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Influence of Statin Therapy at Time of Stroke Onset on Functional Outcome among Patients with Atrial Fibrillation

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Abstract

Background—Statin pretreatment has been associated with reduced infarct volume in nonlacunar strokes. The effect of statins on functional outcomes of strokes related to atrial fibrillation (AF) is unknown. We aimed to define the influence of prestroke statin use on functional outcome in AF.

Methods—We assembled a cohort of consecutive ischemic stroke patients from 2006 to 2010. All patients underwent CT or MRI and were adjudicated by site investigators. AF was confirmed by electrocardiogram in 100% of patients. Site neurologists blinded to the study hypothesis affirmed the type of stroke and assessed the severity of disability at the time of hospital discharge. The frequency of death at 30-days was calculated.

Results—Ischemic stroke (n=1030) resulted in a severe neurological deficit or death (modified Rankin scale 4) at 30 days in 711 patients (69%). Using multivariable logistic regression models adjusting for factors associated with statin treatment and factors associated with functional outcome, prestroke statin use was associated with a 32% reduction in frequency of severe stroke (odds ratio [OR], 0.68; 95% confidence interval [CI], 0.50–0.92; P=0.011). Other independent

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Disclosure of Conflict of Interests

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factors associated with severe stroke included older age, female sex, non-White race, diabetes mellitus, prior ischemic stroke, prior venous thromboembolism, and dementia.

Conclusion—Ischemic strokes in AF are associated with high mortality and morbidity. Statin use at time of stroke onset among patients with AF was associated in this study with less severe stroke and warrants validation.

Keywords

atrial fibrillation; stroke; hydroxymethylglutaryl-CoA Reductase Inhibitors; risk factors; therapy

1. Introduction

The pathobiology of stroke associated with atrial fibrillation (AF) is distinct from arterial, high shear thrombosis, and is more akin to venous, or low shear, thrombosis.[1] The large infarcts characteristically associated with AF reflect the larger size of stasis thrombi that form in the low shear environment of the left atrium. Strokes related to AF are associated with a 30-day mortality of 24%. [2, 3] An additional 35% of patients are rendered unable to live independently. Clinical factors that drive thrombus formation and thrombus growth in the left atrium and left atrial appendage are poorly understood. However, it is believed that prothrombotic forces, coupled with the endothelial dysfunction and stasis (Virchow's triad) characteristic of AF, underlie thrombus formation, thrombus growth, and ultimately the severity of stroke when these large thrombi embolize to the cerebral circulation. It is biologically plausible that statins would attenuate these actions, given their anti-inflammatory, antithrombotic, and antioxidant properties.[4–6] Support for this is found in recent clinical trials that reported decreased risk of incident and recurrent venous thrombosis (deep vein thrombosis or pulmonary embolism) among participants prescribed statins.[7, 8] Pretreatment with statins has been shown in several studies to be associated with reduced infarct volume by magnetic resonance diffusion-weighted imaging.[9, 10] The influence of baseline statin use in AF related ischemic stroke is unknown. Among 177 patients with AF-related stroke in the North Dublin Population Stroke Study, post-stroke initiation of a statin drug was associated with improved 5-year survival.[11] However, post-stroke assessment of statin use is vulnerable to survivor bias whereby patients with better stroke outcomes are preferentially prescribed statin therapy. A recent meta-analysis found statin therapy at time of stroke onset to be associated with improved outcome, but no data were available specific to AF stroke.[12]

We assembled a cohort of patients with validated ischemic stroke and electrocardiogram-confirmed AF from three centers. The objective of our study was to determine the influence of pretreatment with statins on 30-day stroke functional outcome among patients with AF.

2. Methods

2.1 Study population

Patients admitted with ischemic stroke were identified over a 5-year period (2006–2010) at three academic health centers: Boston Medical Center, Geisinger Health System, and the University of Alabama. To be eligible, patients had to have electrocardiogram-confirmed AF

at the time of admission, during the index hospitalization or within the prior 6 months. Patients with mechanical heart valves were excluded. Strokes were initially identified using *International Classification of Diseases* (ICD)-9 codes for ischemic stroke (433–434, 436). All medical records underwent detailed review, including neurology admission notes, consult notes, discharge summaries, and radiology reports. A qualifying ischemic stroke was defined as a neurologic deficit of sudden onset that persisted for >24 hours, corresponded to a vascular territory, and was not explained by other etiologies, such as large artery atherosclerosis, intracerebral hemorrhage, tumor, infection, vasculitis, or procedural or surgical complication[13, 14]. Strokes were adjudicated by site investigators, and electrocardiogram evidence of AF was confirmed in all patients. All strokes underwent final review by site neurologists blinded to the study hypothesis for affirmation of AF-related stroke and assignment of discharge modified Rankin score assignment.

2.2 Patient characteristics

Demographics and clinical characteristics were determined from review of the medical record and included known risk factors for AF-related stroke (age, sex, hypertension, diabetes mellitus, heart failure, prior stroke, vascular disease, and chronic kidney disease). Other variables of interest included dementia, chronic obstructive pulmonary disease, liver disease, and current tobacco use. We also collected data on history of venous thromboembolism. Prestroke medications were determined from admission and neurologist consult notes. For patients with reported baseline warfarin use, the International Normalized Ratio (INR) measured in the emergency department was recorded. Time from symptom onset to presentation was noted as was receipt of thrombolytic therapy. Race was defined by self-report. Socioeconomic status was determined using zip codes. Smoking status was available for 96% of patients. Stroke risk was quantified according to current schemas.[15]

2.3 Functional outcome and 30-day mortality

Stroke disability at the time of discharge was determined by site neurologists using the Modified Rankin Scale (mRS; 0 = no symptoms; 1 = no significant disability despite symptoms; able to carry out all usual duties and activities; 2 = slight disability, but independent in all activities; 3 = moderate disability; requiring some help, but able to walk without assistance; 4 = moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance; 5 = severe disability; bedridden, incontinent and requiring constant nursing care and attention; 6 = death).[16, 17] Source documents for the mRS determination included discharge evaluations from the attending physician, primary nurse, physical and occupational therapists. Deaths occurring during the index hospitalization were recorded; deaths occurring after discharge were identified by review of medical records and statedeath registries.

2.4 Statistical analysis

Strokes that resulted in the loss of ability to take care of one's basic needs (mRS = 4) or in death after discharge but before 30 days were considered to be severe strokes. Baseline characteristics were compared between the statin use and non-statin use groups using the *t*-test for continuous variables and chi-square test for categorical variables (Table 1). Continuous variables were summarized as means $\pm$ standard deviations and categorical

variables as counts (percentages). All p-values correspond to two-sided tests. Baseline characteristics were also compared between the severe stroke and not severe stroke groups (Table 2). In order to examine the association of statin use and stroke severity and adjust for potential confounding variables, we conducted multivariable logistic regression analysis. We included in the final model for stroke severity all the variables included in Table 1 which were associated with statin treatment using an alpha of 0.1: sex, age, congestive heart failure, diabetes mellitus, coronary artery disease, peripheral vascular disease, chronic kidney disease, smoking, use of anticoagulant medication, hypertension, chronic obstructive pulmonary disease, and prior ischemic stroke. To reduce prediction variance, the final model for stroke severity also included all the variables included in Table 2 which were associated with stroke severity using an alpha of 0.1 irrespective of their association with statin treatment: race, dementia, and prior venous thromboembolism in addition to the variables from Table 1. There were 42 subjects with missing status for smoking, for whom we used multiple imputations in 20 datasets. Smoking was predicted using a monotone logistic regression using as predictors all variables from Table 1 that were found to be significantly associated with smoking. Predictors for smoking included sex, race, age, type of AF, dementia, and use of anticoagulant medication. We computed the c-statistic to assess model discrimination and the Hosmer-Lemeshow statistic and p-value to evaluate model calibration. Analyses were performed using SAS software (version 9.3; SAS Institute, Cary, NC).

The research protocol was reviewed and approved by the institutional review board at each institution.

3. Results

3.1 Baseline characteristics

We identified 1030 patients admitted with AF-related ischemic stroke. The time from symptom onset to emergency department presentation was documented for nearly 90%, and was 3 hours or less for 41% (n=425). All patients underwent neuroimaging to exclude primary intracerebral hemorrhage. Their mean age was 77 years, 55.9% were women, and 74.2% were white (Table 1). The mean CHA₂DS₂VASc score was 4.8. One in four strokes occurred in the setting of new onset AF. Among patients with known AF, 36% (n=292) were taking warfarin. The median INR at the time of admission for stroke was 1.6, and was less than 2.0 in 65.4%. Overall, 14% (n=145) received thrombolytic therapy.

3.2 Stroke outcomes and factors associated with stroke severity

Of the 1030 stroke patients included in this analysis, 69% (n = 711) sustained severe neurological deficits (mRS ≥ 4), including 21% (n = 216) who died within 30 days. At the time of stroke, 39% (n=400) of patients was taking a statin (Table 1). Statin users were more often male, had a higher burden of stroke risk factors: CHA₂DS₂VASc score mean (5.2 vs 4.6), congestive heart failure (38% vs 31%), hypertension (95% vs 88%), diabetes mellitus (50% vs 31%), prior ischemic stroke (34% vs 23%), coronary artery disease (54% vs 30%), and chronic kidney disease (23% vs 16%), and more often reported to be taking warfarin at

baseline (33% vs 25%). Statin users were also slightly younger (76 vs 78 years). There was no difference in receipt of thrombolytic therapy by statin group (14.1% vs 14.0%, $p=0.96$)

Patients with severe strokes were older (79 versus 73 years), had a higher baseline risk of stroke (CHA₂DS₂VASc score, mean, 5.0 versus 4.3), were more often female, more often had heart failure, chronic kidney disease, prior ischemic stroke, dementia, and permanent AF. Patients with severe stroke also more often had a history of deep venous thrombosis or pulmonary embolism. There was no difference according to receipt of thrombolytic therapy (14.2% vs 13.8%, $p=0.86$) Prestroke statin use was associated with a reduced risk for severe stroke (Table 2).

3.3 Independent risk factors associated with severe stroke

Using multivariable logistic regression models adjusted for factors associated with statin use and factors associated with stroke severity, prestroke statin use was associated with a 32% reduction in frequency of severe stroke (odds ratio [OR], 0.68; 95% confidence interval [CI], 0.50 to 0.92) (Table 3). Other independent factors associated with severe stroke included older age, female sex, non-White race, diabetes mellitus, prior ischemic stroke, prior venous thromboembolism and dementia (Table 3).

4. Discussion

In this study, we found that prestroke statin use among individuals presenting with ischemic stroke in AF was associated with a 32% reduction in the risk of the stroke being severe or fatal at 30 days. This association persisted after adjustment for factors associated with statin treatment and factors associated with stroke severity. Factors that incite platelet activation, aggregation, and thrombin generation underlie the formation and size of thrombus in patients with AF;^[18] accordingly, they also affect the resultant infarct volume and severity of stroke. Diabetes mellitus has been consistently linked with inflammatory and prothrombotic biomarkers including P-selectin, interleukin-6, and tissue factor; the highest level of tissue factor is found in those with known cardiovascular disease and poor glycemic control.^[19, 20] Hyperglycemia has been shown to accelerate arterial thrombus formation in animal models.^[21] Diabetes mellitus has also been associated with heightened risk for venous thromboembolism,^[20] and a recent population-based study reported that microalbuminuria increased the risk of venous thromboembolism.^[22]

Several studies have demonstrated a beneficial effect of baseline statins on the outcome of patients with stroke [23, 24]; none have focused on stroke associated with AF. Examining AF patients separately is essential, since the source of these strokes is the left atrium or left atrial appendage, and AF cardioembolic strokes are associated with high morbidity and mortality. Strokes in patients without AF are less disabling and more often result from plaque rupture in the wall of the aorta, carotids or intracranial arteries, and therefore potentially expose a study to confounding from the impact of statins on the vessel wall. The largest study enrolled 1,360 ischemic stroke patients; only 221 (16%) had AF, and of these, 53 were taking a statin at baseline.^[24] A post-hoc analysis of lipid lowering treatment in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial demonstrated lower all-cause mortality (hazard ratio [HR] 0.77, 95% confidence interval

[CI] 0.62 to 0.95, $p = 0.01$), cardiovascular mortality (HR 0.71, 95% CI 0.53 to 0.95, $p = 0.02$), and ischemic stroke (HR 0.56, 95% CI 0.36 to 0.89, $p = 0.01$) among individuals with AF prescribed lipid lowering therapy at baseline.[25] This analysis did not evaluate differences in ischemic stroke functional outcomes as defined by the Modified Rankin scale.

There are biologically plausible mechanisms for the association between statin use and decreased stroke severity. Prestroke statin use has been shown to increase collateral blood flow and reduce infarct size in clinical studies [26, 27] and an angiogenic potential of statins has been demonstrated in animal models.[28, 29] Statins are also known to exert antithrombotic effects[30] by inhibiting the coagulation pathway[31–33] and platelet activation.[6, 34, 35] Consistent with the antithrombotic effect of statins, the JUPITER trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) demonstrated a significant reduction in venous thromboembolism, both provoked and unprovoked, with rosuvastatin.[8] Statins have also been reported to improve left ventricular function and reduce levels of C-reactive protein, interleukin-6 and TNF- among individuals with heart failure.[36] Based on our results and these previous studies, it is not possible to distinguish between the two most likely explanations for these findings – that either statin therapy at the time of left atrial thrombus formation influences the size and other characteristics of the thrombus in a way that makes its subsequent embolization less devastating, or, that statins influence the acute injury to the brain after the ischemic insult in a favorable way.

Our study has several limitations. As an observational study, our results are subject to possible residual confounding and need to be confirmed by randomized trials. At baseline, the statin group was sicker with a higher burden of comorbid diseases thereby minimizing the risk of a healthy user bias. We were unable to reliably determine the statin doses or duration of statin exposure to investigate dose-dependent and time-dependent relationships between the use of statin and functional outcome. The time period of our study enabled us to better isolate the potential effect of prestroke statin use, and avoided any confounding survivor bias of more recent acute interventions like mechanical thrombectomy. Although our study preceded use of non-vitamin K oral anticoagulants, any off-target effects would not be expected to alter the underlying hypothesized statin mechanisms. More importantly, one in four of the strokes in our study occurred in the context of first diagnosis of AF. Among those individuals with prevalent AF, anticoagulation was under used and under dosed, effectiveness issues equally germane to newer therapies.

Our large multi-center study of AF-related ischemic stroke allowed for analysis of multiple risk factors. We rigorously validated stroke events, AF, covariates, and prestroke medication use through review of patient admission, progress, and discharge notes thereby overcoming the many limitations of studies reliant on administrative data to determine medication exposure. The focus on prestroke statin exposure avoided the survivor bias of acute or post-stroke treatment assessment. All stroke events were subject to final validation and assignment of a discharge modified Rankin Score by site neurologists who were blinded to the study hypothesis. The association of statins with reduced stroke disability in AF is biologically plausible, supported by animal models, and has corroborating evidence from

another stasis model of thrombosis, venous thromboembolism. Our results need to be validated in randomized trials.

5. Conclusions

Ischemic strokes resulting from AF are associated with high mortality and morbidity. Given the anticipated global increase in AF and AF-related stroke, strategies are needed to mitigate the severity of strokes associated with AF. In this study, statin therapy at the time of stroke onset was the only modifiable risk factor independently associated with less severe stroke.

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Table 1**Baseline Characteristics of Statin Users vs. Non-Users**

Characteristics	Overall (n = 1030)	Statin (n = 400)	No Statin (n = 630)	P value Statin vs No Statin
Women, No. (%)	576 (55.9)	208 (52.0)	368 (58.4)	0.043
White race, No. (%)	764 (74.2)	299 (74.8)	465 (73.8)	0.737
Age, mean ($\pm$ SD), years	77.0 ($\pm$ 11.1)	75.7 ($\pm$ 10.1)	77.9 ($\pm$ 11.6)	0.001
AF Type, No. (%)				
New Onset	258 (25.0)	92 (23.0)	166 (26.4)	0.130
Paroxysmal	250 (24.3)	110 (27.5)	140 (22.2)	
Permanent	522 (50.7)	198 (49.5)	324 (51.4)	
Congestive heart failure, No. (%)	349 (33.9)	151 (37.8)	198 (31.4)	0.037
Hypertension, No. (%)	934 (90.7)	381 (95.3)	553 (87.8)	<.0001
Diabetes mellitus, No. (%)	395 (38.3)	199 (49.8)	196 (31.1)	<.0001
Prior ischemic stroke, No. (%)	278 (27.0)	136 (34.0)	142 (22.5)	<.0001
Peripheral vascular disease, No. (%)	107 (10.4)	50 (12.5)	57 (9.1)	0.077
Coronary artery disease, No. (%)	402 (39.0)	215 (53.8)	187 (29.7)	<.0001
Chronic kidney disease, No. (%)	192 (18.6)	92 (23.0)	100 (15.9)	0.004
Prior deep venous thrombosis or pulmonary embolism, No. (%)	102 (9.9)	45 (11.3)	57 (9.1)	0.249
Dementia, No. (%)	154 (15.0)	54 (13.5)	100 (15.9)	0.298
Smoking status				
Current smoker, No. (%)	110 (10.7)	37 (9.3)	73 (11.6)	0.098
Nonsmoker, No. (%)	878 (85.2)	352 (88.0)	526 (83.5)	
Unknown, No. (%)	42 (4.1)	11 (2.8)	31 (4.9)	
Active malignancy, No. (%)	108 (10.5)	43 (10.8)	65 (10.3)	0.825
Anticoagulant medication, No. (%)	292 (28.4)	133 (33.3)	159 (25.2)	0.005
CHA ₂ DS ₂ VASc				
Mean score (SD)	4.8 (1.8)	5.2 (1.7)	4.6 (1.8)	< .0001

SD: standard deviation; CHA₂DS₂VASc: a risk assessment tool for stroke in patients with AF which assigns 1 point for congestive heart failure, 1 point for hypertension, 2 points for age 75 years or older, 1 point for diabetes mellitus, 2 points for history of stroke or transient ischemic attack, 1 point for vascular disease including prior myocardial infarction or peripheral arterial disease, 1 point for age 65 to 74 years, and 1 point for female sex

Table 2**Baseline Characteristics According to Stroke Severity**

Characteristics	Overall (n = 1030)	Severe stroke (n = 711)	Not-Severe Stroke (n = 319)	P value Severe Stroke vs Not-Severe Stroke
Women, No. (%)	576 (55.9)	425 (59.8)	151 (47.3)	<0.001
White race, No. (%)	764 (74.2)	544 (76.5)	220 (69.0)	0.011
Age, mean ($\pm$ SD), years	77.0 ($\pm$ 11.1)	78.8 ($\pm$ 10.5)	73.2 ($\pm$ 11.6)	< .0001
AF Type, No. (%)				
New Onset	258 (25.0)	170 (23.9)	88 (27.6)	
Paroxysmal	250 (24.3)	157 (22.1)	93 (29.2)	0.005
Permanent	522 (50.7)	384 (54.0)	138 (43.3)	
Congestive heart failure, No. (%)	349 (33.9)	258 (36.3)	91 (28.5)	0.015
Hypertension, No. (%)	934 (90.7)	648 (91.1)	286 (89.7)	0.45
Diabetes mellitus, No. (%)	395 (38.3)	282 (39.7)	113 (35.4)	0.20
Prior ischemic stroke, No. (%)	278 (27.0)	208 (29.3)	70 (21.9)	0.015
Peripheral vascular disease, No. (%)	107 (10.4)	77 (10.8)	30 (9.4)	0.49
Coronary artery disease, No. (%)	403 (39.0)	284 (39.9)	118 (37.0)	0.37
Chronic kidney disease, No. (%)	192 (18.6)	147 (20.7)	45 (14.1)	0.012
Prior deep venous thrombosis or pulmonary embolism, No. (%)	102 (9.9)	81 (11.4)	21 (6.6)	0.017
Dementia, No. (%)	154 (15.0)	135 (19.0)	19 (6.0)	< .0001
Smoking status				
Current smoker, No. (%)	110 (10.7)	66 (9.2)	44 (13.8)	0.041
Nonsmoker, No. (%)	878 (85.2)	611 (85.9)	267 (83.7)	
Unknown, No. (%)	42 (4.1)	34 (4.8)	8 (2.5)	
Active malignancy, No. (%)	108 (10.5)	78 (11.0)	30 (9.4)	0.45
CHA ₂ DS ₂ VASc				
Mean score (SD)	4.8 (1.8)	5.0 (1.7)	4.3 (1.8)	< .0001
Score, No. (%)				
0 – 1	38 (3.7)	16 (2.3)	22 (6.9)	
2	61 (5.9)	29 (4.1)	32 (10.0)	
3	134 (13.0)	89 (12.5)	45 (14.1)	
4	214 (20.8)	140 (19.7)	74 (23.2)	
5	219 (21.3)	154 (21.7)	65 (20.4)	< .0001
6	191 (18.5)	142 (20.0)	49 (15.4)	
7	106 (10.3)	85 (12.0)	21 (6.6)	
8	53 (5.1)	45 (6.3)	8 (2.5)	
9	14 (1.4)	11 (1.5)	3 (0.9)	
Warfarin use, No. (%)	292 (28.3)	206 (29.0)	86 (27.0)	0.51
Admission INR				
Median (IQR)	1.6 (1.2 – 2.3)	2.0 (1.3 – 2.4)	1.8 (1.2 – 2.2)	0.13
Statin use, No (%)	400 (38.8)	260 (36.6)	140 (43.9)	0.026

SD: standard deviation; CHA₂DS₂VASc: a risk assessment tool for stroke in patients with AF which assigns 1 point for congestive heart failure, 1 point for hypertension, 2 points for age 75 years or older, 1 point for diabetes mellitus, 2 points for history of stroke or transient ischemic attack, 1 point for vascular disease including prior myocardial infarction or peripheral arterial disease, 1 point for age 65 to 74 years, and 1 point for female sex; INR: international normalized ratio; IQR: interquartile range

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Table 3

Factors associated with Stroke Severity among Individuals with Atrial Fibrillation

Characteristics	T-test	P value	Adjusted Odds Ratio (95% CI)
Female sex	2	0.046	1.36 (1.01 – 1.83)
White race	−2.45	0.014	0.66 (0.47 – 0.92)
Age, per year	4.78	<0.0001	1.04 (1.02 – 1.05)
Diabetes mellitus	2.16	0.031	1.41 (1.03 – 1.92)
Prior ischemic stroke	2.37	0.018	1.51 (1.07 – 2.11)
Prior deep vein thrombosis or pulmonary embolism	2.41	0.016	1.95 (1.13 – 3.34)
Dementia	3.21	0.001	2.38 (1.41 – 4.00)
Statin	−2.53	0.011	0.68 (0.50 – 0.92)
Warfarin use	−0.46	0.648	0.92 (0.65 – 1.30)

c-statistic: 0.704

Hosmer-Lemeshow test for goodness of fit: 8.1 (p = 0.4263)

CI: confidence interval