Frequency of Development of Connective Tissue Disease in Statin-Users Versus Nonusers

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Statins have pleiotropic properties that may affect the development of connective tissue diseases (CTD). The objective of this study was to compare the risk of CTD diagnoses in statin users and nonusers. This study was a propensity score-matched analysis of adult patients (30 to 85 years old) in the San Antonio military medical community. The study was divided into baseline (October 1, 2003 to September 30, 2005), and follow-up (October 1, 2005 to March 5, 2010) periods. Statin users received a statin prescription during fiscal year 2005. Nonusers did not receive a statin at any time during the study. The outcome measure was the occurrence of 3 diagnosis codes of the *International Classification of Diseases, 9th Revision, Clinical Modification* consistent with CTD. We described co-morbidities during the baseline period using the Charlson Comorbidity Index. We created a propensity score based on 41 variables. We then matched statin users and nonusers 1:1, using a caliper of 0.001. Of 46,488 patients who met study criteria (13,640 statin users and 32,848 nonusers), we matched 6,956 pairs of statin users and nonusers. Matched groups were similar in terms of patient age, gender, incidence of co-morbidities, total Charlson Comorbidity Index, health care use, and medication use. The odds ratio for CTD was lower in statin users than nonusers (odds ratio: 0.80; 95% confidence interval: 0.64 to 0.99; p = 0.05). Secondary analysis and sensitivity analysis confirmed these results. In conclusion, statin use was associated with a lower risk of CTD. Published by Elsevier Inc. (Am J Cardiol 2013;112:883−888)

Statins (hydroxyl-methyl-glutaryl-coenzyme A reductase inhibitors) have been shown to interfere with downstream signaling molecules that have been implicated in both pro-inflammatory and anti-inflammatory processes.[1] Specifically, rheumatologic diseases are characterized by both systemic inflammation and an increased risk of cardiovascular disease,[2] making these diseases an attractive area of statin research. The effects of statins on the development of connective tissue disease (CTD) have been debated. Some studies have noted that statins may be protective against the development of rheumatoid arthritis (RA),[3,4] whereas others did not observe a link between statin use and RA.[5,6] Furthermore, a recent case-control study concluded that statin use was associated with an increased risk of developing RA.[7] The objective of this study was to examine the association of statin therapy with CTD in a propensity score-matched cohort of statin users and nonusers from a military health care system, where patients have similar access and standards of care.

Methods

This study was approved by the Institutional Review Board at the Brooke Army Medical Center. This is a retrospective cohort analysis of patients who were enrolled as Tricare Prime or Tricare Plus in the San Antonio area military health care system. The database and study population have been described elsewhere.[8] Briefly, the extracted data included outpatient medical records, inpatient medical records, administrative data of services offered outside military facilities, and pharmacy data. Outpatient medical records and inpatient medical records contain all medical services activities, diagnosis codes, and procedure codes. Pharmacy data include dispensed medications, regardless of the pharmacy location or affiliation. The Management Analysis and Reporting Tool was used to access and retrieve all patient encounter data and prescription history regardless of encounters location or affiliation. The utility and reliability of this tool in medical research is well described in the literature.[9−12]

The study was divided into baseline period (October 1, 2003 to September 30, 2005), which was used to describe baseline characteristics and follow-up period (October 1, 2005 to March 5, 2010), which was used to identify outcome events. During the baseline period, we identified 2 patient groups, statin users and nonusers. Statin users received a statin prescription of at least 90-day supply during the

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See page 887 for disclosure information.

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Table 1
Baseline characteristics of statin users and nonusers in the unmatched cohort

Variable	Users (n = 13,640)	Nonusers (n = 32,848)	p Value
Age (yrs), mean (SD)	60 (12)	45 (11)	<0.0001
Male gender	7,957 (58.3%)	14,387 (43.8%)	<0.0001
Co-morbid conditions			
Acute myocardial infarction*	798 (5.9%)	121 (0.4%)	<0.0001
Congestive heart failure*	747 (5.5)	164 (0.5%)	<0.0001
Peripheral vascular disease*	859 (6.3%)	190 (0.6%)	<0.0001
Cerebrovascular disease*	553 (4%)	226 (0.7%)	<0.0001
Dementia*	58 (0.4%)	45 (0.1%)	<0.0001
Chronic obstructive pulmonary diseases*	2,062 (15.1%)	2,462 (7.5%)	<0.0001
Rheumatologic diseases*	290 (2.1%)	472 (1.4%)	<0.0001
Peptic ulcer disease*	220 (1.6%)	264 (0.8%)	<0.0001
Mild liver disease*	48 (0.4%)	116 (0.4)	>0.99
Diabetes mellitus*	4,389 (32.2%)	859 (2.6%)	<0.0001
Diabetes mellitus with complications*	1,664 (12.2%)	179 (0.5%)	<0.0001
Hemiplegia/paraplegia	50 (0.4%)	27 (0.1%)	<0.0001
Renal disease*	471 (3.5%)	117 (0.4%)	<0.0001
Malignancy*	1,010 (7.4%)	1,102 (3.4%)	<0.0001
Liver disease (moderate/severe)*	8 (0.1)	41 (0.1%)	0.06
Metastatic neoplasm*	48 (0.4%)	95 (0.3%)	0.3
HIV*	13 (0.1%)	39 (0.1%)	0.5
Illicit drug use	20 (0.1%)	65 (0.2%)	0.3
Alcohol abuse/dependence	133 (1%)	240 (0.7%)	.008
Smoker	1,229 (9.0%)	1,911 (5.8%)	<0.0001
Charlson Comorbidity Index score,* mean (SD)	1.2 (1.6)	0.3 (0.8)	<0.0001
Health care utilization			
Number of outpatient visits during baseline period, mean (SD)	41 (5)	23 (32)	<0.0001
Number of admission during follow-up period, mean (SD)	0.4 (1.0)	0.2 (0.6)	<0.0001
Number of outpatient visits during follow-up period, mean (SD)	119 (149)	64 (79)	<0.0001
Number of admission during baseline period, mean (SD)	3 (3.1)	2 (2)	<0.0001
Medications			
Beta blocker	3,911 (28.7%)	2,167 (6.6%)	<0.0001
Diuretic	5,121 (37.5%)	3,421 (10.4%)	<0.0001
Calcium antagonist	3,516 (25.8%)	1,648 (5.0%)	<0.0001
Nonstatin lipid-lowering drugs	2,324 (17.0%)	575 (1.8%)	<0.0001
Angiotensin-receptor blockers/angiotensin converting enzyme inhibitors	7,988 (58.6%)	3,483 (10.6%)	<0.0001
Oral hypoglycemic	2,821 (20.7%)	385 (1.2%)	<0.0001
Cytochrome p450	1,466 (10.7%)	1,410 (4.3%)	<0.0001
Aspirin	7,279 (53.4%)	2,667 (8.1%)	<0.0001
Nonsteroidal anti-inflammatory drugs	7,572 (55.5%)	20,244 (61.6%)	<0.0001
Selective serotonin reuptake inhibitors	2,514 (18.4%)	4,321 (13.2%)	<0.0001
Systemic corticosteroid	532 (3.9%)	1,372 (4.2%)	0.08
Antipsychotic	180 (1.3%)	326 (1.0%)	0.001
Sedatives	2,864 (21.0%)	5,450 (16.6%)	<0.0001
Tricyclic antidepressants	35 (0.3%)	58 (0.1%)	0.09
Mean HDL in baseline period (mg/dl)†	53 (15)	59 (18)	<0.0001
Mean HDL in follow-up period (mg/dl)†	51 (14)	57 (17)	<0.0001
Mean LDL in baseline period (mg/dl)†	105 (34)	111 (28)	<0.0001
Mean LDL in follow-up period (mg/dl)†	98 (31)	112 (27)	<0.0001

Cytochrome p 450: medications that inhibit the Cytochrome p450 system as identified in a recent Food and Drug Administration warning.[18]
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.
* Diagnosis is based on ICD-9-CM codes as identified in the Deyo method for applying the Charlson Comorbidity Index score.[17]
† Values for these laboratory measurements were missing in 8,647-7,520 patients in statin users and 26,546-18,619 patients in the nonusers.

fiscal year 2005 (October 1, 2004 to September 30, 2005); nonusers did not receive a statin at any time during the study.

Patients had to be 30 to 85 years of age, enrolled in Tricare Prime or Tricare Plus in the San Antonio area military health care system until the date of data extraction, had to have ≥1 outpatient visit during the baseline period and ≥1 outpatient visit during the follow-up period, and had to receive ≥1 prescription medication during the baseline period. Hence, our cohort had complete data throughout the study period.

We excluded burn and trauma patients; these patients were identified based on the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) codes. Codes for burn patients were those identified by the Agency for Health Research and Quality—Clinical Classifications Software (AHRQ-CCS), category 240[13]; trauma codes were compiled