Association of Statin Therapy With Risk of Epilepsy in 2 Propensity Score–Matched Cohorts

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Abstract

Background: Studies have suggested that statins may have a neuroprotective effect against epilepsy. However, evidence from rat models and case reports have suggested an opposite effect. Overall data are limited.

Objective: To examine the association between statin use and epilepsy risk in a general population and in a healthy population (individuals with no severe comorbidities).

Methods: Patients were Tricare beneficiaries from October 2003 to March 2012. Based on patients' characteristics during baseline phase (fiscal year [FY] 2004–2005), 2 propensity score (PS)-matched cohorts of statin users and nonusers were formed: (1) a PS-matched general cohort and (2) a PS-matched healthy cohort. Our outcome was defined using inpatient or outpatient ICD-9 codes for epilepsy during the follow-up phase (FY 2006 to March 2012) in the cohorts of statin users and nonusers.

Results: The study included a total of 43 438 patients (13 626 statin users and 29 812 nonusers). The PS-matched general cohort matched 6342 statin users to 6342 nonusers; the odds ratio (OR) of epilepsy in this cohort during follow-up was 0.91; 95% CI = 0.67–1.23. The PS-matched healthy cohort matched 3351 statin users to 3351 nonusers; OR in the PS-matched healthy cohort during follow-up was 1.08; 95% CI = 0.64–1.83.

Conclusions: This study did not demonstrate a significant beneficial or deleterious effect of statin use on risk of being diagnosed with epilepsy. Clinicians should not withhold statins, whenever indicated, in patients with epilepsy.

Keywords

statins; epilepsy; neuroprotection

Introduction

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are among the most commonly prescribed medications because of their beneficial effects in lowering cardiovascular morbidity and mortality.[1] In recent years, some studies have suggested that, along with their cardiovascular effects, statins may also have neuroprotective effects resulting in lowering the risk of neuropathological conditions, including epilepsy.[2–4] Overall, studies supporting a neuro-protective role for statins noted their potential beneficial effects in 3 directions: preventing recurrence of seizures in humans with epilepsy or animal models of epilepsy; preventing the development of incident epilepsy in the general population; and decreasing incident epilepsy in a population through decreasing the risk of a stroke.

In a rat model of temporal lobe epilepsy, atorvastatin and lovastatin use were associated with reduced seizure activities and excitotoxicity.[5] In addition, atorvastatin treatment has also been shown to attenuate hippocampal cell death as well as prevent quinolinic acid–induced seizures in mice.[6] Studies on mice and rats have shown that statins prevented or reduced seizure activities.[5,6] Statin administration prior to a status epilepticus episode has also been found to improve the outcome of patients.[7]

Few retrospective cohort studies also have shown associations of statin therapy with decreased risk of epilepsy.[8–10] For example, in a population-based case-control study (217 cases and 2170 controls), statin use in older cardiovascular patients, who had undergone a revascularization procedure, was associated with lower risk of hospitalization for epilepsy in both current and past users of statin drugs (adjusted rate ratio for epilepsy among current statin users was 0.65; 95% CI = 0.46–0.92). However, significant differences existed in comorbidities and in the proportions of statin users of cases and controls (58 statin users among cases [27%] and 757 statin users among controls [35%]).[9] In that study, the risk of epilepsy was lower in both current and past users of statin drugs. In an another retrospective study of veterans aged 66 years and older (1 023 376 without epilepsy and 1843 with new-onset epilepsy), statin users had less likelihood of new-onset epilepsy (odds ratio [OR] = 0.64; 95% CI = 0.56–0.73).[10] The study, however, also found, along with statin use, that older age, obesity, and hypercholesterolemia were associated with a lower likelihood of developing epilepsy, which they acknowledge to be inconsistent with epidemiological studies.[11] In another prospective cohort study of patients with a first-ever ischemic stroke and no history of epilepsy before stroke (n = 1832), statin use was associated with a lower likelihood of early-onset seizures (within 7 days of the stroke) but not with epilepsy that devolved later than 7 days after the stroke.[8] Alternative explanations for this association of a lower risk of epilepsy among statin users include statins' effect on primarily decreasing the risk of a stroke.[12]

However, evidence to the contrary exists, demonstrating both harmful and neutral effects of statins on epilepsy risk.[13–16] Atorvastatin given at a dose of 50 mg/kg before kainic acid administration increased the proportion of mice that experienced status epilepticus.[14] A similar intensifying effect was found by lovastatin treatment in rat models.[15] Case reports

have also shown examples where statin use was linked to new-onset seizures, which were reversed by discontinuing treatment.[16] In addition, some studies have found no association between statin use and seizures. For example, fluvastatin and pravastatin were found to have neither antiepileptogenic nor proconvulsant effects.[13,14]

Overall data on the association between statin use and epilepsy in the general population is scant. In addition, data are limited regarding the link between statin use and new-onset epilepsy in a healthy population. The first objective of this study was to further investigate the association between statin use and epilepsy in a cohort of statin users and nonusers who were followed longitudinally for a long period. The second objective was to examine this relationship in a healthy population in whom the risk of stroke is low.

Methods

This was a retrospective cohort study of Tricare Prime or Plus program in the San Antonio region, which spanned the period from October 1, 2003, to March 1, 2012. The study population and cohort assembly were previously published.[17,18] Medical records were extracted for inpatient and outpatient encounters and pharmacy data regardless of point-of-care affiliation or location using the Military Health System Management Analysis and Reporting Tool.[19,20]

The study was divided into 2 phases: a baseline phase (October 1, 2003, to September 30, 2005), which was used to describe baseline characteristics of treatment groups, and a follow-up phase (October 1, 2005, to March 1, 2012), which was used to capture outcomes. The study participants met the following criteria: (1) 30 to 85 years old; (2) at least 1 visit during both the baseline and follow-up phase; and (3) received at least 1 prescription medication during the baseline phase. All eligible patients were included in the database during the baseline and follow-up phases.

Patients categorized as nonusers did not receive a statin during the study period. Statin users filled new statin prescriptions during the period from October 1, 2004, to September 30, 2005, for a summated period of at least 90 days. Patients who began taking statins after the baseline phase—September 30, 2005—were excluded. This allowed equal periods of follow-up between statin users and nonusers.

Outcomes were prespecified using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes defined by the Agency for Healthcare Research and Quality Clinical Classifications Software (AHRQ-CCS) for Epilepsy; convulsions (AHRQ-CCS category 83, appendix A). AHRQ-CCS methods of creation and validation have been previously published.[21,22]

Two main cohorts were identified: a general cohort and a healthy cohort. The general cohort consisted of patients meeting all study criteria. Using the general cohort, a propensity score (PS)-matched general cohort was created using 82 predefined baseline characteristics. The characteristics included patient demographics, relevant comorbidi-ties, Charlson comorbidity index,[23] and the use of 20 different classes of medications. The healthy cohort only included patients from the general cohort who did not have any component of the

Charlson comorbidity index, any cardiovascular disease, or other comorbidities that might decrease physical activity or life expectancy. Similar to the general cohort, a PS-matched healthy cohort was created using 42 baseline characteristics; a full description of this cohort was previously published.[18]

The primary analyses examined the odds of the outcome of epilepsy in the 2 PS-matched cohorts. Three models for calculating the OR of epilepsy during follow-up were used:

1. unadjusted model using conditional logistic regression analysis;

2. logistic regression analysis adjusting OR for the prevalence of epilepsy at baseline; and

3. logistic regression analysis adjusting OR for the prevalence of epilepsy at baseline and PS.

Secondary analyses examined the OR of the outcome of epilepsy in the following cohorts:

1. General cohort: this analysis included all patients who met the study criteria from the general cohort and examined the OR of outcomes adjusting for the PS and epilepsy at baseline.

2. Healthy cohort: this analysis included all patients from the healthy cohort and examined the OR of outcomes adjusting for the PS and epilepsy at baseline.

3. Epilepsy incident general cohort: this analysis excluded from the general cohort patients who had epilepsy at baseline and examined the OR of outcomes adjusting for the PS.

4. Epilepsy incident healthy cohort: this analysis excluded from the healthy cohort patients who had epilepsy at baseline and examined the OR of outcomes adjusting for the PS.

5. High-intensity statin users versus lower-intensity statin users of the general cohort: this analysis only included statin users from the general cohort and examined the OR of outcomes between high-intensity statin users on the one hand and moderate-/low-intensity statin users on the other hand, adjusting for PS and epilepsy at baseline.

6. High-intensity statin users versus lower-intensity statin users of the healthy cohort: this analysis only included statin users from the healthy cohort and examined the OR of outcomes between high-intensity statin users and moderate-/low-intensity statin users, adjusting for PS and epilepsy at baseline.

The intensity of statin use was defined per the 2013 American Colled of Cardiology/American Heart Association cholesterol guidelines; however, simvastatin 80 mg was added to the high-intensity group because it was commonly used at the study time but not at the time of the guideline publication.[24]

Assuming a population prevalence of epilepsy at 1.5%, statins can reduce the prevalence of epilepsy by 35% based on previous literature.[9,10] With these assumptions, a total of 14 672 patients (7336 patients per group) is required to achieve 80% power with a 2-sided α value

of .05. Baseline characteristics of both the PS-matched general and PS-matched healthy cohorts were compared via χ^2 tests for the categorical variables and unpaired 2-tailed *t*-test for continuous variables. PS matching was done using a logistic regression model to obtain a nearest 1:1 match between treatment groups using procedures described previously.[25,26] For the primary analysis, unadjusted ORs using conditional logistic regression and the adjusted OR using logistic regression analysis were calculated as detailed earlier. Secondary analyses were conducted using a separate logistic regression model for each cohort; statin use (or high-intensity use) was the independent variable and the risk of epilepsy was the dependent variable, adjusting for other covariates as mentioned earlier. Statistical significance was defined as a 2-tailed *P* value <0.05. The analysis was conducted with Stata version 12 (College Station, TX) and SPSS version 23 (Armonk, NY). The study was approved by the institutional review board of the Brooke Army Medical Center and VA North Texas Health Care System.

Results

The general cohort included 43 438 patients (13 626 statin users and 29 812 nonusers). The healthy cohort included 25 969 participants (3982 statin users and 21 987 nonusers). Statin users were older, had more comorbidities, and generally used other medications more frequently. The characteristics of the general cohort and healthy cohort have previously been described.[17,18] The mean follow-up duration in the general cohort was 6.19 ± 0.64 years. The distribution of statins prescribed in the general cohort was as follows: simvastatin (73.5%), atorvastatin (17.4%), pravastatin (7%), and rosuvastatin (1.7%). Average statin use was 4.65 ± 1.82 years. In the general cohort, 8412 patients received lower-intensity statins and 5214 high-intensity statins. In the healthy cohort, 2827 received lower-intensity statins and 1155 high-intensity statins.

A total of 6342 statin users were matched to 6342 non-users in the PS-matched general cohort and 3351 statin users to 3351 nonusers in the PS-matched healthy cohort. After matching, there were no significant differences between statin users and nonusers in baseline characteristics include in PS creation (Tables 1 and 2). In the PS-matched general cohort, 5276 (83.2%) statin users continued to dispense their statins for 2 years and 3887 (61.3%) for 4 years. In the PS-matched healthy cohort, nonusers had a higher prevalence of epilepsy at baseline.

Primary Analysis

There was no significant difference in the OR for epilepsy (Table 3) between statin users and nonusers of the PS-matched general cohort (OR = 0.54; 95% CI = 0.67–1.23) or the PS-matched healthy cohort (OR = 0.76; 95% CI = 0.64–1.83).

Secondary Analyses

Table 3 summarizes secondary analyses. The odds of being diagnosed with epilepsy were similar among statin users and nonusers in all secondary analyses. Similarly, the odds of being diagnosed with epilepsy among high-intensity statin and lower-intensity statin users from the general and healthy cohorts in comparison to nonusers were similar (Table 4).

Discussion

This study showed that statin therapy was not associated with increased or decreased risk of being diagnosed with epilepsy. The results were consistent throughout primary and secondary analyses. The proposed association between statins and epilepsy has gained interest, in recent years, because of statins' known vasoprotective effects and postulated neuroprotective effects in some neurological conditions such as stroke, Parkinson disease, Alzheimer disease, and seizures.[13,27]

Only a few studies have investigated the association between statin use and epilepsy risk in a human population.[8–10] Findings have been limited and conflicting, with studies suggesting beneficial, harmful, and no effects of statins on epilepsy.[13] For example, in a population-based case-control study, statin use in older cardiovascular patients, who had undergone a revascularization procedure, was associated with lower risk of hospitalization for epilepsy in both current and past users of statin drugs. However, significant differences existed in comorbidities and in the proportions of statin users of cases and controls, as detailed earlier.[9] Another retrospective study of older veterans, which noted statin users to have less likelihood of new-onset epilepsy, also found, along with statin use, that older age, obesity, and hypercholesterolemia were associated with a lower likelihood of developing epilepsy,[10] which was inconsistent with epidemiological studies.[11] The investigators proposed a "healthy user effect" as an explanation for the perceived protective effects of statins on epilepsy. This healthy user effect suggests that patients prescribed statins may simply be more health conscious and likely to use preventive health services, limiting their risk for comorbidities. In another study investigating poststroke patients, patients taking statins were found to have a decreased risk of seizures.[8]

Evidence to the contrary exists as well. Atorvastatin given at a dose of 50 mg/kg before kainic acid administration increased the proportion of mice that experienced status epilepticus.[14] A similar intensifying effect was found by lovastatin treatment.[15] Case reports have also shown examples of statin use being linked to seizures.[16] In addition, some studies have found no association between statin use and seizures.[13,14]

To investigate if the effect of statins on risk of epilepsy is through decreasing risk of stroke or through an independent neuroprotective effect, this study examined the association between statin use and risk of epilepsy in a healthy population, which, to our knowledge, has not been previously studied. Akin to the general cohort, there was no association between statin use and epilepsy risk in the healthy cohorts throughout analyses. Of interest, however, is that nonusers in the PS-matched healthy cohort had a higher prevalence of epilepsy at baseline, although they were matched in all baseline characteristics, including demographic factors, cardiovascular comorbidities, and health care use. It is likely that a selection bias existed where physicians avoided prescribing statins to patients with epilepsy either to facilitate their care or to limit drug interactions. This clinician bias was demonstrated in a Scottish survey-based study, which asked general practitioners for treatment recommendations for patient vignettes, each with a 10-year cardiovascular risk of 20%. The patient vignettes included patients with diabetes and epilepsy. Statin therapy was recommended by 88% and 85% of respondents for patients with type 1 and type 2 diabetes,

respectively, but by only 31% for patients with epilepsy.[28] These findings demonstrate that clinician bias may reduce the chances of a patient receiving a potentially beneficial statin treatment.

This study is one of the largest retrospective studies investigating epilepsy risk with statin use. To our knowledge, this study is also the only study to include a healthy cohort to investigate if statins have an independent, clinically significant neuroprotective effect. However, several limitations of this study exist. Primarily because of its retrospective nature, some confounding factors may still not be identified. In addition, using ICD-9 codes to identify epilepsy has a 99% sensitivity and 70% specificity[21] and may have missed some cases. Additionally, the use of ICD-9 codes to identify epilepsy was not specifically validated in the Tricare population; however, we are not aware of any specific reason for differential ascertainment between Tricare data and other governmental insurance such as Medicare. The Tricare Prime or Plus program population includes active duty military personnel (approximately 17%), enrolled veterans, and their families; therefore, age and sex distribution can be similar the general population. Health care services for Tricare beneficiaries may be provided within or outside military health care facilities. Studies have shown general similarities between health care services, diagnostic groups, or procedures performed to Tricare beneficiaries and other US populations.[29,30] This study also used statin prescription filling from pharmacy data as a surrogate for their intake. Such an assumption cannot be ascertained; however, 83% and 61% of statin users continued to refill their statin prescriptions at 2 and 4 years of follow-up, respectively, which is higher than the percentage reported in other populations.[31,32] Hence, it is reasonable to assume that statin users actually adhered to their therapy not just filled the prescriptions. Because of the longitudinal nature of the follow-up, in which statin users used different doses and types of statins, it was impossible to differentiate if different types of statins (based on their ability to cross the blood-brain barrier) may have different effects. Finally, Table 3 shows that a total of 43 438 patients were included in the general cohort. The PS-matched cohort had 12 684 patients (6342 patients per group), which does not meet power. However, the estimate in the PS-matched cohort is similar to the estimates found in the general cohort (43 438 participants), healthy cohort (25 969 participants), epilepsy-incident general cohort (43 119 participants), and the epilepsy-incident healthy cohort (25 802 participants). These estimates were found with similar good precision based on the 95% CIs. Therefore, it offers confidence that the lack of association of statins with risk of epilepsy is not a result of lack of power in the study.

In conclusion, this study did not find an association between statin use and epilepsy in a general and a healthy cohort of patients. Moreover, there was no increased risk of epilepsy in patients using statin drugs. These results should offer assurance to clinicians and patients about the safety of statin use in patients with epilepsy. The higher prevalence of epilepsy at baseline among nonusers suggests that clinicians may be avoiding prescribing these beneficial medications among patients with epilepsy. Clinicians should not refrain from prescribing statins to their patients to lower their cardiovascular risk if otherwise indicated based on guidelines.

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Table 1.

Selected Baseline Characteristics of Propensity Score–Matched Statin Users and Nonusers From the General Cohort.[a]

Variable	Statin User		
	No (%), n = 6342	Yes (%), n = 6342	P Value
Age in years: mean ± SD	56.0 ± 12.0	55.7 ± 12.4	0.1
Women	2856 (45.0)	2924 (46.1)	0.2
Alcohol-related disorders	83 (1.3)	78 (1.2)	0.7
Substance-related disorders	24 (0.4)	22 (0.3)	0.8
Smoker[b]	534 (8.4)	509 (8.0)	0.4
Hypertension	3766 (59.4)	3707 (58.5)	0.3
Dysrhythmia	874 (13.8)	887 (14.0)	0.8
Cerebrovascular disease	128 (2.0)	125 (2.0)	0.9
Peripheral and visceral atherosclerosis	153 (2.4)	169 (2.7)	0.4
Aortic, peripheral, and visceral artery aneurysms	39 (0.6)	54 (0.9)	0.1
Charlson comorbidity index[c]: mean ± SD	0.64 ± 1.23	0.66 ± 1.25	0.3
Health care use at baseline			
Number of inpatient admissions during baseline period	0.25 ± 0.75	0.26 ± 0.77	0.8
Number of outpatient medical encounters during baseline period	31.67 ± 36.76	31.81 ± 40.63	0.8
Medications at baseline			
β-Blocker	1099 (17.3)	1123 (17.7)	0.6
Calcium channel blocker	987 (15.6)	1001 (15.8)	0.8
Aspirin	1835 (28.9)	1890 (29.8)	0.3
Nonsteroidal anti-inflammatory drug	3729 (58.8)	3702 (58.4)	0.6
Selective serotonin reuptake inhibitor	1059 (16.7)	1067 (16.8)	0.9
Parameters not included at propensity score matching			
Epilepsy during baseline period	61 (1.0)	40 (0.6)	0.4

[a] Complete results of all variables included were previously published.[17] Diagnosis groups are defined as per the Agency of Health Research and Quality-Clinical Classification Software, except if otherwise specified.

[b] Diagnosis was defined as ICD-9-CM codes 3051 and V1582.

[c] The Charlson comorbidity index was calculated using the Deyo et al method.[23]

Table 2.

Selected Baseline Characteristics of Propensity Score–Matched Statin Users and Nonusers From the Healthy Cohort.[a]

Variable	Statin User		
	No (%), n = 3351	Yes (%), n = 3351	P Value
Age in years: mean ± SD	53.0 ± 11	53.0 ± 11	0.72
Women	1285 (38.3)	1314 (39.2)	0.48
Alcohol-related disorders	29 (0.9)	31 (0.9)	0.80
Substance-related disorders	12 (0.4)	8 (0.2)	0.38
Smoker[b]	241 (7.2)	237 (7.1)	0.89
Comorbidities in baseline period			
Charlson comorbidity index[c]: mean ± SD	0 ± 0.0	0 ± 0.0	
Hypertension[d]	1704 (50.9)	1678 (50.1)	0.54
Overweight/obese	493 (14.7)	455 (13.6)	0.19
Asthma	102 (3.0)	96 (2.0)	0.71
Osteoarthritis, arthropathy, and back disorder	1534 (45.8)	1548 (46.2)	0.75
Rehabilitation care, fitting of prostheses, and adjustment of devices	506 (15.1)	544 (16.2)	0.21
Health care use at baseline			
Number of inpatient admissions during baseline period: mean ± SD	0.08 ± 0.3	0.08 ± 0.3	0.82
Number of outpatient medical encounters during baseline period: mean ± SD	21.1 ± 22.7	21.1 ± 19.1	0.97
Medications at baseline			
β-Blocker	428 (12.8)	459 (13.7)	0.28
Diuretic	728 (21.7)	742 (22.1)	0.71
Calcium channel blocker	384 (11.5)	395 (11.8)	0.70
Aspirin	777 (23.2)	826 (24.6)	0.16
Nonsteroidal anti-inflammatory drug	1911 (57.0)	1926 (57.5)	0.73
Selective serotonin reuptake inhibitor	441 (13.2)	456 (13.6)	0.62
Antipsychotics	30 (0.9)	26 (0.8)	0.69
Sedatives	519 (15.5)	525 (15.7)	0.84
Parameters not included at propensity score matching			
Epilepsy during baseline period	21 (0.6)	9 (0.3)	0.04

[a]Complete results of all variables included were previously published.[18]

[b]Diagnosis was defined as ICD-9-CM codes 3051 and V1582.

[c]The Charlson comorbidity index was calculated using the Deyo et al method.[23]

[d]We included patients with hypertension but excluded those with hypertension with complications, secondary hypertension, or end-organ damage. Similarly, we included patients with asthma but excluded those with chronic obstructive pulmonary disease, bronchiectasis, respiratory failure, or insufficiency.

Table 3.

Risk of Epilepsy in Statin Users and Nonusers.

Variable	Statin User		OR	95% CI	P Value
	No (%)	Yes (%)			
Primary analyses					
PS-matched general cohort: 6342 nonusers and 6342 statin users	141 (2.2)	114 (1.8)	0.91[a]	0.67–1.23	0.54
			0.91[b]	0.67–1.22	0.52
				0.63–1.03	0.09
			0.81[c]		
PS-matched healthy cohort: 3351 nonusers and 3351 statin users	46 (1.4)	37 (1.1)	1.08[a]	0.64–1.83	0.76
			1.08[b]	0.64–1.82	0.78
			0.80[c]	0.52–1.24	0.32
Secondary analyses					
General cohort: 29 812 nonusers and 13 626 statin users	443 (1.5)	327 (2.4)	0.97[a]	0.75–1.25	0.78
Healthy cohort: 21 987 nonusers and 3982 statin users	246 (1.1)	43 (1.1)	0.94[a]	0.60–1.48	0.80
Epilepsy-incident general cohort: 29 602 nonusers and 13 517 statin users	261 (0.9)	240 (1.8)	0.99[d]	0.76–1.29	0.95
Epilepsy-incident healthy cohort: 21 885 nonusers and 3917 statin users	150 (0.7)	33 (0.8)	0.88[d]	0.61–1.52	0.97

Abbreviations: OR, odds ratio; PS, propensity score.

[a] Adjusted OR: adjusting for epilepsy at baseline and propensity score.

[b] Adjusted odds ratio: adjusting for epilepsy at baseline.

[c] Unadjusted odds ratio using conditional logistic regression analysis.

[d] Adjusted OR: adjusting for propensity score.

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Table 4.

Risks of Epilepsy in High-Intensity Statin Users in Comparison to Lower-Intensity Statin Users.

Variable	Lower-Intensity Statin Users (%)	High-Intensity Statin Users (%)	Adjusted OR	95% CI	P Value
Dose response in general cohort: 8412 lower-intensity statin users and 5214 high-intensity statin users					
Epilepsy	187 (2.2)	140 (2.7)	1.02[a]	0.79–1.31	0.90
Dose response in healthy cohort: 2827 lower-intensity statin users and 1155 high-intensity statin users					
Epilepsy	23 (0.8)	20 (1.7)	1.90[a]	0.96–3.77	0.65

[a] Adjusted odds ratio (OR): adjusting for epilepsy at baseline and propensity score.