

# Impact of Increased Early Statin Administration on Ischemic Stroke Outcomes: A Multicenter Electronic Medical Record Intervention

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**Background**—Statin administration early in ischemic stroke may influence outcomes. Our aim was to determine the clinical impact of increasing statin administration early in ischemic stroke hospitalization.

**Methods and Results**—This is a retrospective analysis of a multicenter electronic medical record (EMR) intervention to increase early statin administration in ischemic stroke across all 20 hospitals of an integrated healthcare delivery system. A stroke EMR order set was modified from an “opt-in” to “opt-out” mode of statin ordering. Outcomes were mortality by 90 days, discharge disposition, and increase in stroke severity. We examined the relationship between intervention and outcome using autoregressive integrated moving average (ARIMA) time-series modeling. The EMR intervention increased both overall in-hospital statin administration (from 87.2% to 90.7%,  $P < 0.001$ ) and early statin administration (from 16.9% to 26.3%,  $P < 0.001$ ). ARIMA models showed a small increase in the rate of survival (difference in probability [ $P_{diff}$ ]=0.02,  $P = 0.016$ ) and discharge to home or rehabilitation facility ( $P_{diff} = 0.04$ ,  $P = 0.034$ ) associated with the intervention. The increase in statin administration  $< 8$  hours was associated with much larger increases in survival ( $P_{diff} = 0.17$ ,  $P = 0.033$ ) and rate of discharge to home or rehabilitation ( $P_{diff} = 0.29$ ,  $P = 0.011$ ), as well as a decreased rate of neurological deterioration in-hospital ( $P_{diff} = -0.14$ ,  $P = 0.026$ ).

**Conclusions**—A simple EMR change increased early statin administration in ischemic stroke and was associated with improved clinical outcomes. This is, to our knowledge, the first EMR intervention study to show that a modification of an electronic order set resulted in improved clinical outcomes. (*J Am Heart Assoc.* 2016;5:e003413 doi: 10.1161/JAHA.116.003413)

**Key Words:** electronic medical record intervention • ischemic stroke • order sets • outcome • statin intervention

Statins (HMG Co-A reductase inhibitors) reduce the risk of recurrent ischemic stroke,<sup>1</sup> and American Heart Association/American Stroke Association guidelines support the use of statins in this context.<sup>2</sup> However, it remains unclear when statins should be started in the wake of an ischemic stroke.

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Administration of statins during hospitalization for ischemic stroke is strongly associated with improved ischemic stroke outcomes, particularly when statins are administered early during stroke hospitalization.<sup>3,4</sup> In addition, statin withdrawal (discontinuation of a statin during stroke hospitalization among patients previously taking a statin prior to the stroke) is strongly associated with worsened stroke outcomes.<sup>3–5</sup>

Given the established role for statins in secondary stroke prevention<sup>1,2</sup> and the data supporting commencement or continuation of statins early in stroke hospitalization,<sup>3–5</sup> our institution, a large multicenter integrated healthcare delivery system,<sup>6</sup> deployed an electronic medical record (EMR) intervention designed to increase early statin administration during ischemic stroke hospitalization.

The EMR intervention consisted of a change to an already existing statin ordering section in an ischemic stroke admission order set; after the change was introduced, the statin ordering section had to be addressed before electronically signing the order set as a whole. This change represented a shift from an “opt-in” mode of statin ordering

(in which the practitioner was presented with an optional statin ordering section) to an “opt-out” mode of statin ordering (in which the practitioner was required to either order a statin or document why no statin was ordered).

Here we present the impact of this multicenter EMR intervention on poststroke clinical outcomes.

## Methods

### Data Source and Subjects

The Systematic use of Statins in Stroke (S3) study is a retrospective analysis of a change to a multicenter EMR that was introduced with the intention of increasing early statin administration during hospital admission for acute ischemic stroke.

The EMR (Epic Systems, Verona, WI) is deployed across all 20 hospitals in Kaiser Permanente Northern California, an integrated healthcare delivery system with >3 million members who are demographically representative of the overall population of Northern California.<sup>6</sup> Over a 51-month period from July 2009 to September 2013, flanking the time of an intervention in September 2011 that changed the mode of inpatient statin ordering from “opt-in” to “opt-out” (see below), we identified all patients admitted to any of 20 hospitals in Kaiser Permanente Northern California who had (1) a primary discharge diagnosis of ischemic stroke (International Classification of Diseases, 9th Revision, Clinical Modification codes 433.01, 433.11, 433.21, 433.31, 433.81, 422.91, 434.01, 434.91, and 436), (2) who received neuroimaging performed during the hospitalization (computed tomography and/or magnetic resonance imaging of the brain), and (3) who received at least 1 documented assessment of stroke severity on the modified National Institutes of Health Stroke Scale (mNIHSS) within 24 hours of arrival.<sup>7</sup> Subjects were included if they were 18 years of age or older at the time of the stroke and had a mNIHSS of 1 or higher within 24 hours of arrival. Subjects were excluded if an order for comfort care was entered within the first 24 hours of admission or if the patient had been discharged from a previous stroke admission within 2 days of the present admission.

### Intervention

A simple change was introduced into the EMR order set for ischemic stroke that altered the existing section for statin prescription in a subtle but important way. In the “opt-in” period before the change was made, a section for statin prescription was available that included an option for high-dose statin prescription, but this statin section was not *required*—it was possible for the clinician to sign the order set without selecting

1 of the options in the statin section, and in this scenario, no statin would be prescribed at the time of admission. The introduced change switched the statin ordering mode to “opt-out” by *making the statin section a mandatory requirement*: the clinician must address the statin section (by ordering a statin or documenting why no statin is being ordered) in order to sign the order set. Options for statin prescription across the 2 time periods included high-dose simvastatin (80 mg/day) and high-dose atorvastatin (80 mg/day). After the Food and Drug Administration release of a “black box” warning regarding side effects of the 80-mg dose of simvastatin, this option was removed from the order set options.

The order set modification was made without any specific communication regarding the change to the hundreds of physicians caring for stroke patients across the 20-hospital integrated healthcare delivery system. The presentation of the new order set was not randomized, and the change was made across all 20 hospitals simultaneously. No other changes were made to the order set or other aspects of regional stroke care around the time of the statin order set change, and there were no organized educational activities regarding statin use and stroke during the study time frame that might confound the statin/outcome relationship. All 20 hospitals had 24-hour Emergency Room physician staffing and 24-hour intravenous thrombolysis capability for the full period of the study. The time window for the cohort under study was prior to the presentation or publication of any of the recent randomized controlled trials supporting endovascular stroke treatment, so use of endovascular stroke treatment in this cohort was very uncommon.

### Measurements

Detailed data were available from the EMR and other institutional databases on patient demographics, medical comorbidities (including the components of the Charlson comorbidity score), serial assessments of stroke severity on the mNIHSS, medication prescription and barcode-verified medication administration (including timestamp and route information), dysphagia, use of feeding tubes, code status, comfort care orders, mortality, and discharge disposition. Initial mNIHSS was defined as the maximum mNIHSS recorded in the first 24 hours after initial presentation. Clinical outcome measures were 90-day mortality, discharge disposition (to home or rehabilitation facility versus skilled nursing facility or death in-hospital), and neurological deterioration (an increase of 4 or more points in the mNIHSS from the initial mNIHSS at any point during hospitalization). All included subjects had serial documentation of the mNIHSS according to a standardized regional protocol (across all hospitals), so all subjects in the cohort had multiple mNIHSS measurements available to determine change in mNIHSS.

Information on death was determined from Kaiser Permanente Northern California database information supplemented by California Death Certificates database information linked probabilistically to the subject based on the subject's name, birth date, social security number, sex, and residence.<sup>3</sup> We examined administration of inpatient statins (defined as administration at any time during the inpatient stay) and early administration of inpatient statins (defined as administration within 8 hours of ER triage time).

## Statistical Analysis

For multivariable time-series analysis, we employed autoregressive integrated moving average (ARIMA) modeling (ARMA model subclass) using standard techniques for evaluating interrupted time series<sup>8</sup> to examine the impact of the change made at the switch from opt-in to opt-out statin ordering modes. ARIMA is a well-established multivariable modeling strategy for time series data that has some powerful advantages. Because the relationship between predictor and outcome is analyzed in a month-by-month aggregate fashion, the technique controls for potential confounding at the individual patient level. In addition, the ability to control for trends over time also controls for confounding by broader secular trends at the population level.

We used transfer function models both to estimate the impact of the protocol change, and to estimate the impact of changes in statin provision on clinical outcomes, while avoiding the selection by indication effects that affect individual subject-level models. As required in order to achieve stationarity, we included moving average factors in the models. There were no autoregressive errors. In each case, we initially checked for evidence of a secular trend during the opt-in period (before the new protocol was introduced) or a possibly distinct trend during the opt-out period (after the new protocol was introduced). Within the group of models that resulted in adequate fit as indicated by the absence of autocorrelation within the residuals, we used graphical methods to determine whether the error distribution was roughly normal. Moving average terms were included where doing so helped normalize the error distribution, even if the resulting model did not fit better than one without the moving average term (as indicated by the corrected Akaike Information Criteria): otherwise we used Akaike Information Criteria to select the most parsimonious model. ARIMA models were set up to model the difference in probability ( $P_{diff}$ ) between the opt-in and opt-out periods, such that  $P_{diff} = (\text{probability of outcome in opt-out period}) - (\text{probability of outcome in opt-in period})$ .

To explore the relationship between time of statin administration and clinical outcomes, we used multivariable logistic regression with postestimation determination of marginal means with covariates held at their mean values.<sup>9</sup> Bivariate

analyses comparing subjects in the opt-in and opt-out period were performed with the Fisher's exact test for categorical variables and the nonparametric Kruskal–Wallis equality-of-populations rank test for continuous data.

Statistical analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC) and Stata/MP version 12.1 (StataCorp, College Station, TX).

This study was approved by the Institutional Review Board of the Kaiser Foundation Research Institute with a waiver of the requirement for informed consent.

## Results

### Patient Characteristics

A total of 6 131 ischemic stroke hospitalizations were identified during the 51-month study period across 20 hospitals (2859 patients in the 26-month opt-in [before] period, and 3272 patients in the 25-month opt-out [after] period flanking the introduction of the order set change). Baseline patient characteristics are displayed according to opt-in versus opt-out periods in Table 1. The baseline characteristics were generally similar in the 2 periods, with the exception of initial mNIHSS and Charlson comorbidity index, which were both higher in the opt-out period, indicating slightly higher stroke severity and comorbidity burden in this period (Table 1).

### Impact of the Order Set Change on In-Hospital Statin Administration

The rate of inpatient statin administration at any time during ischemic stroke hospitalization was already high in the opt-in period (87.2%), but it increased a small amount in the opt-out period (90.7%) ( $P < 0.001$ ). Month-by-month statin administration rates are presented in Figure 1A.

As the change in statin ordering mode (opt-in to opt-out) was introduced to an electronic order set used to admit patients from the emergency room to the hospital, a particular effect on early statin administration might be expected. Consistent with this expectation, bar-coded statin administration within 8 hours of initial emergency room triage time increased from 16.9% in the opt-in period to 26.3% in the opt-out period, a relative increase of 56% ( $P < 0.001$ ). Month-by-month rates of statin administration within 8 hours of emergency room triage are shown in Figure 1B.

### Impact of the Order Set Change on Clinical Outcomes

When the impact of the overall change to opt-out statin ordering mode was examined in ARIMA time series models, a small but significant increase in the rate of survival was

**Table 1.** Baseline Patient Characteristics According to Study Period

	Opt-in Period [Before] (n=2859)	Opt-Out Period [After] (n=3272)	All Subjects (n=6131)	P Value
Age, y	74.1±13.0	74.3±13.3	74.2±13.2	0.37
Female	1537 (53.8%)	1753 (53.6%)	3290 (53.7%)	0.90
Initial mNIHSS	4 (2–8)	4 (2–9)	4 (2–9)	0.005
HTN	2433 (85.1%)	2782 (85.0%)	5215 (85.1%)	0.94
DM	890 (31.1%)	1010 (30.9%)	1900 (31.0%)	0.83
AFib	946 (33.1%)	1113 (34.0%)	2059 (33.6%)	0.45
CAD	825 (28.9%)	919 (28.1%)	1744 (28.5%)	0.51
CHF	710 (24.8%)	812 (24.8%)	1522 (24.8%)	0.99
Charlson index	2 (0–4)	2 (1–4)	2 (0–4)	0.001
Prior outpatient statin use	1226 (42.9%)	1424 (43.5%)	2650 (43.2%)	0.62

Age is presented as mean±SD, and mNIHSS and Charlson index are presented as median (interquartile range), with comparisons of these continuous/ordinal measures between the opt-in and opt-out groups made with the nonparametric Kruskal–Wallis equality-of-populations rank test. Dichotomous measures are presented as number (percentage), with comparisons between the groups made with Fisher's exact test. Opt-in period=26-month "before" period during which the statin section of the stroke order set was available not required; Opt-out period=25-month "after" period during which the statin section of the stroke order set was a required element; All subjects=all ischemic stroke admissions across the overall 51-month period. *P* value=significance level for the difference between the distribution of the patient characteristics in the Opt-in period and Opt-out period. *P* values as displayed are from the nonparametric Kruskal–Wallis test for continuous data and Fisher's exact test for categorical data. AFib indicates atrial fibrillation; CAD, history coronary artery disease; Charlson index, Charlson 1-year comorbidity index; CHF, congestive heart failure; DM, diabetes mellitus; HTN, hypertension; Initial mNIHSS, maximum modified National Institutes of Health Stroke Scale score in the first 24 hours; Prior outpatient statin use, active prescription for statin as outpatient at time of admission for ischemic stroke.

observed (difference in probability [ $P_{diff}$ ]=0.02, 95% CI 0.002–0.03,  $P=0.016$ , Figure 2A). Similarly, the change to opt-out statin ordering mode was also associated with an increased rate of discharge to home or rehabilitation facility within 7 days ( $P_{diff}=0.04$ , 95% CI 0.007–0.06,  $P=0.034$ , Figure 2A). The probability of in-hospital neurological deterioration was slightly lower in the opt-out statin ordering period ( $P_{diff}=-0.02$ , 95% CI -0.03 to 0.0,  $P=0.051$ , Figure 2A). In unadjusted assessment of outcomes at the individual patient level comparing the opt-in and opt-out periods, similarly small differences were observed: percentage alive at 90 days increased from 88.4% to 88.9%, discharge to home or rehabilitation increased from 60.7% to 61.2%, and in-hospital neurological worsening decreased from 6.8% to 5.9%.

### Impact of the Increase in Early Statin Administration on Clinical Outcomes

In ARIMA time series models, the increase in statin administration within 8 hours in the opt-out period was associated with larger increases in the probability of survival ( $P_{diff}=0.17$ , 95% CI 0.02–0.31,  $P=0.033$ ) and the probability of discharge to home or rehabilitation ( $P_{diff}=0.29$ , 95% CI 0.08–0.51,  $P=0.011$ ), as well as a decreased probability of in-hospital neurological deterioration ( $P_{diff}=-0.14$ , 95% CI -0.02 to -0.26,  $P=0.026$ ) (Figure 2B). In unadjusted assessment of outcomes at the individual patient level comparing statin administration within 8 hours versus later or no statin administration, similar magnitude differences were observed: percentage alive at 90 days increased from 87.2% to 94.1%,

discharge to home or rehabilitation increased from 57.8% to 72.1%, and in-hospital neurological worsening decreased from 6.9% to 4.2%.

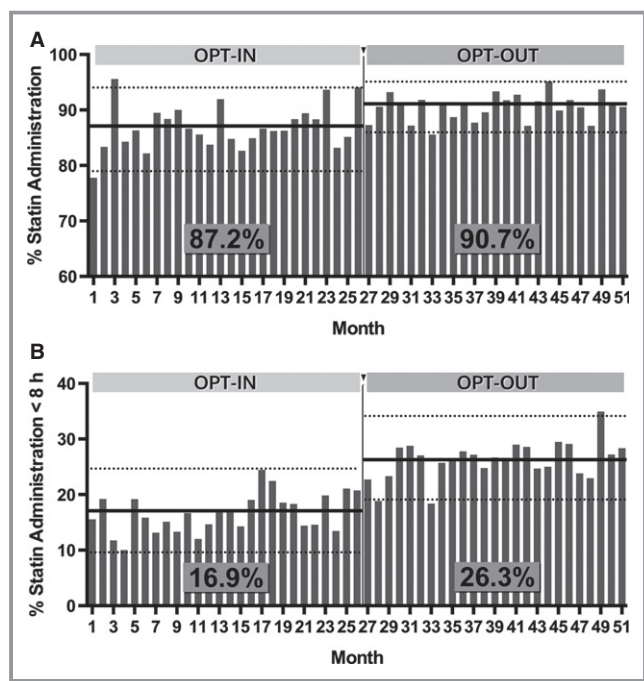
### Hourly Timing of Statin Administration and Clinical Outcomes

Given that early statin administration was increased by the order set intervention and was strongly associated with improved clinical outcomes, one might expect that the hourly timing of statin administration, treated as a continuous predictor, would be associated with clinical outcomes. In logistic regression models of each of our 3 clinical outcomes, shorter time to first statin dose strongly predicted better outcomes, after controlling for age, stroke severity, tissue plasminogen activator administration, comorbidities, and dysphagia (Tables 2 and 3). Figure 3 graphically displays the relationship between hours to first statin dose administered and outcomes as estimated from multivariable models.

### Discussion

We show here that a simple intervention that changed the statin ordering section of an ischemic stroke EMR order set was associated with increased early statin administration and improved clinical outcomes.

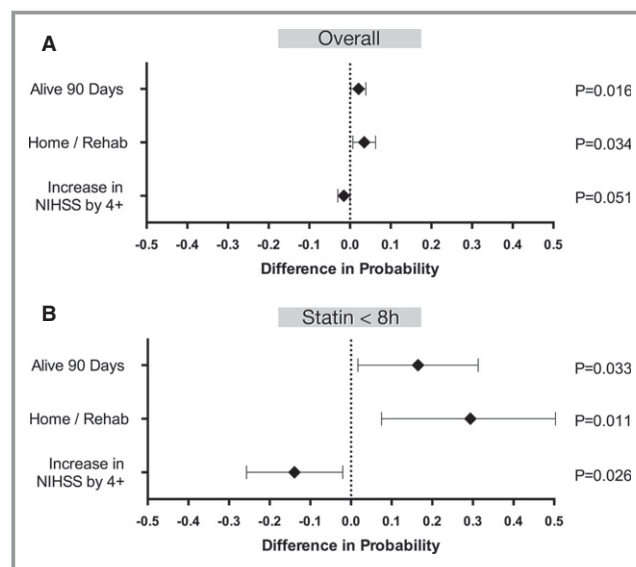
Our results build on prior studies supporting an acute beneficial impact of statins in patients with vascular disease. Laboratory investigations have shown that cessation of statin



**Figure 1.** Month-by-month statin administration according to study period. For both panels, the first 26 months represent the “before” period with an *opt-in* ordering mode for statin prescription, and the second 25 months represent the “after” period with an *opt-out* ordering mode for statin prescription. Arrowhead and solid black vertical line indicate timing of transition from *opt-in* to *opt-out* ordering mode. Solid black horizontal line represents the mean, and dotted black horizontal lines represent the bounds for  $\pm 2$  SD of the mean. A, Percentage of patients in each month (vertical gray bars) administered a statin at any time during hospitalization. B, Percentage of patients in each month (vertical gray bars) administered a statin within 8 hours of ER triage time.

therapy results in rapid worsening of inflammatory parameters such as C-reactive protein<sup>10–12</sup> as well as endothelial function.<sup>13,14</sup> Exposure to statins in the acute phase of experimental stroke appears to promote angiogenesis and synaptogenesis,<sup>15</sup> and additional pleiotropic statin effects such as vasodilatory and antithrombotic properties have been reported.<sup>16</sup> These experimental observations are supported by clinical findings of improved outcomes with acute statin use in myocardial infarction,<sup>17–19</sup> stroke,<sup>3,4,20,21</sup> and major vascular surgery.<sup>22,23</sup>

This is, to our knowledge, the first report of an EMR intervention in which a modification was made to an electronic order set that not only altered prescribing practices but also was associated with improved clinical outcomes. One prior study found that a combination of provider education and a change to an electronic order set increased vitamin D supplementation in hospitalized infants, but this study did not examine the impact on clinical outcomes.<sup>24</sup> Another study showed that targeted order set design changes increased compliance with specific management elements in the care of



**Figure 2.** ARIMA time series models relating the order set change to clinical outcomes. For both panels, the difference in probability ( $P_{diff}$ ) for each outcome is plotted along the X axis, with a solid symbol representing the point estimate for  $P_{diff}$ , and horizontal error bars representing the 95% CI of the estimate. Three separate models are presented in each panel, modeling the outcomes of alive at 90 days poststroke, discharge to home or inpatient rehabilitation center, and neurological deterioration (increase in mNIHSS by 4 or more points). A, ARIMA time series models examining the impact of the *opt-out* vs *opt-in* periods on clinical outcomes. B, ARIMA time series models examining the impact of early statin administration (within 8 hours of initial ER triage time) in *opt-out* vs *opt-in* periods on clinical outcomes. ARIMA indicates autoregressive integrated moving average; ER, emergency room; mNIHSS, modified National Institutes of Health Stroke Scale.

hospitalized children with asthma, but this study also did not examine effects of clinical outcomes.<sup>25</sup> Other studies have compared use of electronic order sets to “a la carte” electronic ordering in specific conditions. For example, an electronic order set for acute myocardial infarction management was associated with better guidelines compliance and improved clinical outcomes when compared with patients treated with individual (“a la carte”) orders.<sup>26</sup>

The efficacy of *opt-out* versus *opt-in* modes of preference indication have been explored in other areas of healthcare utilization research. For example, rates of organ transplantation are higher in countries with *opt-out* preference indication for organ donation (presumed consent) than in countries with *opt-in* preference indication (explicit consent).<sup>27</sup> In some studies, participant recruitment has been shown to be enhanced by an *opt-out* structure,<sup>28</sup> while in others, an *opt-out* structure may have caused perceived loss of autonomy that led to reduced recruitment.<sup>29</sup> On the other hand, preselection of orders (“default to prescribe” mode) within order sets has in some contexts dramatically increased

**Table 2.** Timing of Statin Administration by 8-Hour Bins and Clinical Outcomes

	Change Per 8-Hour Delay in First Statin Dose		
	Odds Ratio	95% CI	P Value
Model 1: Alive at 90 days	0.94	0.91 to 0.96	<0.001
Model 2: Discharge to home or rehabilitation	0.92	0.89 to 0.94	<0.001
Model 3: Increase in mNIHSS by 4+	1.16	1.12 to 1.19	<0.001

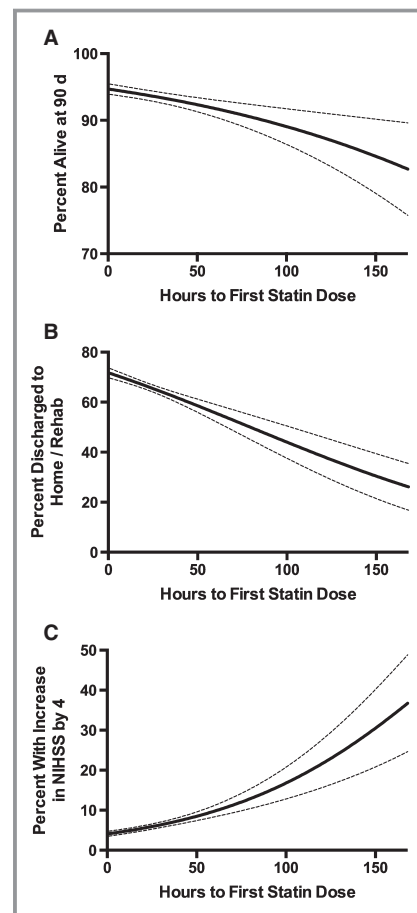
Multivariable logistic regression models for each of the 3 clinical outcomes (Model 1=alive at 90 days, Model 2=discharge to home or inpatient rehabilitation at any time, Model 3=in-hospital increase in mNIHSS by 4 or more points). For each outcome, the primary predictor is time to first statin dose, with the odds ratio presented for every 8 hours passed from ER triage to first statin dose. Models control for age, stroke severity on the mNIHSS, the Charlson comorbidity index, tPA administration, and presence of dysphagia. Only patients receiving a statin during hospitalization are included, and the referent value for the primary predictor is the minimum time bin (0–8 hours from ER triage time). ER indicates emergency room; mNIHSS, modified National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator.

prescription rates,<sup>30</sup> but such practices have the potential to infringe on provider autonomy and may increase the potential for errors (eg, automatic prescription despite an allergy or drug interaction known to the provider). In the intervention analyzed in our study, the change from opt-in to opt-out was introduced with a relatively “soft touch” (a requirement to

**Table 3.** Impact on Clinical Outcomes of Statin Administration <8 Hours Compared to Later or No Statin Administration

	<8 Hour Statin Administration vs (Later Administration or No Administration)		
	Odds Ratio	95% CI	P Value
Model 1: Alive at 90 days	1.41	1.09 to 1.82	0.010
Model 2: Discharge to home or rehabilitation	1.26	1.08 to 1.46	0.003
Model 3: Increase in mNIHSS by 4+	0.69	0.51 to 0.92	0.013

Multivariable logistic regression models for each of the 3 clinical outcomes (Model 1=Alive at 90 days, Model 2=discharge to home or inpatient rehabilitation at any time, Model 3=in-hospital increase in mNIHSS by 4 or more points). For each outcome, the primary predictor is early statin administration (<8 hours of ER arrival), compared to later administration or no administration of a statin. Models control for age, stroke severity on the mNIHSS, the Charlson comorbidity index, tPA administration, and presence of dysphagia. All patients in the cohort are included in these models. ER indicates emergency room; mNIHSS, modified National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator.



**Figure 3.** Time in hours to first statin administration and clinical outcomes. For all 3 panels, multivariable model-derived estimates of clinical outcomes are plotted (solid lines with flanking dashed lines representing 95% CI for the estimates) corresponding to time in hours to administration of first statin dose. Underlying multivariable logistic regression models control for age, mNIHSS, Charlson comorbidity index, and presence of dysphagia. A, Model-estimated percentage of patients alive at 90 days poststroke as a function of time to first statin dose in hours. B, Model-estimated percentage of patients discharged to home or inpatient rehabilitation facility after any duration of hospitalization as a function of time to first statin dose in hours. C, Model-estimated percentage of patients with in-hospital neurological deterioration (defined as an increase in mNIHSS by 4 or more points) as a function of time to first statin dose in hours. mNIHSS, modified National Institutes of Health Stroke Scale.

address the statin section) that maintained provider autonomy and yet was still associated with increased prescribing behavior.

Our study has limitations. This was a retrospective analysis of a prospectively introduced order set change, and intervention assignment was not at random. We control for potential confounding by indication at the individual patient level by using month-by-month ARIMA time series models, but one cannot rule out the possibility of some residual confounding in such analyses. The change that was made to the order set was made across the 20 hospitals at the same time, and timing of the introduced change was not staggered.

In conclusion, a multicenter EMR intervention designed to increase statin utilization in ischemic stroke hospitalization was associated with increased early statin administration, improved poststroke survival and probability of discharge to home or rehabilitation, and reduced chances of neurological deterioration in-hospital. Simple interventions of this kind using a modern EMR represent an important new approach to examining the impact of prescribing changes on measurable clinical outcomes.

## Author Contributions

Flint and Klingman conceived the study. Flint and Johnston provided statistical guidance, and Conell and Flint performed statistical work for the study. Flint drafted the manuscript and all authors contributed substantially to its revision. Flint takes responsibility for the article as a whole.

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## Disclosures

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