Effect of Statin Use During Hospitalization for Intracerebral Hemorrhage on Mortality and Discharge Disposition

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IMPORTANCE Statin use during hospitalization is associated with improved survival and a better discharge disposition among patients with ischemic stroke. It is unclear whether inpatient statin use has a similar effect among patients with intracerebral hemorrhage (ICH).

OBJECTIVE To determine whether inpatient statin use in ICH is associated with improved outcomes and whether the cessation of statin use is associated with worsened outcomes.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study of 3481 patients with ICH admitted to any of 20 hospitals in a large integrated health care delivery system over a 10-year period. Detailed electronic medical and pharmacy records were analyzed to explore the association between inpatient statin use and outcomes.

MAIN OUTCOMES AND MEASURES The primary outcome measures were survival to 30 days after ICH and discharge to home or inpatient rehabilitation facility. We used multivariable logistic regression, controlling for demographics, comorbidities, initial severity, and code status. In addition, we used instrumental variable modeling to control for confounding by unmeasured covariates at the individual patient level.

RESULTS Among patients hospitalized for ICH, inpatient statin users were more likely than nonusers to be alive 30 days after ICH (odds ratio [OR], 4.25 [95% CI, 3.46-5.23]; P < .001) and were more likely than nonusers to be discharged to their home or an acute rehabilitation facility (OR, 2.57 [95% CI, 2.16-3.06]; P < .001). Patients whose statin therapy was discontinued were less likely than statin users to survive to 30 days (OR, 0.16 [95% CI, 0.12-0.21]; P < .001) and were less likely than statin users to be discharged to their home or an acute rehabilitation facility (OR, 0.26 [95% CI, 0.20-0.35]; P < .001). Instrumental variable models of local treatment environment (to control for confounding by unmeasured covariates) confirmed that a higher probability of statin therapy was associated with a higher probability of 30-day survival (with an increase in probability of 0.15 [95% CI, 0.04-0.25]; P = .01) and a better chance of being discharged to home or an acute rehabilitation facility (with an increase in probability of 0.13 [95% CI, 0.02-0.24]; P = .02).

CONCLUSIONS AND RELEVANCE Inpatient statin use is associated with improved outcomes after ICH, and the cessation of statin use is associated with worsened outcomes after ICH. Given the association between statin cessation and substantially worsened outcomes, the risk-benefit balance of discontinuing statin therapy in the acute setting of ICH should be carefully considered.
Statin Use During Hospitalization for Intracerebral Hemorrhage

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) are known to reduce the risk of ischemic stroke. In addition, statin use during hospitalization for ischemic stroke has been found to be strongly associated with improved outcomes, and the cessation of statin use has been associated with worsened outcomes. Ischemic stroke and hemorrhagic stroke (intracerebral hemorrhage [ICH]) have different primary mechanisms, but they share many molecular mechanisms for secondary brain injury that may be influenced by statin use.

Decisions regarding prescription of statins in the acute setting of ICH may be influenced by conflicting data regarding the effect of statins on the risk of brain hemorrhage. Although many observational studies and randomized clinical trials of statin use have found no increased risk of ICH with outpatient statin use, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial reported an increased risk of ICH among patients randomly assigned to a high dose of atorvastatin calcium, particularly among patients with a history of ICH. Although it has been suggested that this observation might have resulted from high crossover rates in the SPARCL trial itself, it is likely that many clinicians have been wary of prescribing statins to patients with ICH in the wake of these findings.

A particular dilemma in this area relates to the patient presenting with ICH who is already taking a statin. Should such a patient have their statin therapy discontinued during hospitalization for fear that the statin therapy might increase their risk of recurrent ICH, or should their statin therapy be continued out of a concern that cessation of statin use in the acute setting could worsen the patient’s outcome? The effect of inpatient statin use, and of the cessation of statin use, on outcomes in a large cohort of patients with ICH who were treated in an integrated health care delivery system, using statistical techniques that allow us to control for potential unmeasured confounding at the individual patient level.

Methods

The institutional review board of the Kaiser Foundation Research Institute approved our retrospective, no-patient-contact study with waiver of informed consent.

Data Source and Patients

We assembled a cohort of 3481 patients spanning a 10-year period who were admitted with a primary discharge diagnosis of ICH to any of 20 hospitals in Kaiser Permanente Northern California (KPNC), an integrated health care delivery system with more than 3 million members who are demographically similar to the overall population of northern California. We included all KPNC plan members older than 50 years of age who were admitted from outside the hospital on an emergency basis to any KPNC hospital between January 2002 and December 2011 and who underwent neuroimaging during hospitalization (computed tomography or magnetic resonance imaging of the brain) and received a primary discharge diagnosis of ICH (code 431 in the International Classification of Diseases, Ninth Revision, Clinical Modification), subject to the following exclusion criteria (in order to maximize information on comorbidities and outcomes): prior qualifying ICH during the study period, less than a full year of membership in KPNC before admission, residence (indicated by zip code) outside the primary plan service area served by KPNC, or prestroke outpatient statin use that could not be accurately determined according to specific criteria.

Outcomes

The main outcomes were 30-day survival and discharge to home or inpatient rehabilitation facility. Patients were observed for 30 days from the date of admission or until death. No patients were lost to follow-up. Date of death was obtained from the KPNC membership database and the State of California Death Certificates database and social security database linked to the patient according to established methods.

Statin Users and Nonusers

Details of statin use before and during hospitalization were obtained from electronic pharmacy records and inpatient order information included in the electronic medical record, as previously described. Inpatient statin use was defined as occurring when statins were ordered by a physician for inpatient administration. Patients were identified as either outpatient statin users or nonusers based on whether or not statin prescriptions were filled at a KPNC pharmacy. Outpatient statin users had active prescriptions at the time of admission for ICH and had filled their last prescription at a KPNC pharmacy recently enough to have enough pills to take through the day of admission. Nonusers had not been prescribed a statin and had not filled any statin prescriptions in the preceding year.

If a patient had a statin prescription but no fills, then he or she had a statin prescription but no fills, then he or she was not included in this analysis.

Covariates

Baseline demographic characteristics and details of the medical history of the patients were extracted from organizational databases and the electronic medical record, including age, sex, race/ethnicity, presence of medical comorbidities (hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, congestive heart failure, or history of stroke), and dysphagia. During the last 4 years of our study, most patients were admitted to hospitals with a complete outpatient and inpatient electronic medical record, providing routinely measured initial ICH severity on the Glasgow Coma Scale (GCS) and/or on the modified National Institutes of Health Stroke Scale (mNIHSS). The correspondence observed between these 2 scores enabled the calculation of mNIHSS equivalents for GCS scores in a generalized severity score; specifically, we estimated generalized linear models for all pairs of mNIHSS and GCS scores within an hour of each other. In this fashion, we measured initial severity at presentation or within 24 hours of admission to the emergency department for 898 of all 3481
patients. For use in multivariable models, this initial severity measure was cut according to quartiles of severity. In a subset of 646 patients within this cohort of 898 patients, complete information on in-hospital code status was also available, including do-not-resuscitate (DNR) status instituted within 24 hours. We also collected additional information on the hospital, including the annual volume of ICH cases (using a 3-year moving average), and on patterns of inpatient statin use over time.

Statistical Analysis
In this observational study, the treatment of interest (inpatient statin use) resulted from clinical decisions that could be affected by clinical characteristics, including initial severity. Consequently, estimating the effect of inpatient statins required controlling for potential selection bias in several ways, to avoid a spurious association between treatment and outcomes. We used multivariable logistic regression to control for several potential confounders in various models, including age, sex, medical comorbidities as listed in the Table, race/ethnicity, dysphagia, and prior statin use as an outpatient (except in the case of models of statin discontinuation, which were performed on the subset of patients receiving statins as outpatients). In separate models, we controlled for initial severity and DNR status instituted within 24 hours. Finally, we used instrumental variable probit models to control for confounding by unmeasured covariates at the individual patient level. The treatment instrument used was the local statin prescription practice, operationalized as the use or nonuse of inpatient statins in the immediately preceding case at the same hospital, matched on outpatient statin use or nonuse (last prior treatment analysis). The instrumental variable used in the present analysis is the same instrument that we have described previously (in a cohort of patients with ischemic stroke). This instrumental variable meets 2 key requirements for an instrument to model a treatment that may be subject to indication bias: first, it has no direct effect on outcome, and, second, it has substantial probabilistic association with the treatment (because the likelihood of inpatient statin prescription varies according to when and where patients are hospitalized). Variation in short-term practice patterns can be an effective instrument to assess treatment impact, and when practice patterns are in flux, information on the immediately preceding patient often provides the best indirect measure of local practice. For univariable analyses, we analyzed categorical data in contingency tables with the Fisher exact test and continuous data with the nonparametric Kruskal-Wallis test. Statistical analyses were performed with SAS version 9.3 (SAS Institute Inc) and StataMP version 12.1 (StataCorp).

Results
Patient Characteristics
Patient characteristics are summarized in the Table, which shows mean age, sex, distribution, and number of comorbidities according to inpatient statin therapy. In addition, the eTable in the Supplement displays patient characteristics for the overall cohort (N = 3481) compared with the subset of patients for whom initial severity measures (mNIHSS or GCS scores) were available (n = 898). Of the 2321 patients not receiving a statin as an outpatient, 425 (18.3%) received a statin as an inpatient, and of the 1160 patients receiving a statin as an outpatient, 391 (33.7%) did not receive a statin as an inpatient. The statins used by the 1194 inpatients were lovastatin (696 patients [58.3%]), simvastatin (453 patients [37.9%]), atorvastatin (38 patients [3.2%]), and pravastatin sodium (7 patients [0.6%]). The median inpatient statin dose (in atorvastatin-equivalent dose) was 10 mg/d (interquartile range, 5-20 mg/d).

Inpatient Statin Use and Outcomes
Patients treated with a statin while in the hospital had an unadjusted 30-day mortality rate of 18.4%, whereas those who were not treated with a statin during admission for ICH had a 30-day mortality rate of 38.7% (Figure 1; P < .001). In multi-
variable logistic regression controlling for age, sex, race/ethnicity, comorbidities, volume of ICH cases by hospital facility, and dysphagia, inpatient statin users were more likely than nonusers to be alive at 30 days (odds ratio [OR], 4.25 [95% CI, 3.46-5.23]), and this association also remained in models controlling for initial severity and for DNR status instituted within 24 hours (Figure 2A).

Patients treated with a statin during hospitalization for ICH were discharged to home or an inpatient rehabilitation facility 51.1% of the time, whereas patients not treated with a statin during admission were discharged to home or an inpatient rehabilitation facility 35.0% of the time ($P < .001$). In multivariable logistic regression, inpatient statin users were also more likely than nonusers to be discharged to home or an inpatient rehabilitation facility (OR, 2.57 [95% CI, 2.15-3.06]; $P < .001$), and this association remained in models controlling for initial severity and for DNR status instituted within 24 hours (Figure 2B).

**Cessation of Statin Use and Outcomes**

Patients whose statin therapy was discontinued (ie, patients taking a statin as an outpatient prior to ICH who did not receive a statin as an inpatient) had an unadjusted mortality rate of 57.8% (Figure 1), compared with a mortality rate of 18.9% for patients using a statin before and during hospitalization ($P < .001$). In multivariable logistic regression, patients whose statin therapy was discontinued were less likely to be alive at 30 days than patients who continued statin therapy (OR, 0.16 [95% CI, 0.12-0.21]; $P < .001$), and

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**Figure 1. Unadjusted Kaplan-Meier Survival Curves According to Whether or Not There Was Inpatient Statin Use**

ICH indicates intracerebral hemorrhage.

**Figure 2. Multivariable Logistic Regression of Inpatient Statin Use and Outcomes**

Multivariable logistic regression models of inpatient statin use and survival to 30 days or discharge to home or inpatient rehabilitation facility, after controlling for quartile of initial ICH severity and do-not-resuscitate (DNR) status instituted within 24 hours (ROC-AUC = 0.888). A, Models of survival to 30 days. The top model of inpatient statin use predicts improved odds of being alive at 30 days in the overall cohort (analysis of receiver operating characteristic area under the curve [ROC-AUC] = 0.71). The middle model of inpatient statin use predicts improved odds of being alive at 30 days in the subcohort of patients with severity data, after controlling for quartile of initial ICH severity (ROC-AUC = 0.86). The bottom model of inpatient statin use predicts improved odds of being alive at 30 days in the subcohort of patients with both severity data and data on code status, after controlling for quartile of initial ICH severity and DNR status instituted within 24 hours (ROC-AUC = 0.79).

Multivariable logistic regression models of inpatient statin use and survival to 30 days or discharge to home or inpatient rehabilitation facility, after controlling for outpatient statin use, age, sex, race/ethnicity, medical comorbidities, volume of intracerebral hemorrhage (ICH) cases by hospital, and dysphagia. The point estimate for the odds ratio (OR) for statin use in each model is shown as a filled diamond, flanked by the upper and lower bounds of the 95% CI. A, Models of survival to 30 days. The top model of inpatient statin use predicts improved odds of being alive at 30 days in the overall cohort (analysis of receiver operating characteristic area under the curve [ROC-AUC] = 0.71). The middle model of inpatient statin use predicts improved odds of being alive at 30 days in the subcohort of patients with severity data, after controlling for quartile of initial ICH severity (ROC-AUC = 0.86). The bottom model of inpatient statin use predicts improved odds of being alive at 30 days in the subcohort of patients with severity data and data on code status, after controlling for quartile of initial ICH severity and DNR status instituted within 24 hours (ROC-AUC = 0.794).
this association remained in models controlling for initial severity and for DNR status instituted within 24 hours (Figure 3A).

The discontinuation of statin therapy was associated with an unadjusted rate of discharge to home or inpatient rehabilitation facility of 22.3%, compared with a rate of 49.8% for patients using a statin before and during hospitalization ($P < .001$). In multivariable logistic regression, patients whose statin therapy was discontinued were less likely than patients who continued therapy to be discharged to home or an inpatient rehabilitation facility (OR, 0.26 [95% CI, 0.20–0.35]; $P < .001$), and this association remained in models controlling for initial severity and for DNR status instituted within 24 hours (Figure 3B).

**Effect of Statin Dose**

In our previous work on statin use during hospitalization for ischemic stroke, we found a dose-response relationship between statin use and outcomes, in part because the distribution of doses was sufficient to explore outcomes at high vs usual or low statin doses.13 In the present cohort, a very small proportion of patients were treated with high-dose statins (113 patients received 40–80 mg/d [atorvastatin-equivalent dose], representing 9.5% of statin users and 3.3% of the total cohort). A formal analysis of the dose-response relationship showed increased point estimates for improved survival and discharge disposition, but the observed differences were not statistically significant (eFigure in the Supplement).

**Relationship Between Time of Exposure and Mortality**

To control for the possible influence of patients not receiving statins because of death within a short period of time in hospital, not allowing for time to receive the medication (an issue known as “immortal time bias”14–19), we fitted additional logistic models factoring in early timing of initial statin use known as “immortal time bias”23), we fitted additional logistic models factoring in early timing of initial statin use and outcomes, in part because the distribution of doses was sufficient to explore outcomes at high vs usual or low statin doses. In the present cohort, a very small proportion of patients were treated with high-dose statins (113 patients received 40–80 mg/d [atorvastatin-equivalent dose], representing 9.5% of statin users and 3.3% of the total cohort). A formal analysis of the dose-response relationship showed increased point estimates for improved survival and discharge disposition, but the observed differences were not statistically significant (eFigure in the Supplement).
admission or never received a statin. Modeled effects controlled for the same background factors, including severity, as the primary model. Both models support our primary result that statin use during hospitalization was significantly associated with being alive at 30 days: model 1 (OR, 3.0 [95% CI, 1.7-5.5]; n = 699; P < .001); model 2 (OR, 3.3 [95% CI, 1.9-5.8]; n = 660; P < .001).

Control for Confounding by Unmeasured Covariates (Instrumental Variable Models)
To control for the possibility of confounding by unmeasured covariates at the individual patient level, we used instrumental variable probit regression models. In these models, individual statin use is removed and replaced with an instrument that encodes the probability of statin therapy, based on the local treatment environment (the statin therapy of the last prior patient treated at the same facility, after matching on outpatient statin therapy). In instrumental variable analysis, we found that inpatient statin use resulted in a 15% absolute increase in the probability of 30-day survival and an 13% absolute increase in the probability of discharge to home or rehabilitation facility, further confirming the relationship between statin use and favorable ICH outcomes (Figure 4).

Discussion
Among patients with ischemic stroke, statin use is associated with improved poststroke outcomes,2,3 as well as reduced risk of recurrent ischemic stroke.1 In ischemic stroke, the cessation of statin use during hospitalization has been associated with worsened outcomes.2-4 Statins affect an array of molecular pathways that may play a role in both ischemic stroke and ICH.5-8 However, it has remained unclear whether statin use is associated with improved outcomes after ICH.

We find that in-hospital statin use is associated with improved outcomes after ICH. The relationship between statin use and better outcomes is robust enough to control for comorbidities, initial severity, early DNR order, and use of instrumental variable modeling to control for unmeasured covariates at the individual patient level.

Our study has certain strengths. Our cohort is large, and the data were collected systematically from a prospectively accumulated electronic medical record database covering 20 hospitals and associated outpatient clinics in an integrated health care delivery system. Our data source included information on all outpatient prescription fills and in-hospital administration records. The KPNC health care system is broadly representative of the overall population of northern California,16 adding to the generalizability of our results. Statin users in the present cohort, as with other cohorts,2,3 had significantly higher rates of all comorbidities, which should tend to worsen outcomes rather than improve them. Because of the nature of our underlying data source, we were able to control for potential confounding at the individual level in several ways. First, we controlled for initial ICH severity and early DNR orders in subsets of the overall data set in which these data were recorded. Second, we controlled for dysphagia, a factor that could otherwise create an association between greater ICH severity and non-use of an oral medication like a statin. Third, we performed instrumental variable modeling of local treatment environment, a technique that allowed us to control for confounding by unmeasured covariates at the individual patient level.

Our study also has weaknesses. This is a retrospective cohort study, and the patients were not randomly assigned to either statin therapy or nontreatment. Not all patients in our study cohort had data available on ICH severity or code status. We do
not include data on the use of other medications that might have influenced outcomes or on radiographic measures of known importance such as initial hematoma volume. Our outcome measure of discharge disposition is only indirectly associated with short-term functional outcome and not a direct assessment of functional outcome. Because our study is restricted to the effect of in-hospital statin use, we cannot address whether statins should be continued long term for such patients or when it would be safe to discontinue a statin. Although we have accurate data on prescriptions and fills, the present study did not involve direct measures of medication compliance such as pill counting or bottle checks. Our mortality end point was all-cause mortality, and we do not have specific data on cause of death. Although the instrumental variable method allowed us to control for confounding at the individual patient level, this technique leaves open the possibility of confounding at other levels, such as bias associated with variation in practice from one group of physicians to another. This risk is minimized, however, by the presence of a single physician practice group across KPNC with regional stroke management guidelines.2,3

The issue of whether statin use in the acute hospital setting might improve post-ICH outcomes is of particular importance because some data have suggested that statin use in this patient population may increase the long-term risk of recurrent hemorrhage.1,11 Concerns about a potential increased risk of recurrent ICH may lead some clinicians to discontinue statin therapy during hospitalization for ICH.3,13-15

While data from some sources have suggested that high-dose statin use may increase the risk of ICH, other data do not support this association. In the SPARCL trial, randomization to atorvastatin at 80 mg/d was associated with an increased risk of ICH in intention-to-treat analysis,1 particularly among patients who were enrolled in the trial as a result of an ICH.11 However, low-density lipoprotein level was not predictive of ICH risk among patients randomly assigned to atorvastatin in the SPARCL trial,13 and it has been pointed out that the apparent difference in ICH rates in the SPARCL trial may have resulted from high crossover rates between the 2 arms.12 In a meta-analysis of 31 randomized controlled trials (patients without recent stroke),3 statin therapy was not associated with an increased risk of ICH, but statin use was associated with a decreased risk of all types of stroke and decreased all-cause mortality. In another very large observational study,24 incidence of ICH was not associated with either statin use or low-density lipoprotein level. One large observational study25 reported that statin use was associated with an increased risk of symptomatic ICH in patients receiving thrombolytic treatment for acute ischemic stroke, despite also being associated with improved poststroke outcomes. However, 2 other large observational studies26,27 did not find such an association.

With regard to the effect of statin use on post-ICH outcomes, several smaller studies have previously suggested an association between pre-ICH statin use and improved outcomes.28,29 A meta-analysis of 12 observational studies showed mixed results, with variation according to the outcomes measured.30 Another meta-analysis and case-control study found an association between pre-ICH statin use and both better functional outcome and reduced mortality, but the included studies were small and did not control for potential unmeasured confounding.31

Several mechanisms have been implicated in secondary brain injury in both ischemic stroke and ICH, including excitotoxicity, oxidative stress, and inflammation, and many of these mechanisms can be modulated by statin use.5-8 In addition, statin use has been associated with a reduction in the volume of perihematoma edema after ICH.31 In animal models of ICH, statin use has been found to downregulate inflammatory gene expression and improve post-ICH outcomes.33 In other experiments using an ICH animal model, statin administration reduced brain tissue loss, increased neurogenesis in the subventricular zone, and improved functional recovery.34 In animal studies of traumatic ICH/traumatic brain injury, statin use up-regulates neurogenesis in the dentate gyrus and improves spatial learning on the Morris water maze test.35

Conclusions
Statin use is associated with improved outcomes after ICH, and the cessation of statin use is associated with worsened outcomes after ICH. The association between statin use and better outcomes remains after controlling for demographics, medical comorbidities, ICH severity, ICH complications, and DNR status instituted within 24 hours. Instrumental variable models further strengthen the association between statin use and improved outcomes by controlling for confounding by unmeasured covariates at the individual patient level. The particular association between cessation of statin use and worsened outcomes merits careful consideration of the risk-benefit balance of discontinuing statin therapy in the acute setting of ICH.
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