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Inpatient statin use predicts improved ischemic stroke discharge disposition

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ABSTRACT

Objective: To determine whether statin use is associated with improved discharge disposition after ischemic stroke.

Methods: We used generalized ordinal logistic regression to analyze discharge disposition among 12,689 patients with ischemic stroke over a 7-year period at 17 hospitals in an integrated care delivery system. We also analyzed treatment patterns by hospital to control for the possibility of confounding at the individual patient level.

Results: Statin users before and during stroke hospitalization were more likely to have a good discharge outcome (odds ratio [OR] for discharge to home = 1.38, 95% confidence interval [CI] 1.25–1.52, p < 0.001; OR for discharge to home or institution = 2.08, 95% CI 1.72–2.51, p < 0.001). Patients who underwent statin withdrawal were less likely to have a good discharge outcome (OR for discharge to home = 0.77, 95% CI 0.63–0.94, p = 0.012; OR for discharge to home or institution = 0.43, 95% CI 0.33–0.55, p < 0.001). In grouped-treatment analysis, an instrumental variable method using treatment patterns by hospital, higher probability of inpatient statin use predicted a higher likelihood of discharge to home (OR = 2.56, 95% CI 1.71–3.85, p < 0.001). In last prior treatment analysis, a novel instrumental variable method, patients with a higher probability of statin use were more likely to have a good discharge outcome (OR for each better level of ordinal discharge outcome = 1.19, 95% CI 1.09–1.30, p = 0.001).

Conclusions: Statin use is strongly associated with improved discharge disposition after ischemic stroke. Neurology® 2012;78:1678–1683

GLOSSARY

CI = confidence interval; FIM = Functional Independence Measure; ICD-9 = International Classification of Diseases, 9th revision, Clinical Modification; KPNC = Kaiser Permanente Northern California; MI = myocardial infarction; OR = odds ratio.

Clinical trials have shown that statins reduce mortality and improve cardiovascular outcomes,1–3 and much of this benefit is thought to derive from improvements in lipid profiles with statin therapy.4 However, statins also have numerous pleiotropic effects,5 including anti-inflammatory, vasodilatory, and antithrombotic properties.6,7

The pleiotropic effects of statins appear to confer acute cardiovascular benefits. For example, early statin therapy for acute myocardial infarction (MI) improves cardiovascular outcomes over a much shorter time frame than would be expected from lipid-lowering effects alone.8 In addition, even short-term cessation of statins may nullify their protective effects9 or cause rebound phenomena resulting in worse outcomes than would be seen without any statin therapy.10,11 Such concerns have been given credence in several clinical studies that have linked withdrawal of statin therapy to higher mortality and morbidity after acute MI12–14 and major vascular surgery.15,16

The acute benefits of statin therapy and risks of statin interruption may also be important in patients with ischemic stroke. Both inpatient17,18 and outpatient17,19,20 statin use has been
associated with improved survival after ischemic stroke. Statin withdrawal has been associated with worsened survival\(^1\) and with worsened functional outcomes.\(^2\)

To clarify the relationship between statin use and short-term functional outcomes, we explored the association between statin use before and during stroke hospitalization and discharge disposition in a large cohort of patients with acute ischemic stroke.

**METHODS**

**Design.** We assembled a cohort of 12,689 patients admitted with ischemic stroke over a 7-year period to hospitals in the Kaiser Permanente Northern California (KPNC) integrated health care delivery system.

**Subjects.** The present cohort of ischemic stroke patients, with detailed a priori inclusion and exclusion criteria, has been described elsewhere.\(^7\) In brief, we included all KPNC plan members older than 50 years of age who were admitted for ischemic stroke to any of 17 hospitals in the KPNC organization between January 1, 2000, and December 31, 2007. The primary inclusion criterion was a principal hospital discharge diagnosis of ischemic stroke (codes 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, and 434.91 from the International Classification of Diseases, 9th revision, Clinical Modification [ICD-9]). CT or MRI of the brain was also required for inclusion. To validate our methods for identifying incident stroke, a nurse analyst reviewed the medical records of 731 patients (5.8%) and confirmed that all patients in this random sample had a correct diagnosis of acute ischemic stroke.

**Measurements.** We searched electronic medical records databases to identify baseline demographic characteristics, details of the medical history such as the presence of hypertension, diabetes, congestive heart failure, coronary artery disease, and atrial fibrillation, and duration of hospitalization. We used electronic pharmacy records to obtain details of statin use prior to and during hospitalization. Patients were considered to be on statin therapy prior to the index stroke if they had an active prescription for a statin at a KPNC pharmacy, and had a filled prescription for a statin at the time of admission, had filled at least 1 therapy prior to the index stroke if they had an active prescription elsewhere.\(^17\) In brief, we included all KPNC plan members older than 50 years of age who were admitted for ischemic stroke to any of 17 hospitals in the KPNC organization between January 1, 2000, and December 31, 2007. The primary inclusion criterion was a principal hospital discharge diagnosis of ischemic stroke (codes 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, and 434.91 from the International Classification of Diseases, 9th revision, Clinical Modification [ICD-9]). CT or MRI of the brain was also required for inclusion. To validate our methods for identifying incident stroke, a nurse analyst reviewed the medical records of 731 patients (5.8%) and confirmed that all patients in this random sample had a correct diagnosis of acute ischemic stroke.

**Outcomes.** Our primary outcome was patient discharge disposition, categorized as an ordinal outcome: 1) discharge to home, 2) discharge to an institution (rehabilitation center or skilled nursing facility), or 3) death in-hospital. Patients discharged to hospice (home or elsewhere) were excluded from this analysis (n = 154 subjects).

**Statistical analysis.** For univariable analyses, categorical data were analyzed by Fisher exact test and Cuzick extension of the Wilcoxon rank sum test for trends across ordered groups. Generalized ordered logistic regression was performed to assess the impact of statin use before and during stroke hospitalization on patients’ discharge disposition while controlling for demographic characteristics and medical comorbidities. As our outcome variable consists of 3 ordered levels (discharge to home, discharge to institution, or dead), generalized ordered logit estimates were obtained for 2 cutpoints, [home] vs [institution or dead] and [home or institution] vs [dead]. For each predictor variable, the parallel lines assumption was tested at the 0.05 level of significance, and those variables meeting the parallel lines assumption were constrained across the 2 generalized ordered logistic models.

To control for the possibility of patient-level confounding, we employed 2 techniques derived from instrumental variable methodology to model local treatment environment (treatment patterns by hospital). We have previously employed the first technique, grouped-treatment analysis, in this same cohort to model 1-year mortality according to hospital-level patterns of statin treatment, and we have described the technique in detail elsewhere.\(^17,22,23\) Here, we use grouped-treatment analysis to model the odds of being discharged to home according to the probability of statin treatment in each hospital center. The second technique, last prior treatment analysis, employs a different measure of local practice. Last prior treatment analysis models the discharge outcome of a given patient based on the statin inpatient treatment status of the last prior patient treated at the same hospital, with matching on outpatient statin treatment assignment (use or nonuse) (see figure e-1 on the Neurology® Web site at www.neurology.org). This proxy is an excellent potential instrument, since it has no direct effect on patient outcome, but it is highly associated with whether the patient receives an inpatient statin. Variation in short-term practice patterns can be an effective instrument to assess treatment impact,\(^24\) and when practice patterns are in flux, information on the immediately preceding patient is often the best indirect measure of local practice.\(^25\) Both methods—grouped treatment analysis and last prior treatment analysis—serve to move the level of analysis away from the individual patient to a broader context of treatment patterns by hospital center, thus avoiding confounding by unmeasured variables at the individual patient level such as confounding by indication or severity.

To estimate the impact of statin use on discharge outcomes based on our last prior treatment predictor (shown in figure 1B, compared with the unadjusted data shown in figure 1A), we used multivariable logistic regression to model the impact of receiving statins based on last prior treatment independent of comorbidities, demographics, and the volume of cases by facility. The impact we report for statin use is an average for the study population, ± 95% confidence interval (CI) for the estimate boundaries.

All multivariable models controlled for a second-order polynomial in age, sex, race/ethnicity, key medical comorbidities (hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, and congestive heart failure), and variation in the volume of cases by hospital center.

Statistical analyses were performed using Stata SE 10.0 (College Station, TX) and SAS 9.2 (Cary, NC).

**Standard protocol approvals, registrations, and patient consents.** The Institutional Review Board of the Kaiser Foundation Research Institute approved this study and waived the requirement for informed consent.

**RESULTS**

**Univariable analyses.** Statin users before stroke hospitalization were more likely to be discharged to home (54.6% for statin users, 50.0% for statin nonusers) and less likely to die in-hospital (7.6% for statin users and 8.6% for statin nonusers) (test for trend, \(p < 0.001\)). Statin users before and
during stroke hospitalization were even more likely to be discharged home (56.5% for statin users, 47.3% for statin nonusers) and even less likely to die in-hospital (5.5% for statin users, 10.6% for statin nonusers) (test for trend, p < 0.001, figure 1A). Patients who underwent statin withdrawal in-hospital were less likely to be discharged home (39.1% for statin withdrawal, 54.9% for statin continuation) and more likely to die in-hospital (22.3% for statin withdrawal, 5.3% for statin continuation) (test for trend, p < 0.001).

**DISCUSSION** In this large observational cohort study, we found that statin use before and during ischemic stroke hospitalization is strongly associated with improved discharge disposition. The beneficial effects of statin use during hospitalization on improved discharge outcome were confirmed by 2 different indirect measures of local statin treatment environment, controlling for the possibility of confounding by unmeasured factors at the individual patient level, such as stroke severity or goals of care decisions.

Statin withdrawal was associated with worsened discharge outcomes in univariable and individual-patient multivariable analyses, but grouped-treatment analysis did not show this association. The lack of association of statin withdrawal and outcome in our grouped-treatment model may indicate that the apparent association in individual-patient models is indeed due to confounding by indication, but it may be in part explained by the few patients who underwent statin withdrawal, limiting the statistical power of the instrumental variable model.

Discharge disposition is an important marker of functional outcomes after stroke, because the ability
to return to living at home has important economic consequences and correlates closely with functional independence. Discharge to home after stroke hospitalization is associated with better functional status by the time of discharge, as measured by the Functional Independence Measure (FIM).

Thrombolytic therapy with IV tissue plasminogen activator, which is the only approved acute stroke treatment that has been shown to improve long-term outcome in randomized controlled trials, increases the probability of discharge to home after stroke hospitalization.

Our findings are consistent with other clinical studies and with basic science data concerning the acute beneficial effects of statins. Statin use has been associated with reduced poststroke mortality. Statin treatment after hospitalization for ischemic stroke has been associated with reduced 10-year mortality. Statin use has been associated with reduced stroke severity and improved long-term functional outcomes. The association between statin use and functional outcome may be particularly notable for small vessel strokes. Secondary analysis of data from the SPARCL trial, a RCT of high-dose atorvastatin in secondary stroke prevention, showed a trend toward improved functional outcomes across the range of the outcome scale (including mortality). In a small RCT of statin withdrawal during ischemic stroke hospitalization, statin withdrawal was associated with increased volume of stroke on neuroimaging, increased risk of deterioration in-hospital, and worsened functional outcome at 3 months. In animal models of stroke, statin treatment reduces the severity of ischemic stroke, and statin withdrawal worsens outcomes. Statins have multiple mechanisms of action of potential importance to the ischemic neurovascular unit. It is therefore possible that statin use before and during ischemic stroke hospitalization may have a neuroprotective effect, thereby improving functional status and chances of discharge to home.

Our study has strengths that support a causal relationship between statin use and improved discharge status. For example, we reduced the risk of individual patient-level confounding by using 2 indirect measures of local statin treatment environment to move the level of analysis away from the individual patient, where such confounding can occur. Because patient assignment to specific hospital centers is related to geography rather than factors related to the patient’s stroke, one can think of patients as being randomly exposed to practice pattern variation among providers. In addition, statin use before hospitalization was associated with improved outcomes, and use patterns before stroke onset cannot be determined by stroke-related factors such as severity or goals of care discussion in-hospital (because the stroke occurs after the treatment decision to take or not take a statin as an outpatient before the stroke). The principal use of lovastatin and simvastatin in our cohort adds to other data more specific to the beneficial effects of atorvastatin in ischemic stroke and thus suggests a statin class effect.

### Table 1

<table>
<thead>
<tr>
<th>Outcome: home vs (institution or dead)</th>
<th>Outcome: (home or institution) vs dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio *</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Model 1</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Before</strong></td>
<td></td>
</tr>
<tr>
<td>1.12&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.11-1.32</td>
</tr>
<tr>
<td><strong>Model 2</strong>&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Before and during use</strong></td>
<td></td>
</tr>
<tr>
<td>1.18</td>
<td>1.08-1.30</td>
</tr>
<tr>
<td><strong>Initiation in hospital</strong></td>
<td></td>
</tr>
<tr>
<td>Statin withdrawal</td>
<td></td>
</tr>
<tr>
<td>0.77</td>
<td>0.63-0.94</td>
</tr>
</tbody>
</table>

**Abbreviation:** CI = confidence interval.

* Odds ratios are from multivariable generalized ordered logistic regression modeling discharge disposition (home vs institution [rehabilitation center or skilled nursing facility] vs death in hospital), adjusted for polynomial in age, sex, race/ethnicity, medical comorbidities, and hospital center by volume. Odds ratios for grouped-treatment analysis are from generalized estimating equations modeling discharge to home with a logit link function, adjusted for age, sex, race/ethnicity, and medical comorbidities.

**Table 2**

<table>
<thead>
<tr>
<th>Model</th>
<th>Individual patient model (logistic regression)</th>
<th>Grouped-treatment model (generalized estimating equations)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio&lt;sup&gt;a&lt;/sup&gt; for home</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>During</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Initiation in hospital</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Withdrawal in hospital</strong>&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.28</td>
<td>1.18-1.37</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Abbreviation:** CI = confidence interval.

* Odds ratios for individual subject analyses are from multivariable logistic regression modeling discharge to home, adjusted for age, sex, race/ethnicity, medical comorbidities, and hospital center by volume. Odds ratios for grouped-treatment analysis are from generalized estimating equations modeling discharge to home with a logit link function, adjusted for age, sex, race/ethnicity, and medical comorbidities.

**b** During = statin use in hospital, irrespective of statin use prior to hospitalization (compared to no statin use in hospital, irrespective of statin use prior to hospitalization) (n = 12,535).

**c** Initiation in hospital = patients not taking a statin prior to stroke who began treatment with a statin in hospital (compared to no statin use before and during hospitalization) (n = 8,823).

**d** Withdrawal in hospital = patients who were taking a statin prior to hospitalization, but who did not receive a statin in hospital (compared to statin use both before and during hospitalization) (n = 3,712).
Table 3 Individual patient and last prior treatment instrumental variable models of discharge disposition

<table>
<thead>
<tr>
<th>Outcome: home vs (institution or dead)</th>
<th>Outcome: (home or institution) vs home</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard model</strong>: inpatient statin use</td>
<td><strong>Last prior treatment model</strong>: inpatient statin use (instrumental variable)</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>1.30</td>
<td>1.21-1.41</td>
</tr>
<tr>
<td>1.19d</td>
<td>1.09-1.30</td>
</tr>
</tbody>
</table>

Abbreviation: CI = confidence interval.

- Odds ratios for both models are from multivariable generalized ordered logistic regression modeling discharge disposition (home, institution [rehabilitation center or skilled nursing facility], or death in hospital), adjusted for age, sex, race/ethnicity, medical comorbidities, statin use before hospitalization, and hospital center by volume. In the standard model, the parallel lines assumption was met for hospital center volume, the polynomial in age, and diabetes mellitus, and these variables were constrained across the 2 levels of the generalized ordered logistic regression model. In the last prior treatment model, the parallel lines assumption was met for inpatient statin use (instrumental variable), statin use before admission, hospital center by volume, the polynomial in age, and diabetes mellitus, and these variables were constrained across the 2 levels of the generalized ordered logistic regression model.

- Standard model — multivariable generalized logistic regression modeling discharge disposition.
- Last prior treatment model — multivariable generalized logistic regression modeling discharge disposition, in which the outcome for a given patient is modeled using the treatment assignment of the last prior patient treated at the same facility, with matching on outpatient statin treatment status.
- d Because the instrumental variable predictor for inpatient statin use was constrained across the 2 levels of the model, the same odds ratio is displayed for both outcome contrasts.

Our study also has limitations. The study was observational, without randomization. Some variables could not be ascertained, such as initial NIH Stroke Scale score and stroke subtype, which are both predictors of stroke outcome. The functional outcome analyzed here, discharge disposition, is a short-term outcome, and we do not have long-term functional outcomes data (although we have presented long-term survival data from this cohort elsewhere). We do not have data on other measures of functional status at discharge, such as the FIM or modified Rankin Scale. While statin use in hospital was confirmed by administration records and we have applied stringent criteria to ensure actively filled outpatient statin prescriptions prior to hospitalization, we do not have measures that ensure compliance with outpatient statin prescription.

Statins are known to reduce the risk of recurrent ischemic stroke after a patient has had an initial stroke, but the timing of when a statin should be started has remained unclear. The data presented here add further evidence to argue that ischemic stroke patients should be treated with a statin at the time of stroke hospitalization, as in-hospital statin use appears to significantly improve not only post-stroke survival but also discharge disposition.

**AUTHOR CONTRIBUTIONS**


**DISCLOSURE**

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received November 18, 2011. Accepted in final form January 23, 2012.

**REFERENCES**


e-Figure: Comparison of Standard Multivariable Model and Last Prior Treatment Analysis (Instrumental Variable Model)

In the standard multivariable model (left), the statin use of an individual patient [Patient N] predicts that same patient’s outcome, after controlling for specific confounders. In the last prior treatment (instrumental variable) model (right), Patient N’s outcome is still modeled after controlling for their confounders, but the predictor variable is the inpatient statin use of the last prior patient [Patient (N-1)] treated at the same facility, with matching for outpatient statin use.