Statin Adherence Is Associated With Reduced Recurrent Stroke Risk in Patients With or Without Atrial Fibrillation

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Background and Purpose—Outpatient statin use reduces the risk of recurrent ischemic stroke among patients with stroke of atherothrombotic cause. It is not known whether statins have similar effects in ischemic stroke caused by atrial fibrillation (AFib).

Methods—We studied outpatient statin adherence, measured by percentage of days covered, and the risk of recurrent ischemic stroke in patients with or without AFib in a 21-hospital integrated healthcare delivery system.

Results—Among 6116 patients with ischemic stroke discharged on a statin over a 5-year period, 1446 (23.6%) had a diagnosis of AFib at discharge. The mean statin adherence rate (percentage of days covered) was 85, and higher levels of percentage of days covered correlated with greater degrees of low-density lipoprotein suppression. In multivariable survival models of recurrent ischemic stroke over 3 years, after controlling for age, sex, race/ethnicity, medical comorbidities, and hospital center, higher statin adherence predicted reduced stroke risk both in patients without AFib (hazard ratio, 0.78; 95% confidence interval, 0.63–0.97) and in patients with AFib (hazard ratio, 0.59; 95% confidence interval, 0.43–0.81). This association was robust to adjustment for the time in the therapeutic range for international normalized ratio among AFib subjects taking warfarin (hazard ratio, 0.61; 95% confidence interval, 0.41–0.89).

Conclusions—The relationship between statin adherence and reduced recurrent stroke risk is as strong among patients with AFib as it is among patients without AFib, suggesting that AFib status should not be a reason to exclude patients from secondary stroke prevention with a statin.   (***Stroke***. 2017;48:1788-1794. DOI: 10.1161/STROKEAHA.117.017343.)

Key Words: atrial fibrillation ■ hydroxymethylglutaryl-CoA reductase inhibitors
■ international normalized ratio ■ stroke ■ warfarin

Statins (hydroxymethylglutaryl coenzyme-A reductase inhibitors) reduce the risk of both initial ischemic stroke[1] and recurrent ischemic stroke.[2] Although many studies have found an impact of statin use on primary stroke prevention,[1] the role of statins in secondary stroke prevention comes from a single randomized controlled trial, SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels), which tested high-dose atorvastatin for prevention of recurrent ischemic stroke among patients with stroke of presumed atherothrombotic cause, excluding strokes caused by atrial fibrillation (AFib).[2]

Given SPARCL's inclusion/exclusion criteria,[2] the role of statins in patients with an initial ischemic stroke attributed to AFib has not been systematically evaluated. It is therefore unclear whether the risk reduction provided by statin therapy applies to all patients with ischemic stroke or only to the atherothrombotic (non-AFib) group tested in SPARCL. Current stroke guidelines support statin prescription for secondary stroke prevention after ischemic stroke of atherothrombotic

cause, but the guidelines do not speak to whether patients who present with an ischemic stroke caused by AFib should be treated with outpatient statin therapy.[3]

Statins were originally developed for their lipid-lowering properties, but this medication class reduces the risk of ischemic stroke even though hyperlipidemia is not an established risk factor for stroke.[4,5] It has been suggested that statins may reduce stroke risk by one of the nonlipid-lowering, pleiotropic mechanisms established for this drug class.[6–9] If nonlipid-lowering mechanisms are indeed at play, it is reasonable to hypothesize that all groups of patients with ischemic stroke might benefit from statin therapy for secondary stroke prevention. The finding that statin use may reduce burden of AFib[10,11] provides an another mechanism by which statin use might reduce recurrent stroke risk in the specific group of patients with AFib: reduced time spent in AFib could translate to reduced stroke risk directly or indirectly via preserved left atrial structure and function.

To address this possibility, we studied a large cohort of ischemic stroke patients in a 21-hospital integrated healthcare delivery system to examine the relationship between outpatient statin adherence and the risk of recurrent stroke, stratified according to whether patients originally presented with a stroke associated with AFib or a stroke of atherothrombotic (non-AFib) cause.

Methods

Setting
Kaiser Permanente Northern California (KPNC), a 21-hospital integrated healthcare delivery system with >3.5 million members whose characteristics are similar to the overall population of Northern California.[12] KPNC members receive clinical care within an integrated system in which all encounters, laboratory studies, radiological studies, and medication prescriptions are documented in a single large inpatient/outpatient electronic medical record (EMR).[13] KPNC members also fill their prescriptions in KPNC pharmacies, providing us with detailed records on prescription fills from pharmacy databases linked to the EMR. For several years before the study period, internal KPNC guidelines have supported the use of statins in all patients with ischemic stroke, starting as early as possible during the initial stroke hospitalization.[13]

Subjects
We captured data from the EMR from 2008 to 2012 for 6116 patients who were admitted to a KPNC hospital with ischemic stroke and were discharged with an active prescription for a statin (either continued from previous outpatient prescription or initiated at the time of hospitalization) and filled a statin prescription within 90 days of discharge. The case definition for the index stroke was a primary discharge diagnosis of ischemic stroke together with the presence of at least 1 neuroimaging study performed during the hospitalization, a definition that we have validated previously as highly specific for ischemic stroke.[14]

Inclusion/Exclusion Criteria
Subjects were included if the age was ≥18 years. KPNC membership was required from 2008 to 2012 to ensure accurate determination of comorbidities and events. Subjects were excluded if they were discharged to a skilled nursing facility or hospice. Independent residence was required because we were interested in patient decisions on outpatient adherence.

Measures
For each subject, we extracted data from the EMR and related databases on age, sex, race/ethnicity, medical comorbidities (AFib, hypertension, diabetes mellitus, hypercholesterolemia, coronary artery disease, and congestive heart failure), history of previous ischemic stroke, and hospital center to which they were admitted for the index stroke. The presence of AFib was defined as the presence of AFib on the problem list or other attached diagnostic code lists at the time of discharge from the index ischemic stroke hospitalization. AFib could have been previously known before the index stroke or discovered by inpatient telemetry or ECG during the index stroke hospitalization. We followed up subjects for the occurrence of recurrent ischemic stroke starting 30 days after the index event and then for up to 3 years or up to the point at which the subject was censored for development of an ischemic stroke, death, or loss to follow-up because of no longer meeting the eligibility criteria. To insure capture of all recurrent stroke events, we included stroke admissions to non-KPNC hospitals and did not require the presence of neuroimaging. Statin adherence was measured in standard fashion using percentage days covered (PDC),[15,16] calculated as (number of pills filled in the pharmacy/number of pills prescribed) for the period under study. For the analyses

presented here, PDC was averaged for each subject across the period of observation, with the exception of time spells that were excluded for nonoutpatient status (eg, periods of hospitalization for causes other than the surveillance outcome, periods of skilled nursing facility residency). For the subgroup of patients with stroke caused by AFib who were treated with warfarin for the secondary stroke prevention, we captured all international normalized ratio laboratory values across the time period and used these data to calculate time in the therapeutic range (TTR) according to the standard technique of Rosendaal et al.[17]

Validation of Statin PDC Adherence Measure Using Change in Low-Density Lipoprotein
Because sustained statin therapy substantially reduces average low-density lipoprotein (LDL) cholesterol,[18,19] we measured change in LDL values in a subgroup of patients to independently validate the PDC adherence measure in our setting. For the analysis of the relationship between PDC and LDL change, we examined data from patients who were (1) not taking a statin in the 180 days before the index stroke and (2) enrolled as KP members for at least 180 days before the index stroke. In this group of patients who were initiated on a statin after the index stroke, we calculated change in LDL as the difference between baseline LDL level (average of LDLs measured ±3 months from index stroke) and the LDL after initiation of statin therapy (average of LDLs measured from 9 to 18 months after index stroke).

Statistical Analyses
Multivariable Cox regression models of ischemic stroke recurrence were constructed with control for age, sex, race/ethnicity, medical comorbidities, history of previous stroke, and hospital center. Because of the skewed distribution of PDC in this cohort and the observed nonlinear relationship between PDC and rate of outcome, models with continuous PDC as the primary predictor were constructed using the natural logarithm of PDC, which substantially improved model fit. For plotting adjusted survival curves, the primary predictor was dichotomized PDC, with a cutpoint of PDC=85 (the mean value of PDC for the cohort).

To estimate the impact of statin adherence across the full range of PDC on the cumulative hazard of recurrent ischemic stroke, we used multivariable Cox regression with post-estimation determination of marginal means with covariates held at their mean values. After Cox regression models were constructed with control for age, sex, race/ethnicity, medical comorbidities, history of previous stroke, and hospital center, marginal means were obtained across the full range primary predictor (the natural logarithm of PDC), together 95% confidence interval bounds. For plotting purposes, model estimates of outcome are displayed graphically with the *x*-axis transformed from log (PDC) back to PDC.

Bivariate analyses were performed with the Fisher 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 (Cary, NC) and Stata/MP version 12.1 (College Station, TX).

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

Results

Patient Characteristics
Baseline patient characteristics are shown in the Table, according to the level of adherence, with a cutpoint of PDC=85, the mean level of adherence for the cohort. Higher levels of adherence (PDC 85+) were associated with older age and lower burden of diabetes mellitus, and higher burdens of AFib, coronary artery disease, and congestive heart failure. Differences in

Table. Baseline Patient Characteristics According to the Statin Adherence (PDC)

|	PDC<85 (n=1853)	PDC 85+ (n=4263)	All Subjects (n=6116)	P Value
Age, y	66.3±13.9	70.4±13.2	69.1±13.6	<0.001
Women	914 (49.3)	2060 (48.3)	2974 (48.6)	0.49
HTN	1257 (67.8)	2790 (65.5)	4047 (66.2)	0.07
DM	651 (35.1)	1323 (31.0)	1974 (32.3)	0.002
AFib	308 (16.6)	1138 (26.7)	1446 (23.6)	<0.001
CAD	299 (16.1)	823 (19.3)	1122 (18.4)	0.003
CHF	178 (9.6)	505 (11.9)	683 (11.2)	0.01
Hyperlipidemia	1252 (67.6)	2823 (66.2)	4075 (66.6)	0.32
Previous stroke	99 (5.34)	258 (6.1)	357 (5.8)	0.29
Race/ethnicity				
White	899 (48.5)	2499 (58.6)	3398 (55.6)	<0.001
Black	332 (17.9)	426 (10.0)	758 (12.4)	<0.001
Hispanic	256 (13.8)	491 (11.5)	747 (12.2)	0.01
Asian	241 (13.0)	516 (12.1)	757 (12.4)	0.33
Other/unknown	125 (6.8)	331 (7.8)	456 (7.5)	0.17

Age is presented as mean±SD and dichotomous measures are presented as n (%). Column categories: PDC<85, low adherence, percentage days covered less than 85; PDC 85+, high adherence, percentage days covered 85 or higher; All subjects, all subjects in the cohort (ischemic stroke hospital admissions prescribed statin). *P* value, significance level for the difference between the distribution of the patient characteristics in the PDC <85 and PDC 85+ categories: *P* values are from the nonparametric Kruskal–Wallis test for continuous data and Fisher exact test for categorical data. AFib indicates atrial fibrillation; CAD, history coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; HTN, hypertension; PDC, percentage days covered; and Previous stroke, history of ischemic stroke before the index admission for the cohort.

level of adherence were also seen among several race/ethnicity categories (Table). AFib was present and identified by the time of initial stroke discharge in 1446/6116 (23.6%).

PDC and Impact on LDL

The level of statin adherence as measured by PDC was overall quite high in this cohort, with a mean of 85±22 and median of 95 (interquartile range, 79–100). The extremely right-skewed distribution of PDC in the overall cohort is shown graphically in Figure 1A.

To validate our statin PDC measure in this population, we explored the relationship between PDC and LDL lowering in a subgroup of 1509 patients who were not taking a statin before the index stroke and for whom serial LDL data were available. In linear regression, increasing PDC was associated with a net negative change in LDL from baseline to follow-up (coefficient, −0.417; 95% confidence interval [CI], −0.486 to −0.348; R^2=0.086; Figure 1B). After controlling for age, sex, comorbidities, race/ethnicity, previous stroke, hospital center, and baseline LDL, the relationship between PDC and change in LDL was not substantially altered, but model fit improved (coefficient, −0.426; 95% CI, −0.496 to −0.357; R^2=0.120). In marginal estimation from the multivariable linear model
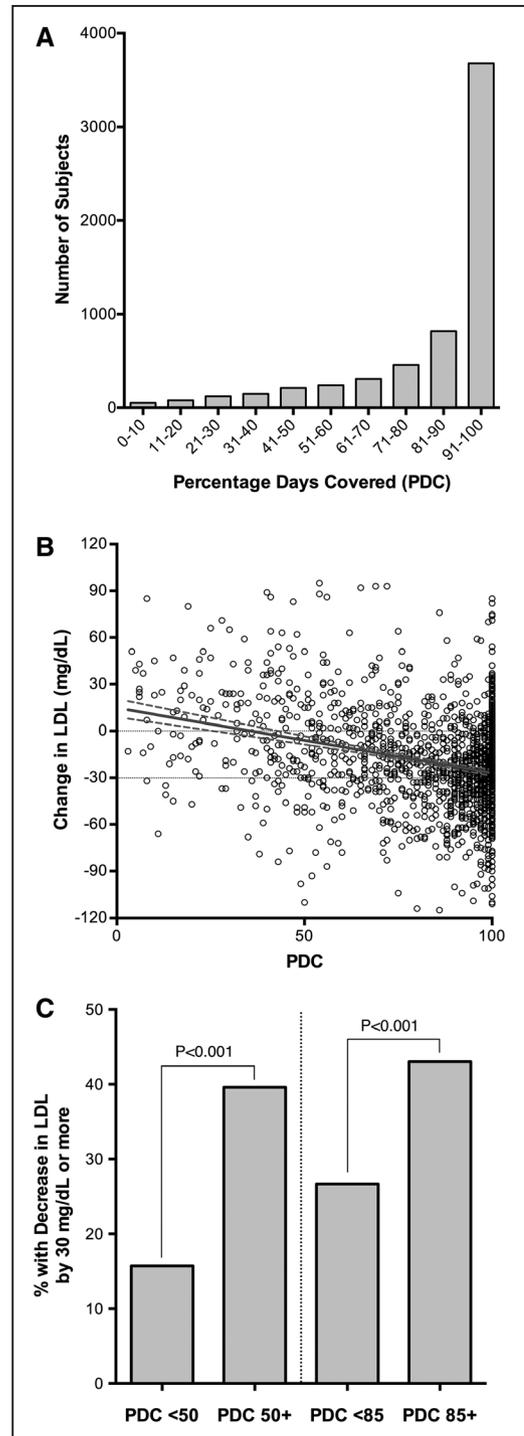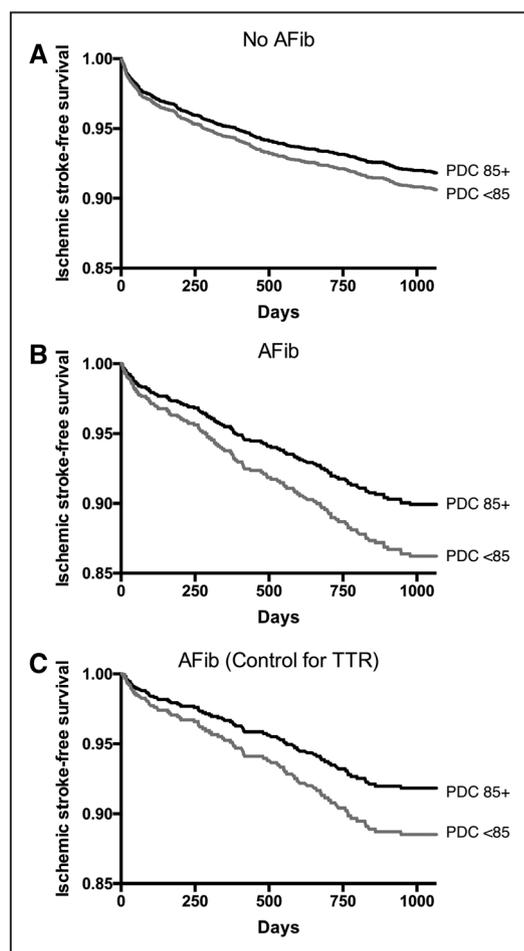

Figure 1. Statin adherence by percentage days covered (PDC) and change in low-density lipoprotein (LDL). **A**, Distribution of PDC in the cohort shows number of subjects (*y*-axis) in each bin on PDC, by 10% (*x*-axis). **B**, Relationship between PDC and change in LDL in the subset of subjects who were not taking a statin at the time of their initial ischemic stroke. PDC is plotted on the *x*-axis against change in LDL in mg/dL over the period of observation on the *y*-axis (negative numbers indicate a decrease in LDL over time). **C**, Percentage of subjects with a decrease in LDL by ≥30 mg/dL over the observation period, according to PDC. On the **left**, the difference is shown according to PDC<50 vs PDC 50+ (adherence level less than or greater than/equal to half the time), and at **right**, the difference is shown for PDC<85 and PDC 85+ (adherence level less than or greater than/equal to the mean PDC for the cohort). *P* values are from the Fisher exact test.

controlling for covariates, the mean estimate for LDL change ranged linearly from a mean change in LDL of ≈+17 mg/dL at PDC=1 to a mean change in LDL of ≈−27 mg/dL at PDC=100. The percentage of patients achieving a 30-mg/dL reduction in LDL while on statin therapy was significantly increased at higher dichotomized levels of adherence (Figure 1C; *P*<0.001).

Survival Free of Stroke at Different Levels of Statin Adherence

Adjusted survival curves, each controlling for age, sex, medical comorbidities, race/ethnicity, previous stroke, and hospital center, all show improved rates of ischemic stroke-free survival over 3 years at higher levels of adherence, with PDC dichotomized at 85 (mean for PDC in the cohort, Figure 2). The relationship between PDC level and survival free of ischemic stroke is present in subjects without AFib (Figure 2A)

and in subjects with AFib (Figure 2B). In the subgroup of patients with AFib treated with warfarin for the secondary stroke prevention (n=1010), the relationship between statin adherence and reduced rate of recurrent stroke is robust to control for degree of warfarin effect on the international normalized ratio, measured as time in the TTR (Figure 2C).

The outcome of hemorrhagic stroke in this group of patients taking statins after ischemic stroke was rare and did not differ according to the statin adherence. Among patients with low statin adherence (PDC<85), hemorrhagic stroke occurred in 9/1837 (0.49%), and among patients with higher adherence (PDC 85+), hemorrhagic stroke occurred in 27/4204 (0.64%; *P*=0.59).

Ischemic Stroke-Free Survival and the Full Range of PDC

To examine the impact of adherence across the full range of PDC without dichotomization, we constructed adjusted Cox survival models of 3-year survival free of ischemic stroke, with a primary predictor of the natural logarithm of continuous PDC and controlling for age, sex, medical comorbidities, race/ethnicity, previous stroke, and hospital center (Figure 3) (use of log(PDC) was determined to substantially improve overall model fit based on R^2). Continuous adherence measured as log(PDC) was significantly associated with reduced rate of ischemic stroke over 3 years in patients without AFib (HR, 0.78; 95% CI, 0.63–0.97; *P*=0.023; n=4669) and in patients without AFib (HR, 0.59; 95% CI, 0.43–0.81; *P*=0.001; n=1446; Figure 3). In the subgroup of patients with AFib treated with warfarin, a similar relationship between statin adherence and reduced rate of recurrent stroke was seen after controlling for warfarin time in the TTR (HR, 0.61; 95% CI, 0.41–0.90; *P*=0.012; n=1010; Figure 3). As would be expected, TTR in patients with AFib treated with warfarin
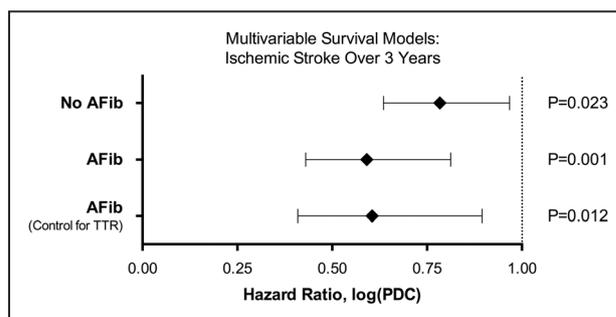

Figure 2. Adjusted ischemic stroke-free survival curves as a function of statin adherence, according to atrial fibrillation (AFib) status. Adjusted ischemic stroke-free survival curves are displayed for a cutpoint of percentage days covered (PDC) <85 vs PDC 85+ (cut at the mean PDC for the overall cohort). **A**, Survival curves for the subgroup without AFib. **B**, Survival curves for the subgroup with AFib. **C**, Survival curves for the subgroup with AFib on warfarin anticoagulation, after control for time in the therapeutic range (TTR) for international normalized ratio values. All survival curves are adjusted for age, sex, race/ethnicity, hypertension, diabetes mellitus, hypercholesterolemia, coronary artery disease, congestive heart failure, history of previous ischemic stroke, and hospital center.


Figure 3. Multivariable survival models showing the relationship between statin adherence and ischemic stroke, according to atrial fibrillation (AFib) status. Three multivariable Cox regression models are shown, displaying the hazard ratio for the relationship between the natural logarithm of percentage days covered (PDC) and ischemic stroke >3 y. Solid triangles represent the hazard ratio point estimates and horizontal error bars show the 95% confidence interval. The **top** row shows the results of the model for the subgroup without AFib (n=4669). The **middle** row shows the results of the model for the subgroup with AFib (n=1446). The **bottom** row shows the results of the mode for the subgroup with AFib on warfarin anticoagulation, after controlling for time in the therapeutic range (TTR) for international normalized ratio values (n=1010). All models controlled for age, sex, race/ethnicity, hypertension, diabetes mellitus, hypercholesterolemia, coronary artery disease, congestive heart failure, history of prior ischemic stroke, and hospital center.

was strongly associated with reduced risk of recurrent stroke (HR, 0.05; 95% CI, 0.02–0.20; $P<0.001$), but this effect was independent of the relationship between statin PDC and stroke risk.

Model Estimation of the Risk of Recurrent Stroke Across the Range of PDC

To explore the relationship between the full range of PDC and the risk of recurrent stroke, we calculated the estimated cumulative hazard of recurrent ischemic stroke over 3 years as a function of log(PDC), holding other patient characteristics constant at the mean values for the study population. The resulting graphs in Figure 4 show the relationship between PDC and the cumulative hazard of ischemic stroke, stratified by AFib status. The risk of recurrent stroke can be seen to
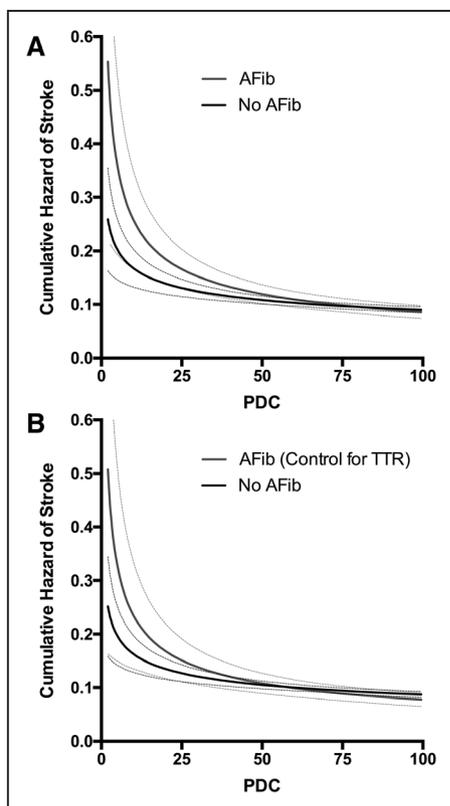
Figure 4. Model estimation of the 3-y cumulative hazard of ischemic stroke according to the adherence (PDC) and atrial fibrillation (AFib) status. **A**, Plot of the model estimates of the cumulative hazard of recurrent ischemic stroke over 3 y (*y*-axis) according to the adherence (PDC). Estimates of the hazard of stroke rose sharply at low levels of PDC for both subjects with AFib (gray curve, 95% confidence interval in flanking dotted lines) and subjects without AFib (No AFib, black curve, 95% confidence interval in flanking dotted lines). **B**, Similar plot of the model estimates of stroke hazard according to PDC, but in this case the AFib group is the subgroup on warfarin anticoagulation with additional control for time in the therapeutic range for international normalized ratio values (AFib [Control for TTR], gray curve, 95% confidence interval in flanking dotted lines). Underlying models for estimation were prediction of ischemic stroke >3 y by natural logarithm of PDC in multivariable Cox regression, controlling for age, sex, race/ethnicity, hypertension, diabetes mellitus, hypercholesterolemia, coronary artery disease, congestive heart failure, and history of previous ischemic stroke. For plotting purposes, natural logarithm of PDC was transformed back to PDC.

decrease nonlinearly with increasing adherence, with particularly high risk of recurrent stroke at low levels of statin adherence, irrespective of AFib status.

Discussion

We find a strong relationship between statin adherence and reduced rate of recurrent ischemic stroke in a large cohort of patients in an integrated healthcare delivery system, regardless of whether the index stroke was atherothrombotic (non-AFib) or associated with AFib. Indeed, there seems to be an even stronger relationship between statin adherence and reduced stroke risk among subjects with AFib, even after controlling for warfarin TTR. In addition, we do not find an association between statin adherence after ischemic stroke and the risk of hemorrhagic stroke.

Adherence to outpatient statin prescription has been previously associated with lowered rates of adverse cardiovascular outcomes,[20] and for this reason, international cardiovascular guidelines underscore the importance of regular monitoring of adherence to statin therapy.[21] Statin adherence after ischemic stroke has been found to reduce the risk of a composite outcome of recurrent ischemic stroke, hemorrhagic stroke, or acute coronary event.[22] Despite the importance of statin adherence, previous reports have shown problematically low levels of average adherence in several different populations.[15,16,21,22] The cohort presented here had, by comparison, unusually high levels of overall statin adherence; it is possible that the right-shifted distribution of PDC shown in Figure 1A may be because of the integrated nature of the healthcare delivery system from which the data are derived. Given that hospital discharge has been shown to be a critical moment to impact long-term adherence to the secondary stroke prevention strategies,[23] it is possible that our previously reported EMR intervention to increase statin prescription during stroke hospitalization[13] may have also contributed to long-term statin adherence in this cohort.

Although statins were originally developed as lipid-lowering agents, many mechanisms of the statins beyond lipid lowering have been identified that may be involved in helping prevent secondary stroke.[6–9] Beyond mechanisms that might reduce the risk of recurrent stroke independent of index stroke cause, there is also evidence that statin use may specifically reduce the risk of AFib. In 2 meta-analyses of randomized controlled trials, a significant association was seen between statin use and reduced risk of AFib, with a particularly strong relationship between statin use and lowered risk of recurrent AFib.[10,11] In addition, statin use before cardiac surgery has been associated with a reduced risk of postoperative AFib.[24] The reduced risk of AFib associated with statin use may be most pronounced among patients with higher $CHADS_2$ and CHA_2DS_2VASc scores,[25] the population of patients with AFib who is at highest risk for ischemic stroke.[26]

Our study has limitations. This is a retrospective cohort study of data prospectively accumulated in an inpatient and outpatient EMR and pharmacy system in an integrated healthcare delivery system, without randomization and thus subject to potential confounding by unmeasured covariates. Although PDC is not a perfect measure of medication adherence, based

on prescription fills as a function of prescriptions available, it is a well-established methodology that can be used if detailed records are available for prescriptions, quantities, and fills.[15,16] By taking advantage of the established relationship between statin use and lower of LDL, we were able to additionally validate the statin PDC measure in our cohort by showing that higher levels of statin PDC are associated with a greater extent of LDL lowering. All studies of adherence to any specific medication are always subject to potential confounding by adherence to other medications, in that adherence to 1 medication may be a surrogate for medication adherence in general. In the setting of the question being addressed here (the role, if any, of statins after AFib-related ischemic stroke), the most concerning source of potential confounding would be collinearity between statin adherence and warfarin adherence in the subgroup of stroke associated with AFib. Given that warfarin is known to dramatically reduce stroke risk in AFib, better warfarin adherence and better international normalized ratio control in this group would be expected to strongly reduce recurrent stroke risk.[3] Indeed, we find that TTR in this group is a strong predictor of reduced stroke risk, as one would expect. Importantly, controlling for TTR did not substantially change the relationship between statin adherence and lowered risk of ischemic stroke. However, despite these adjustments, it remains possible that the relationship between our measure of statin adherence and reduced stroke risk in the AFib group might be partially explained by residual confounding from warfarin adherence and consequent degree of international normalized ratio control. Our categorization of 2 groups as having AFib or non-AFib–associated stroke is limited by the understanding that some subjects in the non-AFib group may have had undetected paroxysmal AFib around the time of the index stroke or may have gone on to develop AFib after the index stroke hospitalization. By choice, we did not include a separate group of patients not prescribed a statin at discharge, but the advantage of our study design, in which all patients were prescribed a statin, is that it avoids the potential for confounding by indication that would be a major problem if subjects not prescribed a statin were included.

Given the evidence that statins do not act exclusively through lipid lowering to reduce the risk of stroke and that statins may reduce the risk of AFib, it is therefore reasonable to suggest that statins could have similar effects to lower the risk of recurrent ischemic stroke irrespective of stroke cause (AFib versus non-AFib). The results of our study support the conclusion that statins reduce the risk of recurrent stroke regardless of AFib status; in fact, a greater effect magnitude is observed for the relationship between statin adherence and recurrent stroke in the setting of AFib. Therefore, AFib should not be used to exclude patients from outpatient statin therapy to reduce secondary stroke risk.

Acknowledgments

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Statin Adherence Is Associated With Reduced Recurrent Stroke Risk in Patients With or Without Atrial Fibrillation

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