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The effect of statin therapy on the incidence of infections: a retrospective cohort analysis

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Abstract

Introduction—Statins have been postulated to prevent infection through immunomodulatory effects.

Objectives—To compare the incidence of infections in statin-users to that in non-users within the same healthcare system.

Methods—This was a retrospective cohort study of patients enrolled as Tricare Prime or Plus in the San Antonio military multi-market. Statin-users were patients who received a statin for at least 3 months between 10/1/2004 and 9/30/2005. Non-users were patients who did not receive a statin within the study period (10/1/2003 to 9/30/2009). Inpatient and outpatient International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes were used to

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determine the incidence of infections during the follow-up period (10/1/2005 to 9/30/2009) via multivariable regression analysis and time to infection via Cox regression analysis.

Results—Of 45,247 patients who met the study criteria, 12,981 (29%) were statin-users and 32,266 were non-users. After adjustments for age, gender, Charlson Comorbidity Score, tobacco use, alcohol abuse/dependence, health care utilization, and use of specific medication classes, statin use was associated with an increased incidence of common infections [odds ratio (OR): 1.13; 95% CI: 1.06–1.19], but not influenza or fungal infections (OR: 1.06, 95% CI: 0.80–1.39; OR: 0.97; 95% CI: 0.91–1.04, respectively). Time to first infection was similar in statin-users and non-users in all infection categories examined.

Conclusion—Statin use was associated with an increased incidence of common infections, but not influenza or fungal infections. This study does not support a protective role of statins in infection prevention; however, the influence of potential confounders cannot be excluded.

Keywords

Statin; infection; fungal; influenza

Introduction

In addition to their beneficial effects on cardiovascular mortality and morbidity, hydroxyl methyl glutaryl coenzyme A reductase inhibitors (statins) have been shown to have pleotropic effects including reversing endothelial dysfunction,[1, 2] decreasing inflammatory cytokines,[3, 4] and limiting sepsis-induced coagulopathy.[5–7] These effects would potentially be beneficial in patients with infection, hence, several studies have investigated the association of statins and infection with mixed results. Some studies have found a beneficial effect of statins on both infection prevention and improved outcomes, including mortality.[8–16] Other studies have found no significant effect,[17–22] while still others found a harmful effect.[23] Several meta-analyses have also yielded conflicting results depending on the included studies.[24–26] Little is known of the relationship between statins and influenza or fungal infections as most of these studies evaluated the effect of statins on bacterial infections.

A major limitation of observational studies in relation to the effects of statins on infection is that statin use may be a surrogate marker for a more “health-conscious patient” (healthy-user bias) or receipt of care in a better health care system.[27–29] The military health care system offers similar accessibility and standards of care for all enrolled patients, thus, research conducted in the military setting greatly reduces the likelihood of such a bias. The objective of this study was to compare the incidence of infections in statin-users to that in non-users in a setting of a more homogenous health care system.

Methods

This was a retrospective cohort study of patients in the San Antonio, TX Department of Defense (DoD) multi-market between October 1, 2003 to September 30, 2009. This study was approved by the Institutional Review Board at the Brooke Army Medical Center and the University of Texas Health Science Center at San Antonio.

Medication fill and medical encounter diagnoses data were extracted using the Military Health System Management Analysis and Reporting Tool (M2). These data encompass all inpatient medical records, outpatient medical records, purchased care from facilities outside military facilities, and medication fill records billed to the Military Health Care regardless of

pharmacy location. The M2 is a reliable source of data, and has been successfully utilized in previous research.[30–32]

The study period was divided into two main intervals. The baseline period encompassed the dates October 1, 2003 to September 30, 2005 (fiscal years [FY] 2004–2005). This period was used to describe patient baseline characteristics. Various comorbidities were determined using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes during this period; the Charlson Comorbidity Score was then calculated using the Deyo *et al* method.[33] Outcomes were assessed during the follow-up period (FY 2006–2009) using ICD-9-CM codes of interest (as defined below).

Patient groups

Patients were eligible for this study if they were 35 to 80 years of age, enrolled as Tricare Prime or Plus to receive care at DoD medical facilities in the San Antonio area in 2009, had at least one outpatient visit in the baseline period and one outpatient visit in the follow-up period, and received at least one prescription medication in the baseline period. Therefore, all our patients in the cohort were active in the Tricare system during the baseline period (FY2004–2005) and in 2009. Patients were divided into two groups. Statin-users were defined as patients who received any statin for at least three months between Oct 1, 2004 and Sep 30, 2005 (FY 2005). Statin non-users did not receive a statin within the study period (FY 2004–2009).

Trauma and burn patients were excluded, since Brooke Army Medical Center (BAMC) is a major burn and trauma center. Burn patients were identified based on ICD-9-CM codes consistent with this diagnosis as compiled by the Agency for Health Research and Quality-Clinical Classifications Software (AHRQ-CCS).[34] Trauma codes were compiled from ICD-9-CM manuals and previous publications.[35, 36] Patients who were newly started on statins after Sep 30, 2005 were excluded to allow for equal periods of follow-up between the two comparison groups.

Outcome measures

The study outcomes included comparisons of the incidence and time-to-event of infectious diseases groups in either the inpatient or outpatient setting between statin-users and non-users:

- Common infections group: This group included a convenience sample of infections commonly encountered in clinical practice and were defined using ICD-9-CM codes. This group included acute respiratory infections (460–466),[37–39] pneumonia (480–483, 485–487), [40, 41] bacteremia (790.7), sepsis (995.91, 995.92, 996.64),[42–44] skin infections (680–686),[45–47] and urinary tract infections (590–599).
- Influenza (487.x): This diagnosis was also included as a part of the common infections group.
- Fungal infections: This group included dermatophytosis (110–111), candidiasis (112), coccidioidomycosis (114), histoplasmosis (115), blastomycotic infection (116), other mycoses (117), and opportunistic mycoses (118).

Statistical analysis

Continuous data were described as means ± standard deviations and dichotomous data were described as percentages. Statin-users and non-users were compared with appropriate two-way tests (i.e., Chi-square and Student's t tests). Each infectious disease outcome was

treated as a separate dependent variable and statin-use as an independent variable in multivariable logistic regression analyses. Other covariates in the model were patient age, gender, total Charlson Comorbidity Score (Deyo method[33]), tobacco use, alcohol dependence/abuse, number of inpatient admissions in the baseline period, number of outpatient visits in the baseline period, and use of the following medications: beta-blockers, diuretics, calcium-channel blockers, ACE inhibitors, oral hypoglycemics, aspirin, and steroids. The use of various classes of medications has been noted by some investigators to characterize comorbidities,[48] and some classes of medications have been noted to affect the outcome of infections in conjunction with statins.[49] Cox proportional hazards regression analyses were used to compare time to infection. The same covariates were used in all regression models. Results were presented as *p*-values, odds ratios, and 95% confidence intervals. Comparisons were considered to be statistically significant if the calculated *p*-value was less than an alpha level of 0.05. Data were analyzed using SAS 9.2 (SAS Institute, Inc., Cary, NC) and JMP 8.0 (SAS Institute, Inc., Cary, NC).

Results

Of 56,028 patients that were identified, 45,247 patients met the study criteria; 10,781 patients were excluded (8,784 patients were newly started on statins after September 30, 2005, and 1,997 were burn or trauma patients). Of patients that met study criteria, 12,981 (29%) were statin-users and 32,266 were non-users. Among statin-users, the mean (standard deviation) of cumulative duration of statin use was 1690 (666) days; 5.6% used statins for less than 1 year, 12.1% for less than 2 years, and 20.5% for less than 3 years. Overall, 34.1% used a maximum dose of statins defined as 80 mg of simvastatin, 80 mg of pravastatin, 80 mg of atorvastatin, or 40 mg of rosuvastatin. Baseline characteristics are presented in Table 1. In comparison to non-users, statin-users were significantly older (mean age 59.3 years vs. 44.4 years) and had a lower proportion of females (41.2% vs. 54.2%), a higher mean Charlson Comorbidity Score (1.2 vs. 0.26), and greater health care utilization for both inpatient and outpatient encounters. Additionally, statin-users had a higher rate of medication utilization for most medication classes, excluding systemic corticosteroids. Statin-users also had lower LDL and HDL levels compared to non-users.

During the follow-up period, the total number of patients who were diagnosed with an infection consistent with the common infection diagnosis group among statin-users was 8,939 (68.9%) and non-users was 19,323 (59.9%). After adjustments for potential baseline confounders, there was a significantly higher odds of having common infection diagnosis among statin-users in comparison to non-users (odds ratio [OR]: 1.13; 95% confidence interval [95%-CI]: 1.06–1.20) (Table 2). The total number of patients diagnosed with influenza during the follow-up period among statin-users was 145 (1.1%) and among non-users was 307 (0.9%). The adjusted OR for influenza infection was similar among statin-users and non-users (OR: 1.06, 95%-CI: 0.80–1.39).

The total number of patients diagnosed with fungal infections during the follow-up period among statin-users was 3,171 (24.4%) and among non-users was 5,667 (17.6%). The adjusted OR for fungal infection was similar among statin-users and non-users (OR: 0.97, 95%-CI: 0.91–1.04).

Table 3 depicts the time-to-event analysis for the occurrence of the first infection. There were no statistically significant differences in the hazard ratio of infectious disease outcome groups.

Discussion

The results of this retrospective study suggest that statin use is associated with higher incidence of common infections, but not influenza or fungal infections. Previous studies that addressed the effect of statin therapy on infections have focused on two general aspects: investigating the association of statins with the incidence of infections (that is, the effect of statins in preventing infections) and the association of statins with severity of infections, such as mortality. This study did not evaluate the effect of statins on the severity of infection or mortality; rather it focused on the association of statin therapy and the incidence of infections.

Several observational studies have investigated the role of statins in the prevention of infection.[16, 50–53] These studies varied by population size, with most including fewer than 5,000 patients. Most studies noted that statin use was associated with decreased risk of infection. Hackam *et al* analyzed data from a large population-based cohort study in Ontario, Canada from 1997 to 2002.[11] Propensity score-match subgroups were created in the identified 141,487 patients older than 65 years who had been hospitalized for an acute coronary syndrome, ischemic stroke, or revascularization. The matched cohort included 69,168 patients (34,584 statin-users and 34,584 non-users). After adjustments for demographic characteristics, sepsis risk factors, comorbidities, and health care use, the risk of sepsis was lower in statin-users (hazard ratio [HR]: 0.81; 95% CI: 0.72–0.90).[11]

However, not all studies support a protective effect of statins from infection. One case-control study (1,125 validated cases of pneumonia and 2,235 matched controls) found no association between statin use and risk of infection after adjusting for functional and cognitive status.[51] Another large population-based cohort study used a propensity score-based method to control for differences between statin-users and non-users in the United Kingdom. Statin-users (n=129,288) were compared with a matched sample of 600,241 people who did not receive statins, with a median follow-up period of 4.4 years. The investigators noted that statin use was not associated with an effect on a wide range of outcomes, including infections.[54]

Two meta-analyses have concluded that statins appear to prevent infections;[25, 26] however, in a recent meta-analysis of large randomized controlled trials that investigated the effects of statins on cardiovascular mortality, statins were not found to be beneficial in preventing infection.[55]

Studies that investigated the effects of statins on the severity of infection, whether the development of severe infection or infection-related mortality, have also yielded mixed results.[11–16, 19, 22] Several studies found that prior use of statins was associated with less mortality in sepsis or pneumonia.[8, 9, 14, 15, 56, 57] Other studies found no difference in mortality in statin-users versus non-users,[20, 21] or worse outcomes.[23]

The present study also investigated the effect of statins on the development of fungal infections, for which there is a paucity of published literature compared to bacterial infections. Forrest *et al* investigated the effect of statins on mortality in ICU patients with candidemia and found a beneficial effect.[58] Another retrospective cohort study on diabetic patients undergoing gastrointestinal surgery found a decreased incidence of candidal infections among statin-users;[59] however, a small case-control study evaluating the effect of statins on the incidence of invasive fungal infections (including zygomycosis, aspergillosis and candidal invasive infections) found no difference between statin-users and non-users.[60]

Fewer studies have been performed to investigate the effect of statins on influenza. A retrospective case-control study on pre-hospital statin use and its effect on the severity of

inpatient influenza infection found no significant correlation.[61] Vandermeer *et al* performed a retrospective cohort of patients hospitalized with laboratory-confirmed influenza infection.[62] Pre-hospital or inpatient statin use was correlated with decreased mortality in patients with influenza. The present study did not evaluate the effect of statins on the severity of influenza, but on the incidence of influenza. The study revealed no difference in the incidence of influenza among statin-users versus non-users; however, these results should be cautiously interpreted due to the small proportion of patients with influenza infection (approximately 1%).

The controversy regarding the cause of these conflicting results regarding the effect of statins on infection prevention includes the choice of outcome measures utilized and the method of adjusting for baseline confounders.[63] One caveat in population-based cohort studies is the “healthy-user bias”. Studies have shown that statin use may be a surrogate marker for a more “health-conscious patient” (healthy-user bias). In a prospective cohort study of patients who initiated statin therapy for primary cardiovascular prevention, statin-adherent patients were less likely than non-adherent patients to have motor vehicle accidents and workplace accidents, after adjusting for potential confounders.[27] Additionally, since adherence to statin therapy was associated with the use of preventive health services,[28] statin use may be a surrogate marker for a better health care system, better access to care, or presence of medical insurance. Additionally, publication bias may play a role in overestimating the benefits of statins. In a systematic review and meta-analysis, seven cohort studies that addressed infection prevention in association with statin use were identified.[26] The pooled effect estimate showed a lower incidence of infection associated with statin use (OR: 0.57; 95% CI: 0.43–0.75).[26] However, the authors noted that the funnel plot summary of identified studies is suggestive of publication bias; hence, the treatment effect may be overestimated.

This study contributes to the current literature in several ways. The study population represents a more homogenous sample of patients in regard to health care system accessibility, affordability, and utilization, which, collectively, minimize biases that may have been encountered in prior investigations. However, equal access to care does not equate to equal utilization of care. This study also included both inpatient and outpatient medical records. Analysis included adjustments for several potential confounders such as age, gender, total Charlson comorbidity score, utilization of specific classes of medications, and health care utilization (number of inpatient admissions and outpatient visits). Health care utilization is an important confounder that may result in ascertainment bias. Frequent health care utilization may result in more disease diagnoses, and hence, a falsely increased incidence of diseases among its population.

There are several limitations to the study. Due to the retrospective study design, there are significant differences in baseline characteristics between the two comparison groups. Despite adjusting for several potential baseline confounders, there may be other differences between the groups that were not accounted for. Other factors, such as severity of illness or other comorbidities may have accounted for differences in outcome between statin-users and non-users. Furthermore, despite the large sample size, some diagnoses had small total numbers of encounters, such as influenza. The lack of effect for these secondary outcomes may be explained by insufficient power to detect a difference. Another limitation for our study is that we used a convenience sample of ICD-9 diagnoses that encompass the most commonly encountered infections in clinical practice. Ideally, we should have included all possible infections, except for the time and cost. Additionally, the use of administrative data to identify some infections such as pneumonia and influenza may not be accurate.[64, 65] The use of pharmacy data and billing claims to account for medication use assumes that patients are actually taking their medications and not simply filling their prescriptions. Such an

assumption cannot be ascertained, though, it may be argued that the long duration of use (approximately 95% of our statin-users dispensed a statin for more than a year) can be considered as a surrogate marker for actual use.

In conclusion, statin use in this study was not associated with a protective role on incidence of infections. Further randomized studies or large registries are required to more definitively ascertain the relationship between statin use and infection.

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Table 1

Baseline characteristics of statin-users and non-users

	Statin-users (n = 12,981)	Non-users (n = 32,266)	
Age (years), mean ± SD	59.3 ± 11.5	44.4 ± 10.7	< 0.0001
Female gender, n (%)	5,342 (41.2)	18,125 (54.2)	< 0.0001
Charlson Comorbidity Score variables:			
Acute myocardial infarction, n (%)	711 (5.5)	112 (0.3)	< 0.0001
Congestive heart failure, n (%)	650 (5)	137 (0.4)	< 0.0001
Peripheral vascular disease, n (%)	767 (5.9)	169 (0.5)	< 0.0001
Cerebrovascular disease, n (%)	478 (3.7)	205 (0.6)	< 0.0001
Dementia, n (%)	41 (0.3)	33 (0.1)	< 0.0001
Chronic obstructive pulmonary diseases, n (%)	1,938 (14.9)	2,398 (7.4)	< 0.0001
Rheumatologic diseases, n (%)	277 (2.1)	456 (1.4)	< 0.0001
Peptic ulcer disease, n (%)	195 (1.5)	249 (0.8)	< 0.0001
Mild liver disease, n (%)	47 (0.4)	113 (0.4)	0.9
Diabetes mellitus, n (%)	4,188 (32.3)	826 (2.6)	< 0.0001
Diabetes mellitus with complications, n (%)	1,577 (12.1)	171 (0.5)	< 0.0001
Hemiplegia/paraplegia, n (%)	45 (0.3)	25 (0.1)	< 0.0001
Renal disease, n (%)	430 (3.3)	110 (0.3)	< 0.0001
Malignancy, n (%)	918 (7.1)	1,042 (3.2)	< 0.0001
Liver disease (moderate/severe), n (%)	7 (0.1)	39 (0.1)	0.05
Metastatic neoplasm, n (%)	43 (0.3)	95 (0.3)	0.5
Human immunodeficiency virus, n (%)	13 (0.1)	39 (0.1)	0.6
Charlson Comorbidity Total Score, mean ± SD	1.2 ± 1.6	0.26 ± 0.8	< 0.0001
Alcohol abuse/dependence, n (%)	128 (1)	234 (0.7)	.006
Tobacco use, n (%)	1,215 (9.4)	1,891 (5.9)	< 0.0001
HDL-C in baseline period, mean ± SD	52.3 ± 14.4	58.3 ± 17.8	< 0.0001
HDL-C in follow-up period, mean ± SD	51 ± 13.5	57 ± 16.5	< 0.0001
LDL-C in baseline period, mean ± SD	105.9 ± 33.9	111.1 ± 27.9	< 0.0001
LDL-C in follow-up period, mean ± SD	98.7 ± 31.5	112.6 ± 27.3	< 0.0001
Number of outpatient visits during baseline period, mean ± SD	39.8 ± 44.3	22.7 ± 31.6	< 0.0001
Number of inpatient admissions during baseline period, mean ± SD	0.4 ± 1	0.18 ± 0.6	< 0.0001
Medications:			
Beta-blocker, n (%)	3,610 (27.8)	2,062 (6.4)	< 0.0001
Diuretic, n (%)	4,764 (36.7)	3,249 (10.1)	< 0.0001
Calcium channel blocker, n (%)	3,214 (24.8)	1,521 (4.7)	< 0.0001
ACEI/ARB, n (%)	7,504 (57.8)	3,303 (10.2)	< 0.0001
Oral hypoglycemic, n (%)	2,707 (20.9)	376 (1.2)	< 0.0001
Aspirin, n (%)	6,839 (52.7)	2,513 (7.8)	< 0.0001
Systemic corticosteroid, n (%)	515 (4)	1,360 (4.2)	0.24

ACEI/ARBs= Angiotensin converting enzyme inhibitors/angiotensin-receptor blockers &; HDL=High-density lipoprotein in mg/dL; LDL= Low-density lipoprotein in mg/dL; SD= standard deviation

Table 2

Comparison of infectious diseases outcome between statin-users and non-users

Infection	Statin-Users (n=12,981)	Non-Users (n=32,266)	Adjusted OR (95% CI) *
	n (%)	n (%)	
Common infections group	8,939 (68.9)	19,323 (59.9)	1.13 (1.06–1.19)
Influenza	145 (1.1)	307 (0.9)	1.06 (0.80–1.39)
Fungal infections	3,171 (24.4)	5,667 (17.6)	0.97 (0.91–1.04)

* Logistic regression analysis; covariates were patient age, patient gender, total Charlson Comorbidity Score, tobacco use, alcohol use/abuse, number of inpatient admissions in the baseline period, number of outpatient admissions in the baseline period, and use of the following medications: beta-blockers, diuretics, calcium-channel blockers, ACE inhibitors/ARBs, oral hypoglycemics, aspirin, and steroids.

OR=odds ratio, CI=confidence interval

Table 3

Comparison of time-to-first infection in statin-users and non-users

Infection, mean ± SD (days)	Statin-Users (n = 12,981)	Non-Users (n = 32,266)	Adjusted HR (95% CI)
Common infections group	614 ± 409	637 ± 412	0.99 (0.95–1.02)
Influenza	745 ± 470	813 ± 463	1.10 (0.83–1.46)
Fungal infections	771 ± 434	727 ± 428	0.99 (0.93–1.05)

* Proportional Hazards Regression; Time in days; covariates were patient age, patient gender, total Charlson Comorbidity Score, tobacco use, alcohol use/abuse, number of inpatient admissions in the baseline period, number of outpatient admissions in the baseline period, and use of the following medications: beta-blockers, diuretics, calcium-channel blockers, ACE inhibitors, oral hypoglycemics, aspirin, and steroids.