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Use of Statins and Outcomes in Intracerebral Hemorrhage Patients

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Abstract

Background and Purpose—Statins use may be associated with improved outcome in ICH patients. However, the topic remains controversial. Our analysis examined the effect of prior, continued or new statin use on ICH outcomes utilizing the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) dataset.

Methods—We analyzed ERICH (A multicenter study designed to examine ethnic variations in the risk, presentation, and outcomes of ICH) to explore the association of statin use and hematoma growth, mortality, and 3-month disability. We computed subset analyses with respect to three statin categories (prior, continued or new use).

Results—2457 enrolled cases (mean age 62, 42% females) had complete data on mortality and 3-month disability (modified Rankin scale). Among those, 1093 were on statins (prior, n=268; continued, n=423; new, n=402). Overall, statin use was associated with reduced mortality and disability without any effect on hematoma growth. This association was primarily driven by

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continued/new statin use. A multivariate analysis adjusted for age and major predictors for poor outcome, showed continued/new statins users had good outcomes over prior users. However, statins may have been continued/started more frequently among less severe patients. When a propensity score was developed based on factors that could influence a physician's decision in prescribing statins and used as a covariate, continued/new statin use was no longer a significant predictor of good outcome.

Conclusions—Although statin use, especially continued/new use, was associated with improved ICH outcomes, this effect may merely reflect the physician's view of a patient's prognosis rather than a "predictor" of survival.

Keywords

Intracerebral Hemorrhage; Hydroxymethylglutaryl-CoA Reductase Inhibitors; mortality; outcome

Intracerebral hemorrhage (ICH), the second most common subtype of stroke, comprises 10%–15% of all stroke cases.[1] It is a devastating disease, with 30-day mortality over 40%.[2] Despite extensive research and allocation of resources, treatment options are limited, typically involving supportive care and control of hypertension. Many neuroprotective agents have failed to find a proven benefit.[3]

Hypocholesterolemia has been associated with increased incidence of ICH, and it has also been associated with hematoma expansion after ICH.[4–10] Hydroxymethylglutaryl-CoA reductase inhibitors (statins) are the class of medications most often used for lowering cholesterol. Current cholesterol management guidelines favor aggressive statin therapy in patients with cardiovascular risk factors.[11] The impact of these guidelines may result in the aggressive use of high-dose statins in the elderly population in coming years, although there may be a modest risk of increased incidence of hemorrhagic strokes after statin use.[12, 13]

The role of statins as a neuroprotective agent has become an area of increasing interest, especially in the setting of a disease with limited treatment options such as ICH. Animal models have supported the use of statins in patients with ICH.[14–18] The potential beneficial pleiotropic effects of statins include endothelial stabilization, antithrombotic properties, anti-inflammatory actions, and up regulation of endothelial nitric oxide synthase.[19]

However, there have been conflicting results regarding ICH outcomes after statin use (Online Supplementary Table I). Limitations of prior studies include: small sample sizes, single center data, retrospective design, and lack of post discharge outcomes. Some studies lack a clear definition of statin use, or they do not account for statin discontinuation. Some rely on unadjusted analyses or multivariate models that are not adjusted for confounding factors such as inability to swallow statins, withdrawal of care, or the treating physician's view of patient's long term prognosis.

Jung et al. performed a recent meta-analysis of sixteen studies that examined the effect of statin use and ICH outcomes. Prior statin use was associated with decreased risk of mortality at three months following symptom onset, as well as an increased probability of good functional outcomes, compared with those who were not on statins before ICH. The authors

acknowledged several limitations, including substantial study-to-study design variations, leading to unresolved heterogeneity, and inability to adjust variables determining ICH outcomes, such as initial injury severity, withdrawal of care, lipid parameters, volume and location of hematoma, and use of antithrombotic medications.[20]

The Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study was a multi-center, prospective recruitment, multi-ethnic study of ICH.[21] Utilizing the ERICH dataset, we explored the association of statin use with ICH outcomes, including ICH mortality and 3-month disability, as well as initial hematoma volume and subsequent expansion. Given the association of hypocholesterolemia with increased risk of ICH, we hypothesized that ICH patients who were on statins would have larger admission hematoma volume, increased risk of hematoma expansion, and higher 3-month mortality and morbidity.

Materials and Methods

Data Source

ERICH was a multicenter prospective study, with a goal of identifying differences in risk factor distribution, neuroimaging parameters, and outcomes of ICH by race/ethnicity. Cases were identified by hot-pursuit and enrolled using standard phenotype and risk factor information. Each case underwent neuroimaging and provided a blood sample.

Patient Population

For the current analysis, we included ICH patients whose 3-month vital status was known and who had data on initial hematoma volume. Functional outcome at 3 months was assessed using modified Rankin Scale (mRS). Baseline data included: statin use, age, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, or Hispanic), prior history of ischemic stroke, Apolipoprotein E (APOE) genotype, coronary artery disease (CAD), diabetes mellitus, dementia or Alzheimer disease, hypertension, hypercholesterolemia, use of antiplatelet or anticoagulants within two weeks prior to onset, and use of alcohol during the three months prior to onset. Statin use was further trichotomized into prior-only use, prior and continued use**,** and new use. Non-statin users were those patients who were not on any statins prior or after ICH. The ICH location was categorized into lobar, deep (including primary IVH), brainstem, and cerebellum. Data collected in the acute setting included Glasgow Coma Scale (GCS) in the emergency department (ED), time from onset to arrival in the ED, hematoma volume on each CT imaging, presence and location of microbleeds, and LDL on admission. Change in hematoma volumes was measured between the initial CT scan (within 6 hours of onset) and the follow-up CT scan (6 hours to 5 days later).

Representativeness of the ERICH Population

Prior studies had identified the potential for a survival and mild severity bias in the recruitment of cases which led to modifications in recruitment procedures instituted for the current study.[22] Hot Pursuit recruitment, rather than retrospective recruitment, utilizes the same methods of acute ICH case identification used for clinical trials, including active screening of admission logs and emergency room, neurosurgical intensive care unit,

neurosurgery, and neurology records. In addition, given that the most severe cases are the least likely to participate, our personnel have received in-person and on-site training on effective ways to approach patients and families for enrollment. Finally, almost all cases had a clinically drawn sample that was available for genetic testing. Families with a moribund case, unable to come to a decision to enroll in the immediate hyper-acute setting were asked if the clinically drawn sample could be held and not discarded so that they could have more time to consider the study allowing us to re-approach later. This innovation reduced recruitment bias that otherwise would have accrued with pre-enrollment attrition of the most severe cases due to early death and inability at time of delayed family consent to obtain the research sample. In no case did the study take possession of the clinically drawn sample until full and finalized consent was formally obtained (This process was approved by the Institutional Review Boards at participating sites).

We evaluated the representativeness of our population by performing chart abstractions of true cases of ICH who were not enrolled in the study over a 6-month period within the case recruitment period (Online Supplementary Table II). Enrolled patients were slightly younger (62 vs. 65 years; $p<0.0001$) but were not different in risk factor comparison for anticoagulant use, frequent alcohol use, hypertension, diabetes, or hypercholesterolemia. Further, discharge disposition to home/relative versus rehabilitation, SNF/assisted living, or other hospital/subacute setting was not different between enrolled versus non-enrolled ($p=0.18$). There was a higher mortality in the not enrolled patients versus enrolled patients (32% versus 11%; $p<0.0001$) within the first 6 month case recruitment period. This creates a potential for survival bias. The study did show that Hispanics were more likely to enroll than non-Hispanic ICH cases.

Primary and secondary outcomes

The primary outcomes of interest were the effect of statin use on 3-month mortality and mRS in ICH patients. Secondary outcome of interest was the effect of statins on hematoma growth in patients whose first CT scan was within 6 hours of onset and had an available follow up CT scan.

Statistical Analysis

All statistical analyses were two-tailed and considered significant if $p \leq 0.05$. We compared patient characteristics, clinical data, and hospital characteristics in ICH patients between statin users (total, prior, new, or continued) and non-statin users. To compare patients' characteristics and outcomes of interest between statin and non-statin users, categorical variables were presented as counts and proportions, and differences between groups were tested using chi-squared or Fisher's exact test for $R \times C$ tables. Means, standard deviations, and medians for continuous variables were reported. Comparisons of hematoma volumes, lipid laboratory values, age, and admission GCS were made using the Kruskal-Wallis test. Comparison of alcohol use, location of ICH, differences in hematoma volumes, and time from onset to arrival at ED were made using the Cochran-Mantel-Haenszel (CMH) test. In multivariate modeling, logistic regression was used for binary outcomes, and linear regression was used for continuous outcomes. The following variables were used in the

modeling based on their prior known associations with ICH outcomes: ICH volume, presenting GCS, ICH location, age, sex, race, pre-stroke mRS, prior uses of antiplatelet or anticoagulants and Intraventricular hemorrhage (IVH). Propensity score methods are statistical tools to attempt to account for potential confounding factors for a non-randomized treatment, here statin use. Thus, a propensity score was computed to estimate the probability of taking statins after ICH for each patient using logistic regression analysis utilizing 10 variables that have been associated with poor outcomes and may influence a treating physician's view about a patient's long term prognosis: presenting GCS, ICH volume, ICH location, IVH, age, sex, race, anticoagulant use, frequent alcohol use, and history of dementia. Multivariable logistic regression analyses were computed, adjusting for potential confounders and the propensity score of post-ICH statin use.

Results

2997 cases of ICH were recruited into the study. Of the 2997 cases enrolled, 431 cases were excluded because of lack of 3-month mRS. An additional 74 were excluded because of missing data on hematoma volume, and another 35 were excluded because of unreliable data on time of onset to first CT or arrival. Our final study population was 2457 patients (1093 statin users, and 1364 non-statin users). In the statin user group, 268 (25%) were prior users, 402 (37%) were newly prescribed, and 423 (39%) were continued on statins after the admission.

Among the final study population, CT head within 6 hours of onset was available for 849 patients (35%), with follow up CT head available in 628 (26%) cases. Data on admission LDL was available for 1416 (58%) patients. The mean age of the study sample was 62 years and 42% patients were women. Table 1 and 2 compare the baseline characteristics and outcomes of interest among statin and non-statin users respectively (A detailed version is included in the online supplemental material (online supplementary table III). The time from symptom onset to ED arrival was similar between two groups. Overall, statin users were older, with significantly higher rates of medical comorbidities, including hypertension, diabetes mellitus, hyperlipidemia, prior history of ischemic stroke, and prior use of antiplatelet and anticoagulant therapy. Statin use was significantly more common in white cases, compared with blacks and Hispanics ($p<0.0001$). A higher proportion of statin users had lobar hemorrhages compared with non-statin users ($p=0.03$). There was no statistical difference in the specific APOE genotypes between the two groups ($p=0.27$). There was no statistical difference in the average rates of microbleeds between the two groups ($p=0.67$). There was also no statistical difference in the location of microbleeds between the two groups (Table 1, online Supplementary Table III). However, when the statin user subgroups were separately analyzed, there was a statistically higher percentage of 'new statin use' in patients with 'non-lobar' and 'non-lobar plus lobar' subgroups and a statistically lower use of 'new statins' in patients with 'lobar only' microbleeds (online supplementary table IV).

Statin use and outcomes of interest

Overall, there was a significantly higher risk of death (in-hospital or post-discharge within 3 months) and disability (3-month mRS) among non-statin users, compared with statin users.

We did not detect an association between statin use and either admission hematoma volume or hematoma growth (Table 2, online supplementary table III).

Several patients were sequentially removed from the multivariate analysis to address various potential biases (Patients with no CT scan within 6 hours of admission, N=1608; patients who were unable to swallow a statin pill or who had care withdrawn, N=155). Despite removing these patients and after adjustment for initial volume of hemorrhage, GCS, presence of IVH, antiplatelet and anticoagulant use, sex, race, ICH location, age, and pre-stroke mRS, the final multivariate analysis continued to show lower mortality with statin use at 3-month follow up (Table 3; p=0.04). Statin use was not significantly associated with 3 month mRS in this analysis. When a subgroup multivariate analysis was performed to compare various statin user groups, prior-only statin users appeared to have significantly higher mortality (p=0.003) and disability (p=0.05) compared with new or continued users (Table 3).

Propensity Score Analysis (Prior-only Statin Users versus New or Continued Statin Users)

The overall good outcome in all statin users but worse outcomes in prior-only statin users create a scientific dilemma. Was the higher mortality and morbidity in prior statin users a result of stopping statins on admission or that prior statin users were a group of extremely sick patients who were not prescribed statins during the hospital course or discharge because of their poor prognosis? To address this question, we developed a propensity score to match the odds of continuing statins and stopping statins based on variables (see Methods) that would influence a treating physician's decision. The set of samples with complete data, after excluding for dysphagia, withdrawal of care, and baseline CT after 6 hours of onset, was much smaller (N=60 prior use, N=267 new/continued use). Prior statin users were significantly older, had significantly lower admission GCS, and significantly higher admission hematoma volume. When this propensity score was added as a covariate in the initial model of prior statin users versus new or continued statin users, the effect of prior statin use was dampened and no longer statistically associated with higher mortality (p=0.17). Age, admission injury severity, and hematoma volume influenced a treating physician's decision of whether to start or continue statins during admission or discharge (Table 4).

Discussion

The findings of our study shed light on the conflicting data regarding the effect of statins on outcomes after ICH. ICH is a complex disease and involves several factors that independently or co-dependently affect the outcome of these patients. In our population, statin use was associated with better outcomes in ICH patients but this effect was driven by patients in whom statins were continued in the hospital. Prior statin users who had their statins stopped had higher 3-month mortality and morbidity that persisted even after controlling for patients with withdrawal of care or dysphagia, limiting the ability to swallow. A superficial analysis may suggest that continued or new use of statins may thus be associated with better outcome in statin users. However, by utilizing propensity score

analysis, we found that factors influencing a treating physician's decision to continue or prescribe new statins were the most likely explanation. Thus, our analysis supports the hypothesis that prescription of statins (whether continued or new), reflected the physician/health care team's view of whether the person would survive. Statins were stopped in patients who were older, had lower admission GCS scores or had larger admission hematoma volume, likely prompting a treating physician to consider these patients a poor candidate for a long-term prevention therapy like statins, even if withdrawal of care was not invoked. The propensity score analysis based on the likelihood of having statins continued showed that after controlling for this factor, the mortality for stopping statins was no different than for continuing. This careful interpretation of the study also explains the findings of prior similar studies that showed improved survival in patients on continued inpatient statins despite matching the groups and controlling for withdrawal of care and dysphagia[23].

There are several other noteworthy findings from our study. Our study failed to show any difference in admission hematoma volumes (when first CT scan was done within 6 hours of time of onset) and hematoma growth (when the follow up scan was available within 5 days of onset). Prior studies had suggested that statin use may have beneficial effects based on reducing hematoma volume or preventing growth but our data do not confirm such an effect. Statin users were overall an older, less healthy population with multiple medical co-morbidities who were on several other medications that could affect ICH volume, growth and overall prognosis of a patient. There was an overall higher use of new statin use in patients with non-lobar and non-lobar plus lobar microbleeds and lower use of new statins in patients with lobar only microbleeds. The higher percentage use of new statins preferentially in the presence of non-lobar microbleeds could be related to several associated vascular risk factors that warrants use of statins in such patients. The lower percentage use of new statins in lobar only microbleed patients could be a reflection of the known association of statin use and recurrent ICH in patients with lobar microbleeds[24].

Overall, our study has several strengths. Our study accounts for many of the limitations noted by Jung et al[20]. Our cohort is large, and the data were collected prospectively from multiple sites across the country. Ample power allowed us to control for multiple potential confounding factors. We initially controlled for traditional factors influencing outcomes in ICH patients followed by removing patients with withdrawal of care and dysphagia from the initial sample and re-analyzing the data. We later developed a propensity score and used it as a covariate to control for factors that may influence a physician's decision making.

Our study has a few limitations. This study was not designed as a randomized trial of statin therapy on ICH patients. We did not study the effect of statin types or strength of dosing. A large percentage of patients did not have admission lipid panels, which limited an analysis based on LDL values and statin use. However, there are numerous studies pointing towards the relationship of low LDL and ICH risk and outcomes that are beyond the scope of this discussion. Additionally, propensity scores were computed based on a small subset of statin users due to missing data for some variables used in calculating the propensity score.

Conclusion

Although statin use, especially continued or new use of statins, was associated with improved outcomes in ICH patients, this effect may merely reflect the physician/health care team's view of whether the person will survive and not a "predictor" of survival. We were unable to identify a substantial effect of statin use on long-term survival, outcomes, and hematoma volume or hematoma growth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. The New England journal of medicine. 2001; 344:1450–1460. [PubMed: 11346811]
2. 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; 33:1190–1195.
3. Morgenstern LB, Hemphill JC 3rd, Anderson C, Becker K, Broderick JP, Connolly ES Jr, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the american heart association/american stroke association. Stroke; a journal of cerebral circulation. 2010; 41:2108–2129.
4. Puddey IB. Low serum cholesterol and the risk of cerebral haemorrhage. Atherosclerosis. 1996; 119:1–6. [PubMed: 8929251]
5. Iribarren C, Jacobs DR, Sadler M, Claxton AJ, Sidney S. Low total serum cholesterol and intracerebral hemorrhagic stroke: Is the association confined to elderly men? The kaiser permanente medical care program. Stroke; a journal of cerebral circulation. 1996; 27:1993–1998.
6. Okumura K, Iseki K, Wakugami K, Kimura Y, Muratani H, Ikemiya Y, et al. Low serum cholesterol as a risk factor for hemorrhagic stroke in men: A community-based mass screening in okinawa, japan. Japanese circulation journal. 1999; 63:53–58. [PubMed: 10084389]
7. Segal AZ, Chiu RI, Eggleston-Sexton PM, Beiser A, Greenberg SM. Low cholesterol as a risk factor for primary intracerebral hemorrhage: A case-control study. Neuroepidemiology. 1999; 18:185–193. [PubMed: 10364719]
8. Roquer J, Rodriguez Campello A, Gomis M, Ois A, Munteis E, Bohm P. Serum lipid levels and in-hospital mortality in patients with intracerebral hemorrhage. Neurology. 2005; 65:1198–1202. [PubMed: 16247046]
9. Ramirez-Moreno JM, Casado-Naranjo I, Portilla JC, Calle ML, Tena D, Falcon A, et al. Serum cholesterol ldl and 90-day mortality in patients with intracerebral hemorrhage. Stroke; a journal of cerebral circulation. 2009; 40:1917–1920.
10. Rodriguez-Luna D, Rubiera M, Ribo M, Coscojuela P, Pagola J, Pineiro S, et al. Serum low-density lipoprotein cholesterol level predicts hematoma growth and clinical outcome after acute intracerebral hemorrhage. Stroke; a journal of cerebral circulation. 2011; 42:2447–2452.
11. Stone NJ, Robinson J, Lichtenstein AH, Merz CN, Blum CB, Eckel RH, et al. 2013 acc/aha guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the american college of cardiology/american heart association task force on practice guidelines. Circulation. 2013

12. Welch KM. Review of the sparcl trial and its subanalyses. Current atherosclerosis reports. 2009; 11:315–321. [PubMed: 19500496]
13. Vergouwen MD, de Haan RJ, Vermeulen M, Roos YB. Statin treatment and the occurrence of hemorrhagic stroke in patients with a history of cerebrovascular disease. Stroke; a journal of cerebral circulation. 2008; 39:497–502.
14. Yang D, Zhang J, Han Y, James E, Chopp M, Seyfried DM. Acute statin treatment improves recovery after experimental intracerebral hemorrhage. World journal of neuroscience. 2013; 3:69–75. [PubMed: 23837132]
15. Yang D, Knight RA, Han Y, Karki K, Zhang J, Ding C, et al. Vascular recovery promoted by atorvastatin and simvastatin after experimental intracerebral hemorrhage: Magnetic resonance imaging and histological study. Journal of neurosurgery. 2011; 114:1135–1142. [PubMed: 20722611]
16. Yang D, Knight RA, Han Y, Karki K, Zhang J, Chopp M, et al. Statins protect the blood brain barrier acutely after experimental intracerebral hemorrhage. Journal of behavioral and brain science. 2013; 3:100–106. [PubMed: 23459792]
17. Yang D, Han Y, Zhang J, Chopp M, Seyfried DM. Statins enhance expression of growth factors and activate the pi3k/akt-mediated signaling pathway after experimental intracerebral hemorrhage. World journal of neuroscience. 2012; 2:74–80. [PubMed: 23482588]
18. Indraswari F, Wang H, Lei B, James ML, Kernagis D, Warner DS, et al. Statins improve outcome in murine models of intracranial hemorrhage and traumatic brain injury: A translational approach. Journal of neurotrauma. 2012; 29:1388–1400. [PubMed: 22233347]
19. Dowlatshahi D, Demchuk AM, Fang J, Kapral MK, Sharma M, Smith EE, et al. Association of statins and statin discontinuation with poor outcome and survival after intracerebral hemorrhage. Stroke; a journal of cerebral circulation. 2012; 43:1518–1523.
20. Jung JM, Choi JY, Kim HJ, Seo WK. Statin use in spontaneous intracerebral hemorrhage: A systematic review and meta-analysis. International journal of stroke: official journal of the International Stroke Society. 2015; 10(Suppl A100):10–17. [PubMed: 26306674]
21. Woo D, Rosand J, Kidwell C, McCauley JL, Osborne J, Brown MW, et al. The ethnic/racial variations of intracerebral hemorrhage (erich) study protocol. Stroke; a journal of cerebral circulation. 2013; 44:e120–125.
22. Gregson BA, Smith M, Lecouturier J, Rousseau N, Rodgers H, Bond J. Issues of recruitment and maintaining high response rates in a longitudinal study of older hospital patients in england--pathways through care study. J Epidemiol Community Health. 1997; 51:541–548. [PubMed: 9425465]
23. Flint AC, Conell C, Rao VA, Klingman JG, Sidney S, Johnston SC, et al. Effect of statin use during hospitalization for intracerebral hemorrhage on mortality and discharge disposition. JAMA neurology. 2014; 71:1364–1371. [PubMed: 25244578]
24. Westover MB, Bianchi MT, Eckman MH, Greenberg SM. Should statins be avoided after intracerebral hemorrhage? Archives of neurology. 2011; 68:573–579. [PubMed: 21220650]

Table 1

Comparison of baseline characteristics of statin users versus non-statin users

Variables	Statin users				Non-statin users
	Total	Prior	Continued	New	
N	1093	268	423	402	1364
Age (years) mean±SD (median) †	65.1±13.6	70.4±12.5	68.2±12.7	58.4±12.5	60.3±15.0
Female	39.7%	41.0%	41.6%	36.8%	43.1%
Race/ethnicity					
Black	29.1%	27.2%	23.9%	35.8%	35.2%
Hispanic	32.8%	27.6%	25.3%	44.0%	35.3%
White	38.2%	45.1%	50.8%	20.1%	29.5%
Risk Factors					
History of ischemic stroke †	18.0%	25.0%	19.1%	12.2%	8.6%
History of Diabetes †	39.2%	47.0%	48.0%	24.9%	21.5%
History of Alzheimer disease	2.0%	2.2%	3.1%	0.7%	1.7%
History of Dementia (non-Alzheimer)	5.0%	11.2%	5.0%	1.0%	3.8%
History of hypertension †	91.0%	92.2%	94.8%	86.3%	80.4%
History of high cholesterol †	69.7%	88.1%	93.6%	31.8%	27.3%
Prior use of antiplatelet therapy †	10.9%	18.3%	14.2%	2.5%	2.7%
Prior use of anticoagulants †	16.7%	22.8%	24.8%	4.2%	8.4%
Prior moderate use of alcohol †	22.6%	19.4%	22.9%	24.4%	25.6%
ICH Category ‡					
Lobar	33.5%	43.3%	38.3%	21.9%	29.8%
Deep (Includes Primary IVH)	54.8%	44.4%	49.9%	66.9%	56.4%
Brainstem	4.1%	4.1%	3.3%	5.0%	6.5%
Cerebellum	7.6%	8.2%	8.5%	6.2%	7.3%

Variables	Statin users				Non-statin users
	Total	Prior	Continued	New	
Admission GCS (median, IQR) †	15, 12–15	13, 7–15	15, 14–15	15, 13–15	14, 9–15
Initial Hematoma volume* (mean±SD)	20.2±26.7	39.2±39.6	13.7±15.8	13.3±15.3	21.2±24.0
Presence of IVH‡	40.3%	54.5%	36.2%	35.1%	46.2%
Microbleed Present	52.2%	51.6%	41.7%	61.9%	53.7%
Microbleed Location					
Lobar only	8.3%	12.5%	13.0%	3.6%	9.4%
Non-Lobar only	16.6%	12.5%	8.1%	24.0%	6.5%
Lobar plus Non-Lobar	27.5%	27.1%	19.5%	33.5%	29.4%
Prestroke mRS †					
0	65.0%	52.5%	61.6%	76.8%	74.4%
1	14.2%	15.8%	16.6%	10.7%	9.4%
2	12.0%	16.6%	12.3%	8.7%	7.9%
3	5.1%	9.1%	5.9%	1.7%	4.6%
4	3.1%	5.3%	2.8%	2.0%	2.9%
5	0.5%	0.8%	0.7%	0.0%	0.8%

* = CT imaging within 6 hours of onset

† =P<0.0001 (P-values reflect the comparison between statin users and non-statin users).

‡ =p<0.05 ((P-values reflect the comparison between statin users and non-statin users).

Table 2

Comparison of Outcomes of Statin Users versus Non-statin Users

Variables	Statin users				Non-statin users
	Total	Prior	Continued	New	
N	1093	268	423	402	1364
In-hospital death†	8.2%	33.6%	0.0%	0.0%	17.0%
3-month Rankin†					
0	3.9%	1.1%	5.9%	3.7%	4.8%
1	15.9%	6.7%	17.0%	20.9%	15.2%
2	17.1%	6.7%	17.5%	23.6%	15.3%
3	16.3%	8.6%	19.4%	18.2%	14.0%
4	21.0%	13.8%	25.1%	21.6%	17.1%
5	8.2%	8.6%	8.3%	8.0%	7.7%
3-month mortality†	17.5%	54.5%	6.9%	4.0%	26.0%
Hematoma volume*	N=294	N=72	N=109	N=113	N=334
First CT (mean±SD)	17.7±21.7	31.7±32.2	14.4±16.7	12.1±11.8	19.1±21.9
Subsequent CT (mean±SD)	21.8±27.1	37.3±39.9	19.0±22.4	14.7±14.6	22.7±24.5
Difference in volume					
CT2 volume < CT1 volume	38.1%	43.1%	30.3%	42.5%	32.9%

†=P<0.0001 (P-values reflect the comparison between statin users and non-statin users).

*=CT imaging within 6 hours with follow-up imaging within 5 days of symptoms onset.

Table 3

Multivariate analysis for 3-month mortality and mRS among ICH patients

Comparison of Statin Users Versus Non-Statin Users (N=694) * †			
	Beta (Standard Error)		P value
3 month mRS	−0.02 (0.10)		0.79
	OR (95% CI)		P value
3-month mortality	0.50 (0.26–0.96)		0.04
Comparison of Prior Only Versus Continued or New Statin Use (N=327) * †			
	Statin Category	Beta (SE)	P value
3 month mRS			0.06
	Continued use	−0.41 (0.19)	0.04
	New use	−0.45 (0.20)	0.02
	Prior use	REF	REF
	Statin Category	OR (95% CI)	P value
3-month mortality			0.003
	Continued use	0.11 (0.03–0.44)	0.002
	New use	0.22 (0.06–0.76)	0.02
	Prior use	REF	REF

*Patients without Hematoma volumes within six hours of onset, withdrawal of care or dysphagia were excluded from the multivariate analysis.

†Following variables were used in the multivariate analysis: Admission hematoma volume (within 6 hours of onset), age, sex, race, intraventricular hemorrhage, location, Glasgow coma scale, pre-stroke modified Rankin scale, and use of antiplatelet or anticoagulants.

Table 4

Comparison of variables used to develop a propensity score for post ICH statin prescription*.

	New/Continued Use (N=267)	Prior Use (N=60)	p-value
Age, mean±SD (median)	61.7 ± 13.4 (61)	65.2 ± 11.2 (66.5)	0.05
Female Sex	102 (38.2%)	24 (40.0%)	0.79
Ethnicity			0.83
• Black	72 (27.0%)	17 (28.3%)	
• Hispanic	104 (39.0%)	25 (41.7%)	
• White	91 (34.1%)	18 (30.0%)	
Initial Hematoma volume mean±SD (median)	13.4 ± 15.7 (8.3)	27.5 ± 31.0 (13.8)	0.0005
GCS, median, IQR	13, 13–15	13.5, 7–15	0.001
Location			0.31
• Posterior fossa	28 (10.5%)	6 (10.0%)	
• Deep	191 (71.5%)	38 (63.3%)	
• Lobar	48 (18.0%)	16 (26.7%)	
IVH	101 (37.8%)	27 (45.0%)	0.30
Use of anticoagulants	32 (12.0%)	10 (16.7%)	0.33
Frequent Alcohol Use	40 (15.0%)	7 (11.7%)	0.51
History of dementia	9 (3.4%)	4 (6.7%)	0.27

*Patients without Hematoma volumes within six hours of onset, withdrawal of care or dysphagia were excluded from the multivariate analysis.

SD=Standard Deviation; GCS=Glasgow Coma Scale; IVH=Intraventricular Hemorrhage