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

Table 2
Baseline characteristics of statin users and nonusers in the propensity score-matched cohort

Variable	Users (n = 6,956)	Nonusers (n = 6,956)	p Value
Age (yrs), mean (SD)	57 (13)	57 (12)	0.2
Male gender	3,759 (54%)	3,816 (55%)	0.3
Co-morbid conditions			
Acute myocardial infarction*	73 (1.0%)	68 (1.0%)	0.7
Congestive heart failure*	144 (2.1%)	124 (1.8%)	0.2
Peripheral vascular disease*	144 (2.1%)	134 (1.9%)	0.6
Cerebrovascular disease*	153 (2.2%)	148 (2.1%)	0.8
Dementia*	33 (0.5%)	28 (0.4%)	0.6
Chronic obstructive pulmonary disease*	836 (12.0%)	876 (12.6%)	0.3
Rheumatologic diseases*	158 (2.3%)	151 (2.2%)	0.7
Peptic ulcer disease*	97 (1.4%)	94 (1.4%)	0.8
Mild liver disease*	30 (0.4%)	31 (0.4%)	1
Diabetes mellitus*	697 (10.0%)	671 (9.6%)	0.5
Diabetes mellitus with complications*	198 (2.8%)	164 (2.4%)	0.08
Hemiplegia/paraplegia*	12 (0.2%)	8 (0.1%)	0.5
Renal disease*	96 (1.4%)	87 (1.3%)	0.6
Malignancy*	440 (6.3%)	439 (6.3%)	1
Liver disease (moderate/severe)*	4 (0.1%)	5 (0.1%)	1
Metastatic neoplasm*	24 (0.3%)	22 (0.3%)	0.9
HIV*	10 (0.1%)	8 (0.1%)	0.6
Alcohol abuse/dependence	66 (0.9)	71 (1)	0.7
Smoker	588 (8.5)	609 (8.8)	0.5
Illicit drug use	12 (0.2)	11 (0.2)	0.8
Charlson Comorbidity Score, mean (SD)	0.59 (1.1)	0.56 (1.3)	0.6
Health care utilization			
Number of outpatient visits during baseline period, mean (SD)	32 (33)	32 (52)	0.6
Number of admission during baseline period, mean (SD)	0.3 (0.8)	0.3 (0.8)	0.2
Number of outpatient visits during follow-up period, mean (SD)	89 (83)	89 (124)	0.8
Number of admission during follow-up period, mean (SD)	0.8 (2)	0.8 (2)	0.4
Medications			
Beta blocker	1,282 (18.4%)	1,279 (18.4%)	0.9
Diuretic	1,967 (28.3%)	1,942 (27.9%)	0.7
Calcium antagonist	1,141 (16.4%)	1,091 (15.7%)	0.2
Nonstatin lipid-lowering drugs	530 (7.6%)	495 (7.1%)	0.3
Angiotensin-receptor blockers/angiotensin converting enzyme inhibitors	2,420 (34.8%)	2,416 (34.7%)	1.0
Oral hypoglycemic	326 (4.7%)	292 (4.2%)	0.2
Cytochrome p450	447 (6.4%)	450 (6.5%)	0.9
Aspirin	2,207 (31.7%)	2,219 (30.5%)	0.1
Nonsteroidal anti-inflammatory drugs	3,998 (57.5%)	3,965 (57.0%)	0.6
Selective serotonin reuptake inhibitors	1,166 (16.8%)	1,135 (16.3%)	0.5
Systemic corticosteroid	275 (4.0%)	272 (3.9%)	0.9
Antipsychotic	95 (1.4%)	100 (1.4%)	0.7
Sedatives	1,375 (19.8%)	1,342 (19.3%)	0.5
Tricyclic antidepressants	16 (0.2%)	12 (0.2%)	0.5

Cytochrome p450: medications that inhibit the cytochrome p450 system as identified in a recent Food and Drug Administration warning.[18]
* Diagnosis is based on ICD-9-CM codes as identified in the Deyo method for applying the Charlson Comorbidity Index score.[17]

from ICD-9 manual and previous publications.[14,15] We also excluded patients who received a statin for <90 days or those who started a statin after the baseline period to allow equal follow-up periods in both patient groups.

The outcome measure was the occurrence of 3 separate ICD-9-CM codes,[16] during the follow-up period in either the inpatient or outpatient setting, consistent with CTD as identified by AHRQ-CCS categories 202, 210, and 211, except for V-codes because they signify previous conditions (Appendix A).[13]

We described patients' co-morbidities using the Charlson Comorbidity Index, Deyo et al method.[17] A propensity score-matched cohort of statin users and nonusers was created using 41 variables (age, gender, 17 co-morbid conditions as listed in Table 1 and identified from ICD-9-CM diagnoses of inpatient or outpatients medical encounters, total Charlson Comorbidity Index using Deyo method,[17] health care utilization, and the use of 14 medication groups as listed in Table 1).[18]

We performed the following analyses: primary analysis in which we determined the risk of CTD in the propensity score-matched cohort; secondary analysis in which we determined the risk of CTD in relation to statin use in all patients who met study criteria (unmatched cohort); and sensitivity analysis in which we excluded patients with

Table 3
Prevalence of selected *International Classification of Diseases, 9th Revision, Clinical Modification* codes of connective tissue diseases in the propensity score-matched group for statin users and nonusers

Selected ICD-9-CM Codes	Diseases Identified by These Codes	Users (n = 6,956)	Nonusers (n = 6,956)
7140, 7142, 71430, 71431, 71432, 71433, 7144, 71481, 71489, 7149	Rheumatoid arthritis	104 (1.5%)	122 (1.8%)
7100	Systemic lupus erythematous	22 (0.3%)	34 (0.5%)
7103−7104	Dermatomyosotis and polymyositis	2 (0.03%)	9 (0.1%)
725	Polymyalgia rheumatica	33 (0.5%)	20 (0.3%)
7102	Sicca syndrome, keratoconjuctivitis sicca, Sjogren's disease	34 (0.5%)	40 (0.6%)
7109	Connective tissue disease (unspecified)	5 (0.1%)	19 (0.1%)

The selected ICD-9-CM codes are not necessarily comprehensive for their diagnoses but are more commonly utilized. Multiple diagnoses occurred simultaneously in the same patients.

Table 4
Risk of outcome in statin users in comparison to nonusers in different cohorts

Variable	Users Diagnosed With CTD	Nonusers Diagnosed With CTD	OR	95% CI		p Value
Primary analysis						
Risk of CTD in propensity score matched cohort	144 (2.1%)	179 (2.6%)	0.80	0.64	0.99	0.05
Secondary analysis						
Risk of CTD in the unmatched cohort*	305 (2.2%)	532 (1.6%)	0.81*	0.65	0.99	0.05
Sensitivity analysis						
Risk of CTD in propensity score incidence cohort	76 (1.1%)	106 (1.6%)	0.72	0.53	0.96	0.03

* Adjusted OR for age, gender, statin use, all comorbid conditions as in Table 1, total Charlson Comorbidity Index, number of outpatient medical encounters, and inpatient admissions during each of the baseline period and the follow-up period, and use of different classes of medications as listed in Table 1.

previous diagnosis of CTD from the propensity score-matched cohort and determined the risk of incidence of CTD diagnosis (propensity score incidence cohort).

Baseline characteristics of statin users and nonusers were compared using chi-square for categorical variables and Student's *t* test for continuous variables. Comparisons were considered to be statistically significant if the calculated p value was ≤ 0.05. We used logistic regression to create the propensity score and test the balance of covariates in our models using the routines developed by Becker and Ichino.[19] We then used the routine by Leuven and Sianesi to perform nearest number matching with a caliper of 0.001.[20]

For our secondary analysis, we used logistic regression analysis to examine the odds ratios (OR) of outcome. Potential confounders (as listed in Table 1) were introduced as covariates in the models. Statistical analyses were performed using STATA 12 (StataCorp, College Station, Texas) and SPSS statistical software version 19 (IBM, Armonk, New York).

Results

A total of 59,604 patients met inclusion criteria: 13,116 were excluded (2,124 burn or trauma patients, 516 who received <90 days of statins, and 10,476 who received statins after September 30, 2005). Of the remaining 46,488 patients, 13,640 were statin users and 32,848 were nonusers. The mean ± SD of cumulative duration of statin use among statin users was 1,694 ± 663 days. Table 1 depicts baseline characteristics of this cohort.

We matched 6,956 pairs of statin users and nonusers using propensity scores. The matched groups had similar baseline characteristics (Table 2). Among statin users, mean total duration of statin use was 1,597 days; SD was 696 days (median = 1,740 days, interquartiles = 1,097 and 2,160 days). Approximately 26% of statin users received the maximum dose of their statin, defined as 80 mg of simvastatin, 80 mg of pravastatin, 80 mg of atorvastatin, and 40 mg of rosuvastatin. Table 3 depicts the prevalence of selected ICD-9-CM codes.

In the sensitivity analysis, the propensity score incidence cohort encompassed 6,798 statin users and 6,805 nonusers; baseline characteristics of the 2 groups remained balanced with no statistically significant differences in any of the matched variables.

Table 4 depicts the incidences and ORs of outcomes in all of our analyses; ORs of CTD were lower among statin users in all analyses.

Discussion

Our study demonstrated that statin use is associated with a lower risk of CTD. This finding was consistent in both matched and unmatched cohorts.

Our results support other studies.[3,4] In a case-control study, 313 patients with RA, who received statins or other lipid-lowering agent, were matched to 1,252 controls.[3] Subjects were matched by patient age, sex, index date of RA diagnosis, and number of years in the medical database. The adjusted OR for developing RA in statin users was 0.59 (95% confidence interval [CI] = 0.37 to 0.96). In another retrospective cohort study, 55,919 persistent statin users (received a statin >80% of the time) were compared with 57,690 nonpersistent statin users (received a statin <20% of the time). Persistent statin users had

a lower risk of developing RA compared with nonpersistent statin users (hazard ratio [HR] = 0.58; 95% CI = 0.52 to 0.65).[4]

The TARA study (Trial of Atorvastatin in Rheumatoid Arthritis) randomized 116 patients with RA to atorvastatin or placebo and showed that atorvastatin use was associated with an improvement in disease activity.[21]

Other studies concluded that statin use was not associated with a difference in the risk of CTD.[5,6] One prospective cohort study of 225,922 new statin users and 1,778,770 nonusers found that, after adjusting for gender, co-morbidities, and statin type, HR for the development of RA in new statin users and nonusers was similar.[5] In another population-based cohort study (129,288 statin users to 600,241 nonusers),[6] the investigators created a propensity score, comprised of age, gender, several co-morbidities, usage of several groups of medications, socioeconomic status, and length of time enrolled in their health care system. There was no association between statin use and the development of RA (HR = 0.93; 95% CI = 0.73 to 1.18) or systemic lupus erythematosus (HR = 1.08; 95% CI = 0.50 to 2.36); however, approximately 10% of the patients in the nonuser group started statins after the initial evaluation.

More recently, a case-control study, including 508 RA patients and 2,369 control subjects, found that statin use was associated with an increased risk of developing RA.[7] In this study, each RA patient was matched to 5 control subjects based on age, gender, and index date of RA diagnosis. After adjustment for cardiovascular disease and other medications, the risk of RA was higher among statin users (adjusted OR = 1.71; 95% CI = 1.16 to 2.53).

These conflicting results may be related to the limitations of both randomized controlled studies and observational studies; randomized controlled studies are not usually powered to detect uncommon adverse events, and observational studies are potentially clouded by factors such as healthy-user bias and the association of statin use with better health care utilization.[22] Observational studies often include heterogeneous patient populations with differences in baseline characteristics between treatment and control groups. Statin users ultimately have higher disease burden necessitating a statin prescription; hence, they may have a higher risk of developing diseases that may be unrelated to statin exposure. Furthermore, the presence of co-morbid conditions increases health care utilization. Frequent evaluations by a physician may result in more diagnoses and the possibility of an ascertainment bias.[23] However, statin users may be more health conscious than nonusers. In a large prospective cohort study, statin-adherent patients were less likely than nonadherent patients to have motor vehicle accidents and workplace accidents, after adjusting for potential confounders.[22] Additionally, statin use may act as a surrogate marker for better access to care, because adherence to statin therapy was associated with the use of preventive health services.[23]

Propensity score matching helps to alleviate some of the limitations of observational studies. We took into account 41 variables that would likely influence the prescription of a statin. Notably, this study included a patient population that has similar access to care and medications. In the military health care system, patients are easily tracked because their medical records are accessible at any military health care facility. Medication distribution is recorded regardless of the dispensing pharmacy and is available electronically. Because of this, we were able to follow all eligible patients for the duration of this study.

This study has some limitations. First, as with any retrospective observational study, some residual baseline confounders may still exist. Second, our study is solely dependent on ICD-9-CM codes for confirmation of diagnosis, which may suffer from inaccuracy[16,24]; hence, we identified the presence of CTD diagnosis by the presence of 3 separate ICD-9-CM codes to improve its positive predictive value.[16] Although not ideal, we believe that any problems with this methodology in terms of predictive value would affect both the statin users and nonusers. Although we used ICD-9-CM codes identified previously for CTD diagnoses,[13] we did not perform an external control of the actual presence of diseases, nor was our study powered to identify which subgroup of diseases resulted in the overall lower incidence of CTD among statin users. This becomes particularly relevant in light of the marginal statistical significance of 0.05 in between groups. Finally, some data suggest that different statins have different anti-inflammatory effects[23]; however, we did not compare different statins in this study because patients were followed longitudinally for several years, in which they used several statins and doses.

The anti-inflammatory properties of statins are postulated to have beneficial effects on cardiovascular diseases and likely CTD.[25,26] This study adds support that statins may reduce the risk of CTD. A recent review by Lazzerini et al demonstrated that inhibiting hydroxyl-methyl-glutaryl-coenzyme A reductase alters downstream processes by blocking cytokines and stimulating bone morphogenetic proteins.[26] Future research should focus on studying the effects of statins in patients with high-risk features for CTD development. This may include patients with positive serologies for rheumatoid factor and anticyclic citrullinated peptide antibodies,[27] or patients with familial history and the shared epitope HLA-DRB1 who are at a higher risk for the development of RA.[28]

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2013.04.059

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