 subjects in the comparison group, found no significant difference in the rate of ICH (OR 1.08; 95% CI, 0.88–1.32; p=0.47).

Although the McKinney meta-analysis result suggests that statin use is not associated with ICH in a general population, the SPARCL data suggest that among stroke patients the use of statins may pose a risk of ICH. In a decision analysis that used SPARCL's estimates of ICH risk with statin use, Westover et al. reported that statin use should be avoided in ICH patients, given the increased risk of ICH recurrence, high morbidity, and mortality associated with recurrent ICH[12]. The major pathophysiologic mechanism of lobar ICH is cerebral amyloid angiopathy, and apolipoprotein E alleles ε-2 and ε-4 (*Apo E2* and *Apo E4*) have been consistently associated with a higher risk of lobar ICH compared with the more common E3 allele[13].

We hypothesize that one explanation for the disparate reports in the literature could be an *ApoE*/statin or *ApoE*/hypercholesterolemia interaction. If statin use is associated with increased risk of ICH specifically in the presence of *ApoE2* or *ApoE4* alleles, then the relative proportion of these genotypes in a cohort could influence whether the risk was identified. We sought to determine whether a history of hypercholesterolemia alone influenced the risk of Apolipoprotein E alleles on risk of lobar ICH. We also sought to determine whether statin users who carry *ApoE2* or *ApoE4* alleles had a higher risk of ICH compared with statin users with *ApoE3/E3* (wild type) genotype among lobar and non-lobar ICH patients and whether statin use attenuated the association with decreased risk observed in non-lobar ICH for HC.

METHODS

Study Design

The discovery cohort is from the Genetic and Environmental Risk Factors for Hemorrhagic Stroke (GERFHS) study, a case-control study of hemorrhagic stroke that uses prospective, population-based case ascertainment with recruitment within a 50-mile radius of the University of Cincinnati[13]. Cases and controls from the multi-center Genetic Risks for Medication-Related Hemorrhagic Stroke study of ICH (GOCHA)[14] were used as a replication cohort.

Setting

The methods of the two studies have been previously described[13,14, 15]. ICH is defined as the non-traumatic abrupt onset of severe headache, altered level of consciousness, and/or focal neurologic deficit associated with a focal collection of blood within the brain parenchyma as observed on neuroimaging, or at autopsy (adapted from Classification of Cerebrovascular Disease III–1989)[13]. Data were abstracted from medical charts of all individuals with apparent hemorrhagic stroke. Case status was verified by study physicians.

Standard Protocol Approvals and Patient Consents

The Institutional Review Board for each hospital system approved the studies. A Certificate of Confidentiality was obtained from the Department of Health and Human Services. Informed consent was obtained for all subjects who underwent interview and genetic analysis.

Participants

GERFHS cases were eligible for the study if they were 18 years of age and resided within a 50-mile radius of the University of Cincinnati. Hemorrhages associated with trauma, brain tumor, encephalitis, endarterectomy, hemorrhagic cerebral infarction, or thrombolytic treatment of ischemic stroke did not meet study criteria. Patients with ICH associated with anticoagulation, primary intraventricular hemorrhage, or prior history of ischemic stroke were included. Study neurologists reviewed clinical and neuroimaging information for each patient and made the final decision about case eligibility. Controls for the GERFHS study were identified by random digit dialing to match cases by age (±5 years), race, and gender. For the current analysis, we disregarded the original matching in order to conduct stratified analysis by cholesterol and genotype status. All analyses included adjustments for age, race, gender, and significantly associated risk factors.

The GOCHA Study is a case-control study of both non-warfarin- and warfarin-related intracerebral hemorrhage (ICH). Enrolled cases included acute ICH subjects aged >55 years presenting to the Massachusetts General Hospital. Exclusion criteria included trauma, brain tumor, hemorrhagic transformation of an ischemic stroke, vascular malformation, or any other perceived cause of secondary ICH. Controls were enrolled from the same population that gave rise to the cases and included individuals aged >55 years attending ambulatory clinics.

Variables

Medical records were abstracted on standardized forms. Each hemorrhage was classified as lobar (involving predominantly the cortex and underlying white matter of the cerebral hemisphere), deep (involving predominately the basal ganglia, periventricular white matter, thalamus, or internal capsule), cerebellar, or brainstem by a study neurologist. When

categorization was unclear, the film was adjudicated by a group of study neurologists for consensus.

Each consented case (or proxy) and control was interviewed face-to-face in a highly structured, identical manner[13]. Race/ethnicity and risk-factor variables were determined by self-report. We used self-reported history of hypertension and hypercholesterolemia rather than measurements from the acute setting because blood pressure may increase in the acute setting and fasting status was not uniformly available. We also recorded medication use by the cases (prior to ICH onset) and controls. Statin use was determined through self-report of medications that included any of the following: atorvastatin, cerivastatin (discontinued in 2001), fluvastatin, lovastatin, pravastatin, rosuvastatin, or simvastatin; or combination medications that include a statin (amlodipine/atorvastatin, ezetimibe/simvastatin). Subjects were classified as normocholesterolemia (NC), hypercholesterolemia treated with statins (HC-S), or hypercholesterolemia not treated with statins (HC-NS). HC-NS subjects included those treated with non-statin lipid-lowering medications (i.e., cholestyramine, colesevelam, colestipol, ezetimibe, fenofibrate, gemfibrozil, niacin), as well as those not treated with any medications for hypercholesterolemia. For *ApoE* genotyping, four buccal brush samples or whole blood were obtained from each case and control at the time of interview in GERFHS and from blood samples in GOCHA. *ApoE* genotype was determined by a polymerase chain reaction (PCR)-based method to determine genotype at SNPs rs429358 and rs7412[13,16] The allelic reads from the 2 assays were then translated to *ApoE* genotypes (e3e3, e3e4, e4e4, e3e2, e2e2, and e2e4). All genotyping personnel were blinded to clinical and neuroimaging data.

Statistical Analysis

All analyses were conducted separately for lobar and non-lobar groups using SAS v.9.3 (SAS Institute, Cary, NC). Demographic characteristics are reported as mean ± SD or n (%), and comparisons between cases and controls are based on unpaired t-tests, chi-squared tests, or Fisher's Exact Test, as appropriate. To examine the role of the rarer *E2* and *E4* alleles, genotypic groups were classified two different ways for analysis: *ApoE2* carriers (*E2/E2*, *E2/E3*, *E2/E4*) vs. *E3/E3*; and E4 carriers (*E2/E4*, *E3/E4*, *E4/E4*) vs. *E3/E3*. Associations between case status and *ApoE2* or *ApoE4* alleles were tested via chi-square and Fisher's Exact analysis of 2x2 contingency tables (case/control status vs. presence/absence of allele). Homogeneity of odds ratios across clinical strata (e.g., HC vs. NC, HC-NS vs. HC-S) was tested using the Breslow-Day test. Logistic regression was used to adjust for clinical variables that differed between cases and controls such as differential genotype by race and history of hypertension.

Results

After removing cases and controls with missing *ApoE* results, the discovery cohort included 558 cases of spontaneous ICH (354 non-lobar, 204 lobar), who were compared with 1444 controls (946 matched to non-lobar ICH and 508 to lobar ICH). In the replication cohort, 1,020 cases (539 non-lobar, 481 lobar) were compared with 382 controls. Table 1 presents the demographic characteristics of the case-control cohorts. *ApoE2 and E4* containing genotypes were associated with risk of ICH in lobar regions but not non-lobar ICH for both the discovery and replication cohort.

Hypercholesterolemia had been previously reported to be associated with a decreased risk of non-lobar ICH. We evaluated whether statin use attenuated the decreased risk of non-lobar ICH with hypercholesterolemia in Table 2. Compared with NC in both the discovery and replication cohorts, history of HC was associated with decreased risk of lobar ICH, and this

protective association was not attenuated by statin use in either the discovery or replication cohorts.

We next evaluated whether HC status itself (with or without statin use) modified the increased risk of lobar ICH associated with *ApoE* alleles (Table 3). In the discovery sample, *ApoE2* carriers exhibited an increased risk of lobar ICH among those with NC (OR=2.06; 95% CI 1.21–3.51), which increased with HC (OR=3.93, 95% CI 2.04–7.55). However, a formal test for interaction did not reach statistical significance (p=0.13), and the finding of differential risk by cholesterol status was not observed in the replication cohort. When evaluating *ApoE4* alleles, carriers had a similar risk of lobar ICH with and without a history of HC. Thus, a history of HC did not appear to modify the association of either *ApoE2 or ApoE4* with lobar ICH.

Finally, we separately evaluated the risk of lobar ICH for specific ApoE genotypes among statin users (HC-S), and the HC-NS and NC groups using *Apo E3/E3* as the referent genotype. Statin users with *Apo E4/E4* had a significant risk of lobar ICH (OR=4.5; 95%CI 1.3–16.0; p=0.02), whereas the risk was non-significant for the *Apo E4/E4* genotype among the NC (OR=1.9; 0.53–6.7; p=0.30) and HC-NS (OR=1.6; 95% CI 0.27–9.4; p=0.63) groups. In the replication cohort, ApoE4*/E4* statin users also had a much higher odds ratio (OR=12; 95% CI 2.5–54; p<0.0001) than the NC (OR=4.9; 95% CI 1.1–22; p=0.04) and HC-NS (OR=3.8; 95% CI 0.2–90; p=0.82) groups. Similarly, the *Apo E2/E4* HC-S group had a higher risk for lobar ICH (OR=11.3; 95% CI 2.0–64; p=0.005) than the NC group (OR=2.0; 95%CI 0.8–5.2; p=0.18). This was also found to be true in the replication sample: HC-S (OR=7.4; 95% CI 1.5–3.7; p=0.008), compared with NC (OR = 3.7; 95%CI 1.3–11; p=0.01). *Apo E2/E4* was not significantly associated with lobar ICH for the HC-NS group in neither the discovery nor replication cohort. When performing a formal test for interaction between statin use and genotype combining the discovery and replication cohorts, a trend was observed for ApoE2/E4 (p=0.09 across all groups) and for ApoE4/E4 (p=0.11). As expected given that Apo E alleles have not been associated with non-lobar ICH, similar analysis of non-lobar ICH revealed no evidence of statin use/ApoE interaction modifying the risk (data not shown).

Discussion

We report several novel observations with respect to our understanding of the association of hypercholesterolemia and ICH. For non-lobar ICH, statin use does not appear to diminish the protective association of hypercholesterolemia. If statin use can be presumed to lower cholesterol level, this would suggest that the actual cholesterol level may not be relevant to the protective association of a history of hypercholesterolemia for non-lobar ICH which is the predominant form of ICH. This would be consistent with the prior large meta-analyses that did not show an increased risk of ICH with statin use or cholesterol level.

However for the less common lobar ICH, we found evidence in both the discovery and replication samples of a signal towards a higher risk of lobar ICH with statin use for specific genotypes. Despite the large sample size that our study began with, once limited by location and specific ApoE genotypes, and by stratification by cholesterol status and treatment with statins, the ability to confirm the finding by direct interaction was limited. This preliminary finding should not warrant a change in management but may warrant further evaluation in future studies.

For over three decades, data from around the world have consistently demonstrated an association with lower risk of ICH among those with hypercholesterolemia[3–9]. *ApoE2* and *E4* are both associated with lobar ICH but apparently by different mechanisms. *ApoE2* is

associated with lobar blood vessel rupture, whereas *ApoE4* appears to be associated with cerebral amyloid angiopathy[17, 18]. *ApoE4* is a well-established risk factor for cardiovascular disease as well as Alzheimer's disease, while *ApoE2* has been associated with a decreased risk of these conditions[19–23]. The association of statin use with an increased risk of lobar ICH in subjects with *ApoE2* and *E4* alleles suggests that lowering of serum lipid levels may be related to the development or progression of amyloid angiopathy and lobar ICH. Interestingly, the drug bexarotene has been associated with amyloid removal in mouse models of Alzheimer's Disease[24]. Bexarotene is associated with increasing hyperlipidemia, and it is thought that bexarotene stimulates expression of *ApoE*, which leads to intracellular clearance of beta-amyloid[24]. By contrast, in predominantly hypertensive non-lobar ICH in which amyloid angiopathy plays little if any role, the protective association between hypercholesterolemia and non-lobar ICH appears to be unaffected by statin agents that lower serum cholesterol. The mechanism by which hyperlipidemia reduces the risk of rupture of the small penetrating arteries and arterioles in the deep brain and brainstem remains unknown.

Our study has several limitations. Fasting lipid levels were not available on controls, and cases did not have uniform collection of lipid levels; thus fasting state could not be determined. Exposure to hypercholesterolemia may lead to the effects observed irrespective of cholesterol level at the time of entry into the study. Future studies that include fasting lipid profiles may help to clarify the relationship. A small number of cases were dropped for lack of ApoE genotype available (5 lobar ICH, 8 non-lobar ICH and a total of 96 controls). Although we have no reason to suspect biased loss of sample by a specific genotype, it is possible that a missing data bias could have occurred in the discovery sample, but it should not have affected the replication sample in a similarly biased fashion. A further limitation is that although the current study represents one of the largest studies of *ApoE*, lobar ICH, and hypercholesterolemia/statin use, the number of individuals for several of the specific *ApoE* genotypes is small. Larger studies are required to confirm this preliminary finding where all *ApoE* containing genotypes have sufficient sample to determine an allele specific effect.

If confirmed, this finding may represent a rationale for genetic testing in lobar ICH patients for those currently on or considered for statin therapy. The finding may have further interest for Alzheimer's disease and cardiovascular disease where statin use and hypercholesterolemia and *Apo E* alleles may also affect risk.

In summary, risk of lobar ICH with statin use may be affected by *ApoE* genotype and may be greater in those with the uncommon to rare *E2/E4* or *E4/E4* genotypes. The association of hypercholesterolemia with a decreased risk of non-lobar ICH does not appear to be attenuated by use of statins.

Acknowledgments

Statistical analysis was conducted by Jessica Woo, PhD at Cincinnati Children's Hospital, Cincinnati, OH. All authors have read and approved the submitted manuscript; the manuscript has not been submitted elsewhere nor published elsewhere in whole or in part.

Sources of Funding

This study was supported by grants from the National Institute of Neurological Diseases and Stroke (R-01-NS 36695), and National Institute of Environmental Health (R-01- ES 06096).

The Genetics of Cerebral Hemorrhage with Anticoagulation study was funded by NIH-NINDS grant R01NS059727, the Keane Stroke Genetics Research Fund, the Edward and Maybeth Sonn Research Fund, by the University of Michigan General Clinical Research Center (M01 RR000042), and by a grant from the National Center for Research Resources.

Dr. Falcone was supported by the NIH-NINDS SPOTRIAS fellowship grant P50NS061343.

Dr. Anderson was supported by a Clinical Research Training Fellowship from the American Brain Foundation.

Disclosures

O. Adeoye, D. Kleindorfer: Genentech, Speaker's Bureau, <$10K/yr

Matthew Flaherty: CSL Behring, Advisory Board / Consultant, <$10K/yr

S. Greenberg: research Grant NIH; Honoraria: Medtronic, Pfizer, Consultant; advisory board Hoffman-La Roche, Janssen Alzheimer Immunotherapy, Bristol-Myers Squibb Company

C. Anderson: research grant from the American Brain Foundation

Jonathan Rosand: research Grant NIH and American Heart Association; editorial board member of *Stroke* and *Lancet Neurology*.

D. Woo: Research Grant NIH. Editorial board member of *Stroke* and Associate Editor of *Stroke Research and Treatment*.

References

1. Kissela B, Schneider A, Kleindorfer D, Khoury J, Miller R, Alwell K, et al. Stroke in a biracial population: The excess burden of stroke among blacks. Stroke; a journal of cerebral circulation. 2004; 35:426–431.
2. Taylor CL, Yuan Z, Selman WR, Ratcheson RA, Rimm AA. Mortality rates, hospital length of stay, and the cost of treating subarachnoid hemorrhage in older patients: Institutional and geographical differences. Journal of neurosurgery. 1997; 86:583–588. [PubMed: 9120619]
3. Konishi M, Ozawa H, Iida M, Simamoto T, Ueshima H. Epidemiological studies of cerebro- and cardiovascular diseases in the northeast of japan part i. Pathological approach to the study in akita prefecture. Japanese circulation journal. 1976; 40:723–728. [PubMed: 966361]
4. Ueda K, Hasuo Y, Kiyohara Y, Wada J, Kawano H, Kato I, et al. Intracerebral hemorrhage in a japanese community, hisayama: Incidence, changing pattern during long-term follow-up, and related factors. Stroke; a journal of cerebral circulation. 1988; 19:48–52.
5. Yano K, Reed DM, MacLean CJ. Serum cholesterol and hemorrhagic stroke in the honolulu heart program. Stroke; a journal of cerebral circulation. 1989; 20:1460–1465.
6. Jacobs DR. The relationship between cholesterol and stroke. Health reports / Statistics Canada, Canadian Centre for Health Information = Rapports sur la sante / Statistique Canada, Centre canadien d'information sur la sante. 1994; 6:87–93.
7. Thrift A, McNeil J, Donnan G. Reduced frequency of high cholesterol levels among patients with intracerebral haemorrhage. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2002; 9:376–380. [PubMed: 12217665]
8. Woo D, Kissela BM, Khoury JC, Sauerbeck LR, Haverbusch MA, Szaflarski JP, et al. Hypercholesterolemia, hmg-coa reductase inhibitors, and risk of intracerebral hemorrhage: A case-control study. Stroke; a journal of cerebral circulation. 2004; 35:1360–1364.
9. Martini SR, Flaherty ML, Brown WM, Haverbusch M, Comeau ME, Sauerbeck LR. Risk factors for intracerebral hemorrhage differ according to hemorrhage location. Neurology. 2012; 79:2275–2282. [PubMed: 23175721]
10. Goldstein LB, Amarenco P, Szarek M, Callahan A 3rd, Hennerici M, Sillesen H. Hemorrhagic stroke in the stroke prevention by aggressive reduction in cholesterol levels study. Neurology. 2008; 70:2364–2370. [PubMed: 18077795]
11. McKinney JS, Kostis WJ. Statin therapy and the risk of intracerebral hemorrhage: A meta-analysis of 31 randomized controlled trials. Stroke; a journal of cerebral circulation. 2012; 43:2149–2156.
12. Westover MB, Bianchi MT, Eckman MH, Greenberg SM. Statin use following intracerebral hemorrhage: A decision analysis. Archives of neurology. 2011; 68:573–579. [PubMed: 21220650]

13. Woo D, Sauerbeck LR, Kissela BM, Khoury JC, Szaflarski JP, Gebel J, et al. Genetic and environmental risk factors for intracerebral hemorrhage: Preliminary results of a population-based study. Stroke; a journal of cerebral circulation. 2002; 33:1190–1196. discussion 1190-1196.

14. Group GfCHoAGC. Exploiting common genetic variation to make anticoagulation safer. Stroke; a journal of cerebral circulation. 2009; 40:S64–S66.

15. Flaherty ML, Woo D, Haverbusch M, Sekar P, Khoury J, Sauerbeck L, et al. Racial variations in location and risk of intracerebral hemorrhage. Stroke. 2005; 36:934–937. [PubMed: 15790947]

16. Rebeck GW, Reiter JS, Strickland DK, Hyman BT. Apolipoprotein e in sporadic alzheimer's disease: Allelic variation and receptor interactions. Neuron. 1993; 11:575–580. [PubMed: 8398148]

17. Greenberg SM, Rebeck GW, Vonsattel JP, Gomez-Isla T, Hyman BT. Apolipoprotein e epsilon 4 and cerebral hemorrhage associated with amyloid angiopathy [see comments]. Annals of Neurology. 1995; 38:254–259. [PubMed: 7654074]

18. McCarron M, Nicoll J. High frequency of apolipoprotein e e2 allele is specific for patients with cerebral amyloid angiopathy-related haemorrhage. Neuroscience letters. 1998; 247:45–48. [PubMed: 9637406]

19. Corder E, Saunders A, Risch N, Strittmatter WJ, Schmechel DE, Gaskell PC Jr, et al. Protective effect of apolipoprotein e type 2 allele for late onset alzheimer's disease. Nature genetics. 1994; 7:180–184. [PubMed: 7920638]

20. Saunders AMSW, Schmechel D, George-Hyslop PH, Pericak-Vance MA, Joo SH, Rosi BL, et al. Association of apolipoprotein e allele epsilon 4 with late-onset familial and sporadic alzheimer's disease. Neurology. 1993; 43:1467–1472. [PubMed: 8350998]

21. Hixson JE. Apolipoprotein e polymorphisms affect atherosclerosis in young males. Pathobiological determinants of atherosclerosis in youth (pday) research group. Arteriosclerosis and thrombosis : a journal of vascular biology / American Heart Association. 1991; 11:1237–1244. [PubMed: 1680392]

22. Sheehan D, Bennett T, Cashman K. Apolipoprotein e gene polymorphisms and serum cholesterol in healthy irish adults: A proposed genetic marker for coronary artery disease risk. Irish journal of medical science. 2000; 169:50–54. [PubMed: 10846860]

23. Hill JS, Hayden MR, Frohlich J, Pritchard PH. Genetic and environmental factors affecting the incidence of coronary artery disease in heterozygous familial hypercholesterolemia. Arteriosclerosis and thrombosis : a journal of vascular biology / American Heart Association. 1991; 11:290–297. [PubMed: 1998646]

24. Strittmatter WJ. Medicine. Old drug, new hope for alzheimer's disease. Science. 2012; 335:1447–1448. [PubMed: 22442467]

Table 1

Demographics

	Discovery Sample						Replication Sample				
	Lobar ICH			Non-Lobar ICH							
	Cases	Controls	p	Cases	Controls	p	Lobar ICH	Non-Lobar ICH	Controls	P vs. Lobar	P vs. non-Lobar
N	204	508		354	936		481	539	382		
Age (years ± SD)	66.4 ± 16.2	63.1 ± 15.6	0.01	64.7 ± 15.1	61.3 ± 14.0	0.0001	74.7 ± 10.5	70.9 ± 12.6	74.2 ± 7.8	0.43	<0.0001
Male Sex (n, %)	91 (45%)	216 (43%)	0.61	188 (53%)	468 (50%)	0.32	240 (50%)	308 (57%)	211 (55%)	0.12	0.57
Black Race (n, %)	30 (15%)	73 (14%)	0.91	82 (23%)	227 (24%)	0.68					
Hypertension (n, %)	111 (55%)	267 (53%)	0.61	262 (75%)	467 (50%)	<0.0001	308 (64%)	454 (84%)	263 (69%)	0.14	<0.0001
Hypercholesterolemia (n, %)	85 (42%)	223 (44%)	0.59	114 (32%)	400 (43%)	0.0006	152 (32%)	190 (35%)	226 (59%)	<0.0001	<0.0001
Frequent alcohol use (n, %)	14 (7%)	31 (6%)	0.68	24 (7%)	55 (6%)	0.50	12 (3%)	29 (7%)	9 (2%)	0.66	0.004
Prior ischemic stroke (n, %)	16 (8%)	6 (1%)	<0.0001	39 (11%)	24 (3%)	<0.0001	64 (13%)	66 (12%)	33 (9%)	0.03	0.08
Apo E genotype (n, %) E2/E2 E2/E3 E2/E4 E3/E3 E3/E4 E4/E4	2 (1%) 42 (21%) 17 (8%) 85 (42%) 46 (23%) 12 (6%)	6 (1%) 59 (12%) 15 (3%) 297 (59%) 114 (22%) 17 (3%)	<0.0001	8 (2%) 49 (14%) 10 (3%) 195 (55%) 82 (23%) 10 (3%)	12 (1%) 131 (14%) 22 (2%) 550 (59%) 195 (21%) 26 (3%)	0.69	9 (2%) 69 (14%) 32 (7%) 237 (49%) 106 (22%) 28 (6%)	2 (<1%) 56 (10%) 11 (2%) 346 (64%) 110 (20%) 14 (3%)	1 (<1%) 41 (11%) 6 (2%) 251 (66%) 79 (21%) 4 (1%)	<0.0001	0.67

Table 2

Risk of non-lobar ICH among subjects with hypercholesterolemia, stratified by statin use

	Discovery Sample					Replication Sample				
	Cases	**Control**	**Unadjusted OR**	**Adjusted OR[a]**	**p**	**Cases**	**Control**	**Unadjusted OR**	**Adjusted OR[a]**	**p**
Hypercholesterolemia	114 (32%)	400 (43%)	0.64 [0.49–0.82]	0.48 [0.36–0.63]	<0.0001	190 (35%)	226 (59%)	0.38 [0.29–0.49]	0.31 [0.23–0.42]	<0.0001
-Hypercholesterolemia without statin use	52 (15%)	201 (21%)	0.63 [0.45–0.88]	0.57 [0.40–0.80]	0.0013	31 (8%)	28 (15%)	0.49 [0.29–0.85]	0.40 [0.22–0.72]	0.003
-Hypercholesterolemia with statin use	62 (18%)	199 (21%)	0.79 [0.57–1.08]	0.59 [0.42–0.82]	0.0017	159 (31%)	198 (56%)	0.36 [0.27–0.48]	0.30 [0.22–0.41]	<0.0001

[a]Non-lobar ICH OR adjusted for age, sex, race, first degree relative with ICH and hypertension status

Table 3

Risk of Lobar ICH by Apo E carrier status and Hypercholesterolemia vs. No Hypercholesterolemia

	Discovery Sample				Replication Sample			
ApoE2* carriers vs. *E3/E3	**Case**	**Control**	**OR (CI)**	**p**	**Case**	**Control**	**OR (CI)**	**p**
-Normocholesterolemia	33 (39%)	53 (24%)	2.06 (1.21, 3.51)	0.01	86 (36%)	20 (17%)	2.87 (1.65, 4.97)	0.0002
-Hypercholesterolemia	28 (46%)	27 (18%)	3.93 (2.04, 7.55)	<0.0001	24 (22%)	28 (16%)	1.69 (0.91, 3.32)	0.09
ApoE4 carriers vs. *E3/E3*								
-Normocholesterolemia	42 (45%)	73 (30%)	1.90 (1.17, 3.11)	0.01	112 (42%)	40 (29%)	1.82 (1.17, 2.83)	0.008
-Hypercholesterolemia	33 (50%)	73 (37%)	1.71 (0.98, 3.00)	0.08	54 (39%)	49 (25%)	2.00 (1.25, 3.21)	0.004