The Effect of Statin Therapy on the Incidence of Infections: A Retrospective Cohort Analysis

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Abstract: *Background:* Statins have been postulated to prevent infection through immunomodulatory effects. *Objectives:* To compare the incidence of infections in statin users to that in nonusers within the same health care system. *Methods:* This was a retrospective cohort study of patients enrolled as Tricare Prime or Plus in the San Antonio military multimarket. Statin users were patients who received a statin for at least 3 months between October 1, 2004 and September 30, 2005. Nonusers were patients who did not receive a statin within the study period (October 1, 2003-September 30, 2009). Inpatient and outpatient International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes were used to determine the incidence of infections during the follow-up period (October 1, 2005-September 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 nonusers. 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% confidence interval [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 nonusers in all infection categories examined. *Conclusions:* 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.

Key Indexing Terms: Statin; Infection; Fungal; Influenza. **[Am J Med Sci 2014;347(3):211–216.]**

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] whereas 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 nonusers in a setting of a more homogenous health care system.

METHODS

This was a retrospective cohort study of patients in the San Antonio, Texas Department of Defense multimarket between October 1, 2003 and 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 used in previous research.[30–32]

The study period was divided into 2 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[33] method. 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 Department of Defense medical facilities in the San Antonio area in 2009, had at least 1 outpatient visit in the baseline period and 1 outpatient visit in the follow-up period and received at least 1 prescription medication in the baseline period. Therefore, all our patients in the cohort were active in the Tricare system during the baseline period (FY, 2004-2005) and in 2009. Patients were divided into 2 groups. Statin users were defined as patients who received any statin for at least 3 months between October 1, 2004 and September 30, 2005 (FY, 2005). Statin nonusers did not receive a statin within the study period (FY, 2004-2009).

Trauma and burn patients were excluded because Brooke Army Medical Center 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 September 30, 2005 were excluded to allow for equal periods of follow-up between the 2 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 nonusers:

- 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 Analyses

Continuous data were described as means $\pm$ standard deviations, and dichotomous data were described as percentages. Statin users and nonusers were compared with appropriate 2-way tests (ie, χ^2 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 et al[33] method), 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).

RESULTS

Of the 56,028 patients who were identified, 45,247 patients met the study criteria and 10,781 patients were excluded (8784 patients were newly started on statins after September 30, 2005, and 1997 were burn or trauma patients). Of patients who met study criteria, 12,981 (29%) were statin users and 32,266 were nonusers. Among statin users, the mean $\pm$ standard deviation of cumulative duration of statin use was 1690 $\pm$ 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 nonusers, statin users were significantly older (mean age, 59.3 versus 44.4 years) and had a lower proportion of females (41.2% versus 54.2%), a higher mean Charlson Comorbidity Score (1.2 versus 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 low-density lipoprotein and high-density lipoprotein levels compared with nonusers.

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 8939 (68.9%) and nonusers was 19,323 (59.9%). After adjustments for potential baseline confounders, there were significantly higher odds of having common infection diagnosis among statin users in comparison with nonusers (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 nonusers was 307 (0.9%). The adjusted OR for influenza infection was similar among statin users and nonusers (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 3171 (24.4%) and among nonusers was 5667 (17.6%). The adjusted OR for fungal infection was similar among statin users and nonusers (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 2 general aspects: investigating the association of statins with the incidence of infections (ie, the effect of statins in preventing infections) and