Statin Use During Ischemic Stroke Hospitalization Is Strongly Associated With Improved Poststroke Survival

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Background and Purpose—Statins reduce infarct size in animal models of stroke and have been hypothesized to improve clinical outcomes after ischemic stroke. We examined the relationship between statin use before and during stroke hospitalization and poststroke survival.

Methods—We analyzed records from 12 689 patients admitted with ischemic stroke to any of 17 hospitals in a large integrated healthcare delivery system between January 2000 and December 2007. We used multivariable survival analysis and grouped-treatment analysis, an instrumental variable method that uses treatment differences between facilities to avoid individual patient-level confounding.

Results—Statin use before ischemic stroke hospitalization was associated with improved survival (hazard ratio, 0.85; 95% CI, 0.79–0.93; $P<0.001$), and use before and during hospitalization was associated with better rates of survival (hazard ratio, 0.59; 95% CI, 0.53–0.65; $P<0.001$). Patients taking a statin before their stroke who underwent statin withdrawal in the hospital had a substantially greater risk of death (hazard ratio, 2.5; 95% CI, 2.1–2.9; $P<0.001$). The benefit was greater for high-dose (>60 mg/day) statin use (hazard ratio, 0.43; 95% CI, 0.34–0.53; $P<0.001$) than for lower dose (<60 mg/day) statin use (hazard ratio, 0.60; 95% CI, 0.54–0.67; $P<0.001$; test for trend $P<0.001$), and earlier treatment in-hospital further improved survival. Grouped-treatment analysis showed that the association between statin use and survival cannot be explained by patient-level confounding.

Conclusions—Statin use early in stroke hospitalization is strongly associated with improved poststroke survival, and statin withdrawal in the hospital, even for a brief period, is associated with worsened survival. **(*Stroke*. 2012;43:147-154.)**

Key Words: brain ischemia ■ outcomes ■ statins ■ stroke management ■ survival analysis

Outpatient statin use reduces the risk of having a first or recurrent ischemic stroke.[1–3] Smaller observational studies have suggested that statin use around the time of stroke hospitalization may reduce mortality and improve functional outcomes.[4–7] In one small randomized controlled trial and an observational study, statin withdrawal at the time of ischemic stroke appeared to worsen poststroke outcomes.[8,9] Statins have several mechanisms of action distinct from their lipid-lowering effects that may explain a potentially protective role in the setting of an acute ischemic stroke.[10,11] Thus, statins may have two parallel actions relevant to ischemic stroke; on the one hand, they reduce the risk of a stroke occurring, and on the other, they may improve the outcome after a stroke should one occur. However, the potential association between statin use at the time of stroke and improved poststroke outcomes remains a subject of debate.

As a result, the question of when to start statin therapy for a patient with an acute ischemic stroke remains unanswered. Current guidelines recommend statin therapy for secondary stroke prevention but do not address when statin therapy should be started during hospital care of the patient with acute stroke.[12,13]

Given the uncertainty and clinical implications surrounding this question, we examined the relationship between statin use before and during stroke hospitalization and long-term poststroke survival in a large cohort of patients hospitalized with ischemic stroke in an integrated healthcare delivery system.

Methods

Study Design

We identified all patients admitted to any of 17 hospitals operated by Kaiser Permanente Northern California (KPNC) between January 2000 and December 2007 with a primary discharge diagnosis of ischemic stroke (International Classification of Diseases, 9th Revision, Clinical Modification codes 433.01, 433.11, 433.21, 433.31,

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433.81, 433.91, 434.01, 434.11, 434.91, and 436) and who had neuroimaging performed during hospitalization (CT and/or MRI of the brain). KPNC is a large integrated healthcare delivery system with >3 million members who are similar demographically to the overall population of Northern California.[14] Because of the integrated nature of KPNC, data are available for patient demographics, medical comorbidities, periods of hospitalization, medication prescription details, and outpatient prescription fills. The 17 hospitals in this study are staffed by a single large physician group, The Permanente Medical Group, with a single set of Clinical Practice Guidelines established for the treatment of patients with ischemic stroke. Subjects were included for analysis if they were >50 years of age (to focus on conventional stroke etiologies) and had no prior stroke during the search period (only the first eligible stroke in the search period was observed for each subject). Subjects were excluded if they had not been a member of the KPNC Health Plan for 1 year before the date of ischemic stroke admission, if the stroke occurred at the time the patient was hospitalized for another reason, or if the subject's zip code was outside the area served by KPNC. Subjects were excluded if prestroke outpatient statin use could not be accurately determined according to the specific criteria defined below.

To define prestroke statin use as accurately as possible, statin use was considered positive if the member had (1) an active statin prescription at the time of admission; (2) at least 1 statin prescription filled at a Kaiser pharmacy; and (3) had sufficient supply remaining from the number dispensed to cover the time between the prescription fill and the date of hospital admission. Patients with no statin prescription filled during the year before admission were considered to be statin nonusers. Patients in neither the statin use nor statin nonuse category as defined previously were excluded from analysis. Statin use during hospital admission was determined from inpatient pharmacy databases. Because both outpatient and inpatient prescriptions in the Kaiser Permanente integrated care delivery system are generated and processed within the Kaiser pharmacy computer system, all outpatient and inpatient prescriptions are captured. No data are presented regarding statin treatment after ischemic stroke hospitalization.

Data were collected on date of admission, date of discharge, date of death (if any), demographics (age, gender, and race/ethnicity), medical comorbidities (hypertension, diabetes, atrial fibrillation, congestive heart failure, or coronary artery disease), and history of prior stroke (before the search period of 2000–2007). To validate our principal inclusion criterion of hospitalization for acute ischemic stroke, a nurse analyst manually reviewed the paper and/or electronic medical records of 731 randomly chosen patients (5.8%) and confirmed that all patients in this subsample had a primary diagnosis of ischemic stroke.

Observation for each subject began with the date of admission and continued for 1 year after the admission date. The observation period was truncated when the subject died or was lost to follow-up due to withdrawal from Kaiser Permanente Health Plan membership (plan disenrollment was treated as censoring in survival analysis to ensure 100% capture of all deaths). Six hundred fifty-five cases were censored for disenrollment (5.2%). Information on death occurrence and date of death was obtained from the KPNC membership database and the State of California Death Certificates database linked to the subject according to established methods.[15]

Statin Treatment Definitions and Reference Groups

The following statin treatment definitions and their corresponding reference groups were used: before=statin use before hospitalization for stroke, irrespective of statin use in the hospital (compared with no statin use before hospitalization, irrespective of statin use in the hospital); during=statin use in the hospital, irrespective of statin use before hospitalization (compared with no statin use in the hospital, irrespective of statin use before hospitalization); before & during=statin use both before and during hospitalization (compared with no statin use before and during hospitalization); initiation in hospital=patients not taking a statin before stroke who began treatment with a statin in the hospital (compared with no statin use before and during hospitalization); and withdrawal in hospital=patients who were taking a statin before hospitalization but who did not receive a statin in the hospital (compared with statin use both before and during hospitalization). Note that statin use is compared with the appropriate reference group of nonusers and statin withdrawal is compared with the appropriate group of statin users who were continued on the drug in-hospital (outpatient statin users who did not undergo withdrawal). For analysis of different doses of statin use, the reference group is the appropriate group of statin nonusers. For analysis of timing of statin use in the hospital, the reference group is patients not treated with a statin in the hospital.

Statistical Analysis

General

For univariable analysis, categorical data were analyzed by Fisher exact test and continuous data were compared using Student *t* test. Multivariable methods included Cox proportional hazards models, logistic regression, and grouped-treatment analysis using generalized estimating equations with a logit link for binary outcomes (see subsequently for details of grouped-treatment analysis).[16,17] Unless otherwise specified, all multivariable models included the following variables: age (polynomial in age), gender, race/ethnicity (white non-Hispanic, black, Hispanic, Asian, or other), hospital center, medical comorbidities (presence of hypertension, diabetes, atrial fibrillation, congestive heart failure, or coronary artery disease), and year of hospital discharge. For grouped-treatment analysis, hospital center and statin use were not included (see subsequently for details). To compare survival functions across different levels of statin doses and across different levels for timing of in-hospital statin administration, we used the log-rank test for trend. All reported probability values are for 2-sided tests with a prespecified α of 0.05. Statistical analysis was performed using Stata (Version 10.0; Stata Corporation, College Station, TX).

Grouped-Treatment Analysis

Grouped-treatment analysis is an instrumental variable method[18] that can be used to avoid the influence of individual patient-level confounding such as confounding by indication.[16,17] Instrumental variable techniques center on the use of a predictor variable that cannot mathematically interact with unmeasured confounders at the individual subject level, yet measure the treatment environment of interest. In our grouped-treatment analyses, we calculated the proportion of patients treated with a statin at each hospital and then entered this proportion into a generalized estimating equations multivariable model as a predictor variable without individual patient statin use as a variable in the model. For example, for analysis of statin treatment in-hospital, the proportion treated with a statin in-hospital is determined for each hospital center and this proportion is used as the predictor in the grouped-treatment model. In this fashion, all patients from a given center share the same treatment proportion as a predictor variable, thus eliminating sources of potential confounding that take place at the individual patient level because individual statin use is no longer in the model. At the same time, known potential confounders for individual patients are controlled for in the multivariable model, improving model specification (see Supplemental Figure I; http://stroke.ahajournals.org). For grouped-treatment analyses and their corresponding individual-patient logistic regression analyses, only facilities with ≥100 subjects were included to minimize error in the estimation of the proportion treated according to hospital center; in the statin withdrawal grouped-treatment model, 1 facility with 74 patients was dropped for this reason, but all centers were included in the other 2 grouped-treatment models. Only in-hospital treatment decisions are addressed in the grouped-treatment models (separately examining use in-hospital, initiation in-hospital, and withdrawal in-hospital), because only hospital-level treatments may be analyzed with this technique. The grouped-treatment models are built using generalized estimating equations with a logit link with an outcome of death by 1

Table 1. Patient Characteristics According to Statin Use by Epoch

	Before Hospitalization			During Hospitalization		
	No Statin	Statin	*P*	No Statin	Statin	*P*
No. of patients	8940 (70.5%)	3749 (29.5%)	. . .	6395 (50.4%)	6294 (49.6%)	. . .
No. of patients, lovastatin	. . .	2715 (72.4%)	. . .	. . .	4964 (78.9%)	. . .
No. of patients, simvastatin	. . .	852 (22.7%)	. . .	. . .	1122 (17.8%)	. . .
No. of patients, other statin	. . .	182 (4.9%)	. . .	. . .	208 (3.3%)	. . .
Mean age, y	75.5	73.8	<0.001	76.5	73.5	<0.001
Female	4922 (55.1%)	1808 (48.2%)	<0.001	3595 (56.2%)	3135 (49.8%)	<0.001
Hypertension	6875 (76.9%)	3304 (88.1%)	<0.001	4816 (75.3%)	5363 (85.2%)	<0.001
Diabetes mellitus	2313 (25.9%)	1905 (50.8%)	<0.001	1769 (27.7%)	2449 (38.9%)	<0.001
Atrial fibrillation	2230 (24.9%)	944 (25.2%)	0.788	1771 (27.7%)	1403 (22.3%)	<0.001
Coronary artery disease	1368 (15.3%)	1700 (45.4%)	<0.001	1154 (18.1%)	1914 (30.4%)	<0.001
Congestive heart failure	1448 (16.2%)	919 (24.5%)	<0.001	1179 (18.4%)	1188 (18.9%)	0.538
Prior stroke	739 (8.3%)	390 (10.4%)	<0.001	654 (10.2%)	475 (7.6%)	<0.001

Columns are organized into 2 epochs: before hospitalization for stroke and during hospitalization for stroke, with each epoch divided into nonusers of statins and statin users. Prior stroke indicates history of stroke before the study period (2000–2007). *P* values are for Student *t* test for comparing age between statin nonusers and statin users and for Fisher exact test for comparing all other variables between statin nonusers and statin users.

year and are compared with the corresponding individual patient logistic regression model of death by 1 year.

The Institutional Review Board of the Kaiser Foundation Research Institute approved this study.

Results

Patient Characteristics

Between January 2000 and December 2007, we identified 12 689 subjects meeting inclusion criteria. The median age was 75 years (range, 50–105 years), and 53% were female. The distribution of race/ethnicities was as follows: 62.3% white non-Hispanic, 10.5% black, 10.4% Hispanic, 8.7% Asian, and 8.1% other. Distribution of statin medication use and patient demographics are presented in Table 1. Among patients treated with a statin in hospital, 4388 of 6294 (70%) were treated during the first 24 hours of admission, 1341 of 6294 (21%) were treated during the second 24 hours of admission, and 565 of 6294 (9%) were treated after the first 48 hours of admission. Statins were used by 3749 of 12 689 (30%) before admission; and 468 of 3749 (13%) of these patients were not treated with a statin in-hospital (statin withdrawal). Among the statin nonusers before admission, 3013 of 8940 (34%) had a statin initiated during the hospitalization.

Statin Use Before and During Stroke Hospitalization

Statin use before and during stroke hospitalization was associated with improved survival over the year after stroke onset (Figure 1; Table 2). Because patients were cumulatively exposed to statins across the 2 epochs of interest (before and during stroke hospitalization), there was an increased strength of association with poststroke survival in both univariable and multivariable analysis (Table 2). Similar results were obtained using lovastatin and simvastatin as predictors in separate models (data not shown). All multivariable models were adjusted for age, sex, medical comorbidities, year of discharge, race/ethnicity, and hospital center (see "Methods").

Statin Initiation In-Hospital

To determine whether statin pretreatment is requisite for the association with poststroke survival, we examined the effect of statin initiation in hospital among patients not taking a statin before their stroke (Figure 1C; Table 2). As shown in Table 2, the hazard ratios for the cumulative 1-year risk of death among patients with statin initiation in the hospital (0.55) was similar to that seen for patients taking a statin before and during hospitalization (0.59), suggesting that the association between statin use and poststroke survival is largely explained by use during stroke hospitalization.

Statin Withdrawal

Because previous reports have suggested that statin withdrawal at the time of stroke hospitalization may worsen outcomes,[8,9] we next asked whether subjects who were taking a statin before stroke hospitalization had worsened survival if their statin was discontinued in the hospital (Figure 1D; Table 2). As shown in Table 2, the survival rate was substantially lower among patients who underwent statin withdrawal. Compared with either statin use or statin nonuse, statin withdrawal was associated with a higher mortality rate (Figure 1D; Table 2). In multivariable Cox survival analysis comparing patients who underwent statin withdrawal with patients who did not receive a statin before or during stroke hospitalization, the hazard ratio for death was 1.86 (95% CI, 1.58–2.17; $P<0.001$).

Dose–Response Relationship

If a causal relationship indeed exists between statin use and poststroke survival, a dose–response relationship may be expected. We therefore examined whether higher statin doses are associated with better poststroke survival (Figure 2). For statin use before stroke hospitalization, Cox regression anal-

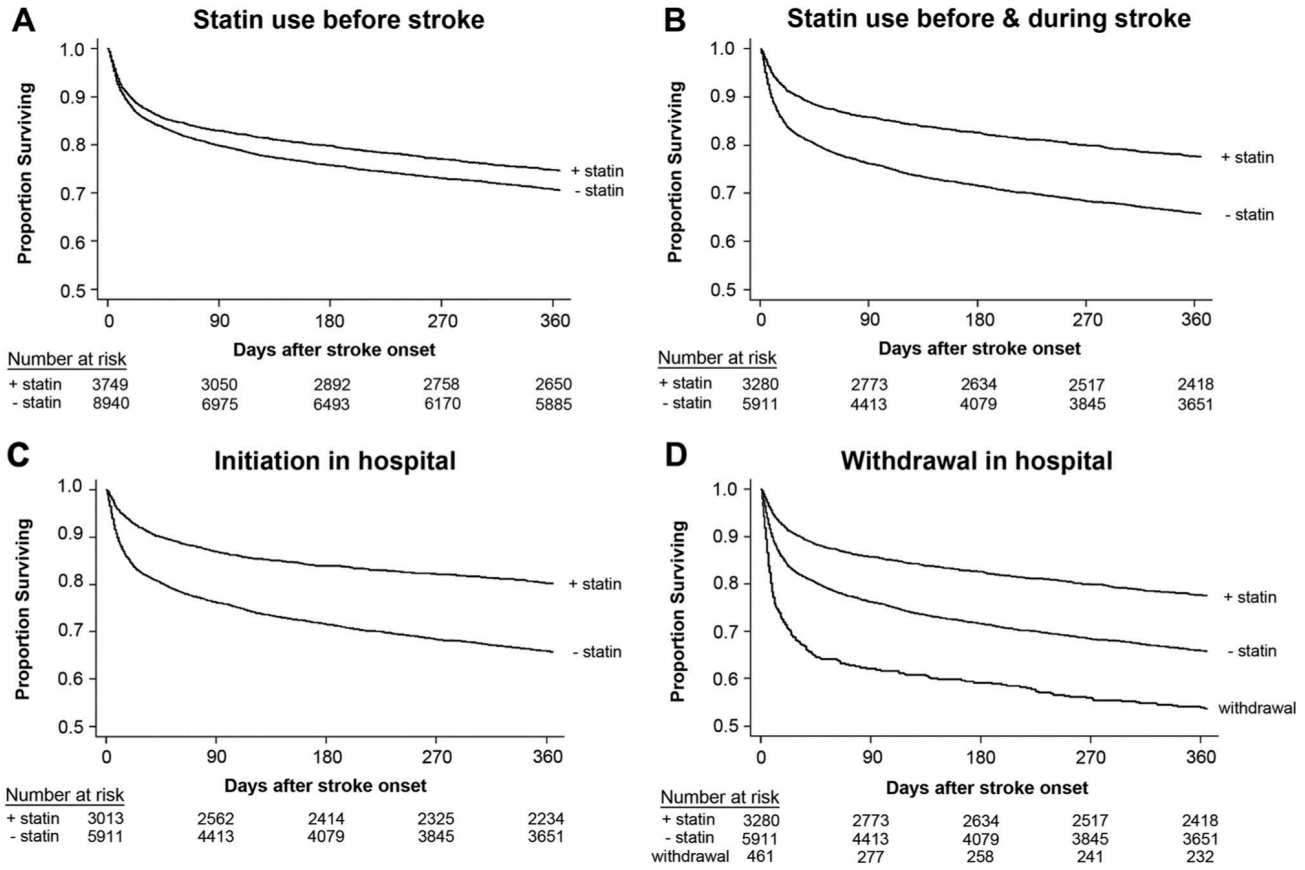

Figure 1. Statin use before and during stroke hospitalization is associated with improved poststroke survival. **A**, One-year Kaplan-Meier survival curves for statin users before hospitalization (+ statin) and for statin nonusers before hospitalization (− statin). **B**, Survival curves for statin users before and during hospitalization (+ statin) and for statin nonusers before and during hospitalization (− statin). **C**, Survival curves for patients not on a statin before stroke hospitalization but initiated on statin therapy in hospital (+ statin) and for statin nonusers before and during hospitalization (− statin). **D**, Survival curves for statin users before and during hospitalization (+ statin), for statin nonusers before and during hospitalization (− statin), and for patients who were taking a statin before stroke hospitalization but did not receive a statin in hospital (withdrawal).

ysis modeling cumulative hazard of death over 1 year poststroke yielded a hazard ratio of 0.89 (95% CI, 0.82–0.97; $P=0.01$) for low to moderate statin dose (<60 mg/day) and a hazard ratio of 0.65 (95% CI, 0.54–0.79; $P<0.001$) for high statin dose (≥60 mg/day) as compared with no statin use after controlling for potential confounders ($P<0.001$, log-rank test for trend). For statin use before and during stroke hospitalization, the hazard ratios were 0.60 (95% CI, 0.54–0.67; $P<0.001$) for low- to moderate-dose statin use and 0.43 (95% CI, 0.34–0.53; $P<0.001$) for high-dose statin use ($P<0.001$, log-rank test for trend). Hazard ratios in both models at each level of statin use are with reference to no statin use. To

Table 2. Raw Mortality Rates and Adjusted Cox Regression Analysis of Statin Use and Poststroke Survival

Model	1-Y Mortality, No Statin	1-Y Mortality, Statin	*P*	Hazard Ratio for Death	95% CI	*P*
Before	28.9%	25.1%	<0.001	0.85	0.79–0.93	<0.001
Before and during	33.8%	22.1%	<0.001	0.59	0.53–0.65	<0.001
Initiation in the hospital	33.8%	19.4%	<0.001	0.55	0.50–0.61	<0.001
Withdrawal in the hospital	46.2%	22.1%	<0.001	2.5	2.1–2.9	<0.001

Before indicates statin use before hospitalization for stroke, irrespective of statin use in the hospital (compared with no statin use before hospitalization, irrespective of statin use in the hospital); Before and during, statin use both before and during hospitalization (compared with no statin use before and during hospitalization); Initiation in the hospital, patients not taking a statin before stroke who began treatment with a statin in the hospital (compared with no statin use before and during hospitalization); Withdrawal in the hospital, patients who were taking a statin before hospitalization but who did not receive a statin in the hospital (compared with statin use both before and during hospitalization).

Percentages for 1 y mortality are unadjusted; *P* values for unadjusted mortality calculated from Fisher exact test. Hazard ratios represent cumulative 1 y hazard of death from multivariable Cox regression analysis adjusted for age, sex, medical comorbidities, race/ethnicity, year of discharge, and hospital center.

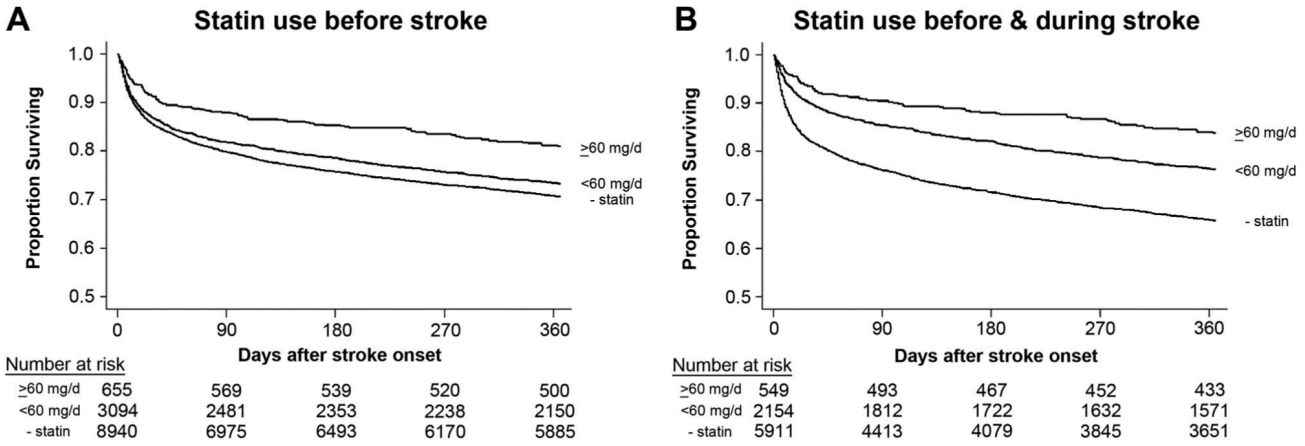

Figure 2. Higher doses of statins are associated with greater poststroke survival. **A**, One-year Kaplan-Meier survival curves for high-dose statin users before hospitalization (≥60 mg/day), for low- to medium-dose statin users before hospitalization (<60 mg/day), and for statin nonusers before hospitalization (− statin). **B**, Survival curves for the same 3 levels of statin use before and during hospitalization.

control for differences in statin potency, we performed additional survival analyses and Cox regression using patients on lovastatin and simvastatin (95.1% of the cohort) after adjustment for the approximately 2-fold difference in lipid-lowering potency between these 2 statins.[19] In the potency-adjusted analyses, the hazard ratios for statin use before hospitalization were 0.75 (95% CI, 0.68–0.83; $P<0.001$) for low to moderate statin dose and 0.69 (95% CI, 0.59–0.80; $P<0.001$) for high statin dose, and the hazard ratios for statin use before and during hospitalization were 0.60 (95% CI, 0.53–0.67; $P<0.001$) for low to moderate statin dose and 0.43 (95% CI, 0.31–0.59; $P<0.001$) for high statin dose ($P<0.001$, log-rank test for trend for both models). Similar and statistically significant results were obtained when lovastatin and simvastatin dose–response analyses were performed separately (data not shown). We do not present the relationship between the 2 dose levels examined and other treatment paradigms (eg, statin withdrawal) because the sample size is inadequate to do so.

Timing of Statin Administration In-Hospital

Because the results described previously show that statin administration in hospital (or statin withdrawal in the hospital) is strongly associated with poststroke outcome, we next examined whether the day-by-day timing of statin administration (or withdrawal) in the hospital influences poststroke survival. Survival curves showed that earlier treatment with a statin in-hospital was associated with improved poststroke survival both among patients not treated with a statin as an outpatient before their stroke (Figure 3A) and among those taking a statin as an outpatient before their stroke (Figure 3B). Similar results were obtained from multivariable Cox regression modeling survival after controlling for potential confounders (Figure 3C–D). A difference in hazard ratios (with reference to statin nonusers) was seen for increasing delay of statin initiation in hospital: there was a hazard ratio of 0.51 (95% CI, 0.45–0.58) for patients initiated on Day 1, a hazard ratio of 0.57 (95% CI, 0.48–0.67) for patients initiated on Day 2, and a hazard ratio of 0.68 (95% CI, 0.56–0.84) for patients initiated on Day 3 or later ($P<0.001$ for log-rank test for trend). The difference in hazard ratios was particularly marked in the analysis of brief periods of statin withdrawal; there was a hazard ratio of 0.38 (95% CI, 0.32–0.45; $P<0.001$) for patients continued on statin treatment on hospital Day 1, a hazard ratio of 0.43 (95% CI, 0.34–0.53; $P<0.001$) for patients restarted on hospital Day 2, and a hazard ratio of 0.66 (95% CI, 0.47–0.94; $P<0.019$) for patients restarted on hospital Day 3 or later ($P<0.001$ for log-rank test for trend).

Control for Severity

To control for the possibility that severity of illness might confound the relationship between statin use and survival, we next added multiple measures of severity to each of the models presented previously. Addition of intubation, mechanical ventilation, or tracheostomy (entered as an aggregate variable), gastrostomy tube placement, and hospital-acquired pneumonia to all of the multivariable Cox regression models described previously had no impact on the hazard ratios for poststroke mortality (Supplemental Table I).

Control for Patient-Level Confounding: Grouped-Treatment Analysis

To further control for individual-subject confounding, we used the technique of grouped-treatment analysis to move the level of analysis to the treating hospital center.[16,17] In grouped-treatment analysis, variation in unmeasured individual patient factors cannot influence the relationship between statin use and outcome because individual-subject statin use is not present in the models (see Supplemental Figure I); instead, the predictor variable (the instrumental variable) is the proportion of patients treated with a statin at each hospital center. Across the 17 hospitals in our study, we observed variation from hospital to hospital in the use of statins in-hospital; the median center prescribed a statin to 50.3% of stroke inpatients, and a range of inpatient statin prescription was observed (lowest center, 37%; highest center,72.5%; SD, 10.3%). Table 3 shows the results of individual patient-level logistic regression analysis in comparison with hospital-level grouped-treatment analysis for statin treatment during hospi-

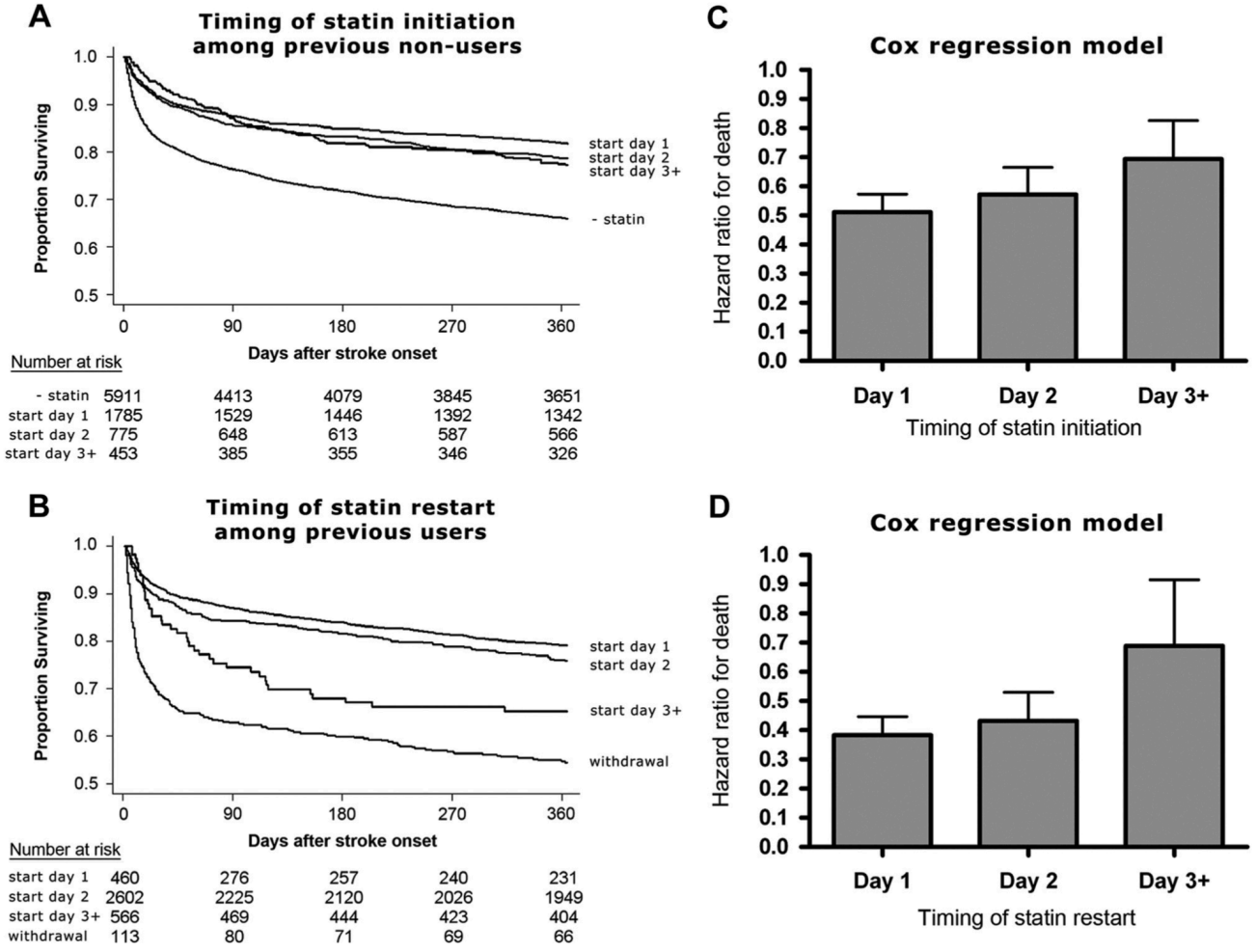

Figure 3. Statin administration early in stroke hospitalization is associated with greater poststroke survival. **A**, One-year Kaplan-Meier survival curves for patients not taking a statin before stroke hospitalization. Survival curves based on in-hospital statin initiation are as follows: −statin=not treated with a statin; start day 1=statin started Day 1; start day 2=statin started Day 2; and start day 3+=statin started Day 3 or later. **B**, One-year Kaplan-Meier survival curves for patients who were taking a statin befire stroke hospitalization. Survival curves based on in-hospital statin resumption are as follows: withdrawal=not treated with a statin in-hospital; start day 1=statin started Day 1; start day 2=statin started Day 2; and start day 3+=statin started Day 3 or later. **C**, Increasing hazard of death with delayed in-hospital statin treatment among patients not taking a statin before stroke hospitalization. Hazard ratios from multivariable Cox regression are with reference to the hazard of death among patients not treated with a statin (hazard ratio [HR], 1.0). Error bars indicate upper limit of 95% CI ($P<0.001$ for each, $P<0.001$ for log-rank test for trend). **D**, Increasing hazard of death with delayed in-hospital statin treatment among patients who were taking a statin before stroke hospitalization. HRs from multivariable Cox regression are with reference to the hazard of death among patients not treated with a statin (HR, 1.0; $P<0.001$ for Day 1 and Day 2, $P=0.019$ for Day 3+, $P<0.001$ for log-rank test for trend).

talization, statin initiation in-hospital, and statin withdrawal. Hospital-level grouped-treatment analysis confirmed the primary analysis in each case, demonstrating that the relationship between statin use and improved poststroke survival cannot be explained by confounding at the individual patient level. In the case of the statin withdrawal grouped-treatment model, the CIs become quite broad when compared with the individual patient model. Although confounding cannot entirely explain the withdrawal results, this observation suggests that some degree of confounding is likely present in the individual patient statin withdrawal models.

Discussion

We found that statin use before and during stroke hospitalization is associated with improved poststroke survival and that statin withdrawal in the hospital is associated with worsened poststroke survival. The highest survival rates were associated with earlier statin treatment in-hospital and higher doses. The worst survival rates were observed among outpatient statin users who underwent statin withdrawal in the hospital, even for a brief period. Grouped-treatment analysis showed that our results cannot be explained by confounding at the individual patient level.

Our findings are consistent with smaller clinical studies. Statin use before ischemic stroke onset has been associated with reduced stroke severity,[20] improved long-term functional outcome,[5] and lower poststroke mortality.[4,21] Statin treatment after discharge from hospitalization for ischemic stroke has been associated with reduced 10-year mortality.[7] In secondary analysis of data from the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, a randomized trial of high-dose atorvastatin in secondary

Table 3. Adjusted Logistic Regression Analysis and Grouped-Treatment Analysis for Hospital-Based Statin Treatments Modeling Death by 1 Year Poststroke

	Individual Patient Model (Logistic Regression)			Grouped Treatment Model (Generalized Estimating Equations)		
Model	OR for Death	95% CI	*P*	OR for Death	95% CI	*P*
During	0.48	0.43–0.53	<0.001	0.37	0.23–0.60	<0.001
Initiation in the hospital	0.49	0.43–0.56	<0.001	0.42	0.25–0.68	<0.001
Withdrawal in the hospital	3.1	2.4–3.8	<0.001	10.0	1.4–72.1	0.02

During indicates statin use in the hospital, irrespective of statin use before hospitalization (compared with no statin use in the hospital, irrespective of statin use before hospitalization); Initiation in the hospital, patients not taking a statin before stroke who began treatment with a statin in the hospital (compared with no statin use before and during hospitalization); Withdrawal in the hospital, patients who were taking a statin before hospitalization but who did not receive a statin in the hospital (compared with statin use both before and during hospitalization).

ORs for individual subject analyses are from multivariable logistic regression modeling death by 1 y adjusted for age, sex, medical comorbidities, race/ethnicity, year of discharge, and hospital center. ORs for grouped treatment analysis are from generalized estimating equations analysis modeling death by 1 y with a logit link function adjusted for age, sex, medical comorbidities, race/ethnicity, and year of discharge.

stroke prevention, a trend toward improved functional outcomes across the range of the outcome scale (including mortality) was observed.[22]

Our findings are also consistent with laboratory data addressing the effects of statins in acute ischemic stroke. In addition to their lipid-lowering actions, statins have several additional biochemical effects that are collectively referred to as "pleiotropic actions."[10,23,24] The pleiotropic actions of statins may be particularly important in stroke, because the effects of statins on ischemic stroke prevention appear to occur independent of cholesterol level before statin initiation,[25] and cholesterol levels are not a significant risk factor for ischemic stroke.[26,27] In animal models of ischemic stroke, statin pretreatment reduces stroke severity, but statin withdrawal abrogates this effect.[28] Because statins have effects on several biochemical pathways of relevance to the ischemic neurovascular unit,[29,30] statins may have a neuroprotective effect during the acute phase of hospitalization for ischemic stroke.[11,23]

Several aspects of our study support a potential causal relationship between statin use and poststroke survival. First, we removed the risk of an important source of bias in observational studies of drug effects, individual patient-level confounding, by using the technique of grouped-treatment analysis to move the level of analysis away from the individual patient. Second, we controlled for the possibility of confounding by severity, which did not alter the association between statin use and survival. Third, dose–response effects were observed in our study in 2 ways: higher daily doses of statin use and increasing exposure to a statin across time (before and during stroke hospitalization) were each associated with improved survival. Fourth, we found that pretreatment with a statin (use of a statin as an outpatient before the stroke) was associated with improved outcome, an association that cannot be explained by differences in individual patient factors related to the stroke. Fifth, we found reduced survival among patients who underwent statin withdrawal. Lastly, we found that initiation of statins early in hospitalization was associated with improved survival and that statin withdrawal early in the hospital, even for a brief period, was associated with worsened survival.

Our study also has limitations. It was observational in design without randomization. To avoid bias in outcome assessment, we used the outcome of all-cause mortality and therefore we do not present information that might speak to a possible mechanism of statin use in this setting (eg, a selective association with specific causes of death). Some variables of interest could not be ascertained. For example, we do not have data on initial National Institutes of Health Stroke Scale, which also might help clarify the mechanisms by which statin use influences survival. We also do not have data on long-term outcomes other than mortality such as a functional outcome scale. The exclusive outcome of mortality presented here raises the possibility that statin use might have prolonged life without improving function or quality of life in some patients. Although grouped-treatment analysis confirmed our primary findings, it should be noted that for the statin withdrawal grouped-treatment model, the CIs are much broader than those for the individual patient model, suggesting that indeed some individual patient confounding is taking place in the individual patient model for statin withdrawal. This is consistent with the notion that confounding by indication may be a particular problem in analyzing medication withdrawal, because medication withdrawal may take place in the context of limitation of care.

Based on the SPARCL trial,[3] statins are recommended for secondary stroke prevention.[12,31] However, current guidelines for acute care of the ischemic stroke patient do not address statin use in the hospital setting,[13] and Joint Commission guidelines in the United States assess hospital rates of statin use in patients with stroke only at the time of hospital discharge.[32] Because we found a strong association between early hospital statin use and long-term survival, it seems clinically prudent to treat patients with ischemic stroke with a statin from the beginning of stroke hospitalization. Given the association between statin withdrawal and worsened survival, care should be taken to avoid interruption of statin therapy among patients taking a statin before hospitalization.

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Disclosures

None.

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