Statins and Musculoskeletal Conditions, Arthropathies, and Injuries

Ishak Mansi, MD; Christopher R. Frei, PharmD, MSc; Mary Jo Pugh, PhD; Una Makris, MD; Eric M. Mortensen, MD, MSc

IMPORTANCE Statin use may be associated with increased musculoskeletal adverse events, especially in physically active individuals.

OBJECTIVE To determine whether statin use is associated with musculoskeletal conditions, including arthropathy and injury, in a military health care system.

DESIGN A retrospective cohort study with propensity score matching.

SETTING San Antonio Military Multi-Market.

PARTICIPANTS Tricare Prime/Plus beneficiaries evaluated from October 1, 2003, to March 1, 2010.

INTERVENTIONS Statin use during fiscal year 2005. On the basis of medication fills, patients were divided into 2 groups: statin users (received a statin for at least 90 days) and nonusers (never received a statin throughout the study period).

MAIN OUTCOMES AND MEASURES Using patients’ baseline characteristics, we generated a propensity score that was used to match statin users and nonusers; odds ratios (ORs) were determined for each outcome measure. Secondary analyses determined adjusted ORs for all patients who met study criteria and a subgroup of patients with no comorbidities identified using the Charlson Comorbidity Index. Sensitivity analysis further determined adjusted ORs for a subgroup of patients with no musculoskeletal diseases at baseline and a subgroup of patients who continued statin therapy for 2 years or more. The occurrence of musculoskeletal conditions was determined using prespecified groups of International Classification of Diseases, Ninth Revision, Clinical Modification codes: Msk1, all musculoskeletal diseases; Msk1a, arthropathies and related diseases; Msk1b, injury-related diseases (dislocation, sprain, strain); and Msk2, drug-associated musculoskeletal pain.

RESULTS A total of 46,249 individuals met study criteria (13,626 statin users and 32,623 nonusers). Of these, we propensity score–matched 6967 statin users with 6967 nonusers. Among matched pairs, statin users had a higher OR for Msk1 (OR, 1.19; 95% CI, 1.08-1.30), Msk1b (1.13; 1.05-1.21), and Msk2 (1.09; 1.02-1.18); the OR for Msk1a was 1.07 (0.99-1.16; \( P = .07 \)). Secondary and sensitivity analyses revealed higher adjusted ORs for statin users in all outcome groups.

CONCLUSIONS AND RELEVANCE Musculoskeletal conditions, arthropathies, injuries, and pain are more common among statin users than among similar nonusers. The full spectrum of statins’ musculoskeletal adverse events may not be fully explored, and further studies are warranted, especially in physically active individuals.

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Statins (hydroxyl-methylglutaryl-coenzyme-A reductase inhibitors) effectively lower cardiovascular morbidity and mortality. However, the full spectrum of statin musculoskeletal adverse events (AEs) is unknown. Statin-associated musculoskeletal AEs include a wide array of clinical presentations, including myalgias, muscle weakness, muscle cramps, rhabdomyolysis, autoimmune muscle disease, and tendinous diseases.1-10 In contrast, other authors11 have postulated that statins’ anti-inflammatory properties may be beneficial in osteoarthritis.

These conflicting data are not surprising, since there is no standard definition for statin-associated musculoskeletal AEs.12 Randomized clinical studies are not powered to detect uncommon AEs, and observational studies are potentially clouded by confounders.13

The objective of this study was to examine the association of statin use with musculoskeletal conditions in a propensity score–matched cohort of statin users and nonusers in a military health care system in which patients have similar health care access and standards.

Methods

Study Design

This study was approved by the institutional review board at Brooke Army Medical Center, San Antonio, Texas. This was a retrospective cohort study of patients enrolled in the San Antonio Military Area as Tricare Prime/Plus. Enrolees included active-duty soldiers (17.1%), as well as veterans and their families (82.9%). We extracted archival data (October 1, 2003, to March 1, 2010) from the Military Health System Management Analysis and Reporting Tool (M2). The M2 is a powerful and reliable tool that includes administrative, clinical, and financial data from the entire military health care system.14 The M2 is managed under a published and approved protocol14-16; it has been used in administrative decision making,15,16 health care outcomes,17-18 and utilization research.19-21

Collectively, M2 encompasses the full spectrum of clinical care regardless of location or affiliation of its providers: outpatient electronic medical records, inpatient electronic medical records, medical benefits claims data, laboratory data, and pharmacy data. Outpatient medical records contain all outpatient service activities; clinicians document encounter details, review and order investigations, prescribe medications, and close each encounter by selecting diagnosis codes. The inpatient electronic medical record is used to document all inpatient service activities. Professional coders code discharge diagnoses. Medical benefit claims data contain services and medications from providers outside of military facilities. Laboratory data include results of laboratory tests performed within the military system. Pharmacy data include issue date, strength, and supply days for medications dispensed regardless of pharmacy location or affiliation.

The study was divided into 2 periods. The baseline period included October 1, 2003, to September 30, 2005, to allow for adequate description of baseline characteristics, and the follow-up period included October 1, 2005, to March 1, 2010, for adequate duration of follow-up for all patients in the cohort. All patients were enrolled in the system throughout the study period; hence, there were no missing data.

Patient Population

Inclusion Criteria

The study was open to patients aged 30 to 85 years. The inclusion criteria were (1) enrolled in Tricare Prime/Plus in the San Antonio Multi-Market Area, (2) had at least 1 outpatient visit during the baseline period and 1 outpatient visit during the follow-up period, and (3) received at least 1 prescription medication during the baseline period.

Exclusion Criteria

Three groups of patients were excluded from the study. The first was patients with trauma or burns (based on International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes). Codes for burn patients were those identified by the Agency for Healthcare Research and Quality (AHRQ) Clinical Classifications Software, category 240,22 and trauma codes were compiled from the ICD-9-CM manual and previous publications.23-24 Brooke Army Medical Center is a burn and trauma center, and these patients may have comorbidities and outcomes different from those of the general population.25-26

The second excluded group were patients who began statin therapy after September 30, 2005 (end of the baseline period). This allowed the creation of statin-user and nonuser groups with equal periods of follow-up. The third excluded group were patients who received statins for less than 90 days during the study period.

Identification of 2 Treatment Groups

Statin users were defined as patients who received and filled a prescription for a statin medication for a cumulative period of at least 90 days from October 1, 2004, to September 30, 2005. Statin therapy was prescribed at the physician’s discretion and was not compulsory. Nonusers were defined as patients who did not receive a statin at any time throughout the study period.

Outcome Measures

An event was defined as the occurrence of an ICD-9-CM code during the follow-up period, as defined below, in either the inpatient or outpatient setting. We used prespecified diagnosis groups to define musculoskeletal diseases (Supplement [eTable]) as follows:

1. Musculoskeletal disease diagnosis group 1 (Msk1): includes ICD-9-CM codes as compiled from the musculoskeletal section in the ICD-9-CM manual. These codes have been used previously in identifying musculoskeletal diseases in relationship to statin use.10 We incorporated a broad definition for musculoskeletal diagnosis to capture all possible musculoskeletal AEs, since studies have indicated their significant heterogeneity.1,27,28 There is no standard definition or validated model of ICD-9-CM codes for statin-related musculoskeletal AEs.29 These broadly defined codes capture all potential musculoskeletal diseases.
2. Musculoskeletal disease diagnosis group 1a (Msk1a): a subgroup of Msk1 that includes all ICD-9-CM codes in AHRQ Clinical Classifications Software indicative of degenerative joint diseases and related disorders (arthropathies).22

3. Musculoskeletal disease diagnosis group 1b (Msk1b): a subgroup of Msk1 that includes all ICD-9-CM codes in the AHRQ Clinical Classifications Software of musculoskeletal injury (strain and sprain of joints and adjacent muscles and dislocation).22

4. Musculoskeletal disease diagnosis group 2 (Msk2): includes ICD-9-CM codes that were validated in other studies (sensitivity, 67.7%, and specificity, 61.3%) to investigate musculoskeletal pain in relationship to medications (musculoskeletal pain).29

Data Analyses
Patients’ comorbidities were identified using ICD-9-CM codes, and their score on the Charlson Comorbidity Index was calculated using the method of Deyo et al30 (Table 1). Using propensity score, we matched statin users to similar nonusers using 42 variables that encompassed patients’ baseline characteristics (age, sex, and comorbidities as listed in Table 1; total Charlson comorbidity score; presence of arthropathy at baseline; presence of musculoskeletal injury at baseline; health care utilization; and use of 14 classes of medications as listed in Table 1).22 Table 2 summarizes the study cohort groups and methods.

Primary Analysis
We determined the risk of musculoskeletal conditions in statin users and nonusers in the propensity score–matched cohort. Since baseline characteristics of statin users and nonusers were balanced in this cohort, no further adjustments were needed in determining the risk of outcomes.

Secondary Analysis
We determined outcome measures in 2 cohorts. In the all-patients cohort, we evaluated outcome measures in the whole population that met the inclusion and exclusion criteria. We used a logistic regression model with adjustments for potential confounders (Table 2). In the no–Charlson comorbidity cohort, we excluded patients with any Charlson comorbidity score30; hence, all statin users and nonusers had a Charlson comorbidity score of 0.

Sensitivity Analysis
We also performed sensitivity analyses. The musculoskeletal incident cohort excluded patients with preexisting osteoarthritis or injury–related diseases at baseline (Msk1a and Msk1b). In this analysis, we used a logistic regression model adjusting for propensity scores.

In analysis of the 2-year statin-users cohort, we excluded individuals who used drugs from this class for less than 2 years and determined the adjusted risk of outcomes between statin users and nonusers.

Statistical Analysis
Baseline characteristics of the groups were compared using χ² analysis for categorical variables and an unpaired 2-tailed t test for continuous variables. Comparisons were considered to be statistically significant at P ≤ .05.

Propensity Score Matching
We used a logistic regression model to create the propensity score and test the balance of covariates using the routines developed by Becker and Ichino.32 We then used the routine by Leuven and Sianesi13 to perform nearest number matching with a caliper of 0.001. We included candidate variables in the propensity score that we believed would be potentially associated with either the use of statins or the outcome of interest. Table 1 lists all variables included in the propensity score.

For the propensity score–matched analyses, we calculated the odds ratios (ORs) using univariable logistic regression. Secondary analyses and sensitivity analyses included multivariable logistic regression predicting each outcome measure independently with statin use as a predictor variable. Covariates for these analyses are described in Table 2. For the musculoskeletal incident cohort, we used a multivariable logistic regression model that used the propensity scores as a covariate to adjust for potential confounders in the model. Finally, we calculated the number needed to be exposed for 1 additional person to be harmed according to a published formula.34 Statistical analyses were performed using commercial software (Stata, version 12, StataCorp Inc, and SPSS, version 19; SPSS Inc).

Results
Based on our inclusion criteria, 59 365 patients were identified. Of these, 13 116 were excluded: 2124 with trauma or burns; 10 476 who received statins after September 30, 2005; and 516 who received statins for less than 90 days (Figure). Of the remaining 46 249 patients, 13 626 were statin users and 32 623 were nonusers. Overall, the statins prescribed were simvastatin (73.5%), atorvastatin calcium (17.4%), pravastatin sodium (7%), rosuvastatin calcium (1.7%), and fluvastatin sodium or lovastatin (0.24%). The mean (SD) cumulative duration of statin use was 1698 (663) days. Approximately 34% of statin users had been prescribed maximal doses (simvastatin, 80 mg/d; pravastatin, 80 mg/d; atorvastatin, 80 mg/d; or rosuvastatin, 40 mg/d). Because statin users received prescriptions for various forms and dosages of the drugs during the study period, we calculated the cumulative product of years of statin use and simvastatin–equivalent doses for each patient (ie, cumulative simvastatin years). Determination of the equivalent statin dose was based on the statin’s relative potency in lowering low-density lipoprotein cholesterol in comparison with simvastatin as identified in a recent Food and Drug Administration report33 and as used in other research.35

Table 3 describes selected characteristics of the population that met the study criteria. A detailed description of this cohort was described elsewhere.36
Table 1. Baseline Characteristics and Outcomes of Propensity Score–Matched Statin Users and Nonusers

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Statin Users (n = 6967)</th>
<th>Nonusers (n = 6967)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>56.5 (12.4)</td>
<td>56.8 (12.3)</td>
<td>.2</td>
</tr>
<tr>
<td>Male sex</td>
<td>3712 (53.3)</td>
<td>3720 (53.4)</td>
<td>.9</td>
</tr>
<tr>
<td>Comorbidities in baseline period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction*</td>
<td>78 (1.1)</td>
<td>66 (0.9)</td>
<td>.3</td>
</tr>
<tr>
<td>Congestive heart failure*</td>
<td>144 (2.1)</td>
<td>129 (1.9)</td>
<td>.4</td>
</tr>
<tr>
<td>Peripheral vascular disease*</td>
<td>130 (1.9)</td>
<td>139 (2.0)</td>
<td>.6</td>
</tr>
<tr>
<td>Cerebrovascular disease*</td>
<td>148 (2.1)</td>
<td>154 (2.2)</td>
<td>.8</td>
</tr>
<tr>
<td>Dementia*</td>
<td>27 (0.4)</td>
<td>29 (0.4)</td>
<td>.8</td>
</tr>
<tr>
<td>Chronic obstructive lung disease*</td>
<td>853 (12.2)</td>
<td>842 (12.1)</td>
<td>.8</td>
</tr>
<tr>
<td>Rheumatologic diseases*</td>
<td>159 (2.3)</td>
<td>153 (2.2)</td>
<td>.8</td>
</tr>
<tr>
<td>Peptic ulcer disease*</td>
<td>101 (1.4)</td>
<td>101 (1.4)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Mild liver disease*</td>
<td>30 (0.4)</td>
<td>27 (0.4)</td>
<td>.8</td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td>702 (10.1)</td>
<td>659 (9.5)</td>
<td>.2</td>
</tr>
<tr>
<td>Diabetes mellitus with complications*</td>
<td>193 (2.8)</td>
<td>162 (2.3)</td>
<td>.1</td>
</tr>
<tr>
<td>Hemiplegia/paraplegia*</td>
<td>8 (0.1)</td>
<td>10 (0.1)</td>
<td>.8</td>
</tr>
<tr>
<td>Renal disease*</td>
<td>101 (1.4)</td>
<td>86 (1.2)</td>
<td>.3</td>
</tr>
<tr>
<td>Malignant neoplasm*</td>
<td>425 (6.1)</td>
<td>434 (6.2)</td>
<td>.8</td>
</tr>
<tr>
<td>Liver disease, moderate/severe*</td>
<td>4 (0.1)</td>
<td>4 (0.1)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Metastatic neoplasm*</td>
<td>24 (0.3)</td>
<td>23 (0.3)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>HIV*</td>
<td>8 (0.1)</td>
<td>6 (0.1)</td>
<td>.8</td>
</tr>
<tr>
<td>Charlson comorbidity total score, mean (SD)</td>
<td>0.58 (1.1)</td>
<td>0.56 (1.1)</td>
<td>.4</td>
</tr>
<tr>
<td>Osteoarthritis at baseline</td>
<td>3600 (51.7)</td>
<td>3663 (52.6)</td>
<td>.3</td>
</tr>
<tr>
<td>Musculoskeletal injury at baseline</td>
<td>1284 (18.4)</td>
<td>1283 (18.4)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Obesity</td>
<td>1060 (15.2)</td>
<td>1085 (15.6)</td>
<td>.6</td>
</tr>
<tr>
<td>Illicit drug use</td>
<td>14 (0.2)</td>
<td>10 (0.1)</td>
<td>.4</td>
</tr>
<tr>
<td>Alcohol abuse/dependence</td>
<td>60 (0.9)</td>
<td>66 (0.9)</td>
<td>.6</td>
</tr>
<tr>
<td>Smoking</td>
<td>572 (8.2)</td>
<td>583 (8.4)</td>
<td>.7</td>
</tr>
<tr>
<td>No. of outpatient visits during baseline period, mean (SD)</td>
<td>32.4 (32.5)</td>
<td>32.2 (31.5)</td>
<td>.7</td>
</tr>
<tr>
<td>No. of inpatient admission during baseline period, mean (SD)</td>
<td>0.28 (0.8)</td>
<td>0.28 (0.8)</td>
<td>.5</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>1303 (18.7)</td>
<td>1287 (18.5)</td>
<td>.7</td>
</tr>
<tr>
<td>Diuretic</td>
<td>1947 (27.9)</td>
<td>1949 (28.0)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>1130 (16.2)</td>
<td>1110 (15.9)</td>
<td>.7</td>
</tr>
<tr>
<td>Nonstatin lipid-lowering drug</td>
<td>526 (7.5)</td>
<td>503 (7.2)</td>
<td>.5</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>2472 (35.5)</td>
<td>2415 (34.7)</td>
<td>.3</td>
</tr>
<tr>
<td>Oral hypoglycemic</td>
<td>325 (4.7)</td>
<td>289 (4.1)</td>
<td>.2</td>
</tr>
<tr>
<td>Cytochrome P450™</td>
<td>447 (6.4)</td>
<td>446 (6.4)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Aspirin</td>
<td>2222 (31.9)</td>
<td>2171 (31.2)</td>
<td>.4</td>
</tr>
<tr>
<td>NSAID</td>
<td>4018 (57.7)</td>
<td>4052 (58.2)</td>
<td>.6</td>
</tr>
<tr>
<td>SSRI</td>
<td>1178 (16.9)</td>
<td>1162 (16.7)</td>
<td>.7</td>
</tr>
<tr>
<td>Systemic corticosteroid</td>
<td>284 (4.1)</td>
<td>276 (4.0)</td>
<td>.7</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>86 (1.2)</td>
<td>92 (1.3)</td>
<td>.7</td>
</tr>
<tr>
<td>Sedative</td>
<td>1360 (19.5)</td>
<td>1387 (19.9)</td>
<td>.6</td>
</tr>
<tr>
<td>Tricyclic antidepressant</td>
<td>13 (0.2)</td>
<td>16 (0.2)</td>
<td>.7</td>
</tr>
<tr>
<td>Musculoskeletal diseases outcome*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Msk1, all musculoskeletal diseases</td>
<td>6053 (86.9)</td>
<td>5905 (84.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Msk1a, osteoarthritis/arthropathies</td>
<td>5127 (73.6)</td>
<td>5032 (72.2)</td>
<td>.07</td>
</tr>
<tr>
<td>Msk1b, dislocation/strain/sprain</td>
<td>2452 (35.2)</td>
<td>2265 (32.5)</td>
<td>.001</td>
</tr>
<tr>
<td>Msk2, musculoskeletal pain</td>
<td>5113 (73.4)</td>
<td>4989 (71.6)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; HIV, human immunodeficiency virus; NSAID.
Propensity Score-Matched Analysis
Using propensity scores, we matched 6967 statin users to 6967 nonusers. After matching, there were no significant differences in baseline characteristics between the groups (Table 1). In the propensity score-matched cohort, statin users had higher ORs for Msk1 (all musculoskeletal diseases: OR, 1.19; 95% CI, 1.08-1.3), Msk1b (dislocation/strain/sprain: 1.13; 1.05-1.21), and Msk2 (musculoskeletal pain: 1.09; 1.02-1.18), but not for Msk1a (osteoarthritis/arthropathy: 1.07; 0.99-1.16) (Table 4). We repeated logistic regression analysis for our outcomes using cumulative simvastatin years as an independent variable instead of statin use. Simvastatin years was not a significant predictor of any of our outcome measures. The numbers needed to be exposed for 1 additional person to be harmed were Msk1, 47 (95% CI, 32-103); Msk1b, 37 (23-92); and Msk2, 58 (31-249).

Secondary Analyses
For our secondary analyses, the no–Charlson comorbidities cohort constituted 33,527 patients: 6,119 statin users and 27,408 nonusers. The adjusted ORs for the secondary analyses were higher for statin users (Table 6).

Sensitivity Analyses
In the musculoskeletal incident cohort, 5692 were statin users and 16,888 were nonusers. The incidence of musculoskeletal outcomes in statin users and nonusers was Msk1, 80.0% vs 72.0%; Msk1a, 61.0% vs 52.6%; Msk1b, 25.2% vs 28.2%; and Msk2, 62.9% vs 55.8%. The adjusted ORs were consistently higher for statin users in both sensitivity analyses (Table 6).

Discussion
To our knowledge, this is the first study, using propensity score matching, to show that statin use is associated with an increased likelihood of diagnoses of musculoskeletal conditions, arthropathies, and injuries. In our primary analysis, we did not find a statistically significant association between statin use and arthropathy; however, this association was statistically significant in all other analyses. These findings are concerning because starting statin therapy at a young age for primary prevention of cardiovascular diseases has been widely advocated. Moreover, the numbers needed to be exposed for 1 additional person to be harmed were 37 to 58 individuals for various outcomes. On the other hand, cumulative simvastatin years was not a significant predictor of any of our outcome measures. This is not surprising given that the dose equivalency of various statins to simvastatin was based on efficacy in lowering low-density lipoprotein cholesterol rather than on the prevalence of AEs.

Several studies and a meta-analysis have reported that statins may reduce muscle strength and exercise tolerance. However, a randomized clinical trial (420 healthy participants) showed no significant changes in muscle strength or exercise capacity among users of high-dose atorvastatin vs placebo. An observational study that involved almost 2 million individuals reported an association between statin use and myopathy (hazard ratio, 6.68). Time-varying analysis demonstrated that the myopathy risk persisted 3 years after stopping treatment (adjusted hazard ratios, 4.65 in women and 5.86 in men). In a study that examined muscle biopsy specimens from individuals undergoing vascular surgical procedures, electron microscopic pictures and biochemical tests were compared in 14 asymptomatic statin users and 8 nonusers. The investigators noted a characteristic pathologic pattern that included breakdown of the T-tubular system and sarcosomal rupture, which was reproduced by extraction of cholesterol from skeletal muscle fibers in vitro.

The increased incidence of strain, sprain, and dislocation with statin use has not been previously reported. Several publications have indicated that physically active individuals experience a higher prevalence of statin-related muscle injury manifested as muscular pain and elevation of serum creatine kinase. The relationship between musculoskeletal injury and statin use deserves further study in a larger population because it carries a special relevance to our study population, which included active-duty soldiers. Active-duty soldiers and veterans have been reported to have a high prevalence of musculoskeletal diseases that exceeds that of the general population, which may be related to their strenuous muscular activity. The increased risk of injury in our population suggests that statin therapy may compromise soldiers’ musculoskeletal preparedness.

Several factors may explain the musculoskeletal AEs of statin therapy, including the inhibitory effect on coenzyme Q10 synthesis, selenoprotein synthesis, and the mitochondri-
Musculoskeletal disease outcome groups are described in the Outcome Measures subsection of the Methods section.

Table 2. Cohort Groups and Study Methods

<table>
<thead>
<tr>
<th>Cohort Name</th>
<th>Cohort Description</th>
<th>Potential Confounders Identified and Used in Adjustment in Logistic Regression Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis</td>
<td></td>
<td>None; cohort groups were matched with no imbalance</td>
</tr>
<tr>
<td>Propensity score–matched cohort</td>
<td>Pairs of statin users and nonusers were matched according to propensity score</td>
<td></td>
</tr>
<tr>
<td>Secondary analyses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-patients cohort</td>
<td>Whole population that met the inclusion and exclusion criteria</td>
<td>Baseline characteristics, including age, sex, statin use, all Charlson comorbidity conditions as in Table 1, total Charlson comorbidity score, presence of osteoarthritis/arthropathy at baseline, presence of musculoskeletal injury at baseline, obesity, smoking, alcohol use, illicit drug use, number of all admissions in baseline period, number of all outpatients visits in the baseline period, and use of different classes of medications as listed in Table 1</td>
</tr>
<tr>
<td>No-Charlson comorbidities cohort</td>
<td>We excluded patients with any Charlson comorbidity score</td>
<td>Same factors listed for the all-patients cohort except for Charlson comorbidity total score and its components</td>
</tr>
<tr>
<td>Sensitivity analyses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal incident cohort</td>
<td>We excluded patients with preexisting osteoarthritic or injury-related diseases at baseline (Msk1a and Msk1b)</td>
<td>Propensity score</td>
</tr>
<tr>
<td>2-y Statin-users cohort</td>
<td>We excluded statin users who used statins for &lt;2 y</td>
<td>Same factors listed for the all-patients cohort</td>
</tr>
</tbody>
</table>

* Musculoskeletal disease outcome groups are described in the Outcome Measures subsection of the Methods section.

Statins and Musculoskeletal Diseases

In the absence of symptoms, Statin-associated necrotizing autoimmune myopathy was noted to persist or progress despite cessation of statin therapy.\(^7\)–\(^9\) In addition, several reports\(^1\)–\(^3\) have recognized an increased incidence of tendinopathies in relationship to statin use. Hence, it is conceivable that these effects may result in increased incidence of soft-tissue–related injuries, such as dislocation, sprain, and strain.

Reported rates of statin-associated muscle symptoms from randomized clinical studies are 1.5% to 3.0%,\(^2\)–\(^5\) whereas rates from observational studies are approximately 10%.\(^6\) Observational studies may be limited by the presence of baseline differences among study groups. In addition, statin use may be a surrogate marker for a more health-conscious patient, healthy user effects, healthy tolerator effect, or better access to health care.\(^3\),\(^5\) Our study design helped us overcome some of these limitations, particularly access and availability of health care. Our study population has similar access to health care and levels of health insurance coverage (ie, Tricare Prime/Plus). All patients in this relatively large cohort had complete follow-up. Our propensity score–matched cohort showed no imbalance in their baseline characteristics. Last, we repeated the analyses in the whole study cohort, as well as several subgroups, and found a consistent relationship between statin use and musculoskeletal AEs.

Our findings have potentially significant implications for clinical practice and need to be confirmed by other studies. First, our results indicate that the full spectrum of statin AEs has not been fully explored. Hence, extrapolating AE information from the carefully selected patients in randomized clinical studies to other populations is unsound. Second, evaluating musculoskeletal AEs of statins particularly in physically active individuals needs further study. Last, information about the full spectrum of statin AEs will provide more complete data for cost-benefit and cost-effectiveness analyses of statin use.\(^6\)^1

Our study has several limitations. First, we used ICD-9-CM codes for identification of baseline characteristics and statin-associated AEs, which may lack sensitivity toward some variables such as smoking and obesity. However, the proportions of patients with these diseases were similar to those of other studies; this may be because of the longitudinal, comprehensive database, with complete follow-up and frequent visits. We also evaluated obesity instead of body mass index because the latter may not be reliable in identifying obesity in athletic and military populations.\(^6\)^1\(^,\)\(^6\) In addition, ICD-9-CM codes do not provide information on severity of illness.

Second, the codes used in our diagnosis group Msk1 were not validated; however, statin-associated AEs have no validated diagnosis codes. In contrast, the codes used in our diagnosis group Msk2 have been validated for drug-associated musculoskeletal pain\(^8\); nevertheless, studies\(^8\) have shown that ICD-9-CM codes of soft-tissue disorders may lack specificity of coding when compared with actual medical record review. Coding in the primary care setting often results in over-reliance on general codes.\(^8\) The use of pharmacy data to account for medication use assumes, but cannot ascertain, that patients are taking their medications. Approximately 88% of our statin users filled their statin prescription for 2 years, which may be considered a surrogate marker for actual use of medications. Although it is possible that medications were pur-

Figure. Study Cohort

![Fig]
chased outside of Tricare Prime/Plus, this is unlikely, since those costs would be unnecessary out-of-pocket expenses for these beneficiaries.

Although we identified several important baseline characteristics and created propensity score–matched groups, the persistence of baseline confounders that may amplify or attenuate our findings cannot be excluded. We did not perform time-to-event analysis to compare the risk of AEs, which may be a limitation of our study. However, the timeline of statin-related musculoskeletal AEs and persistence of AE risks after discontinuation of statins are not well delineated. Therefore, we opted to assess the cumulative risk of disease across the entire follow-up period. Because statin users were examined more frequently by their providers, ascertainment bias may play a role in attributing more diseases to this study group. In our secondary analyses, we adjusted for the number of visits during the baseline period but not in the follow-up period. Our analysis did not account for the type or dose of the statin used; however, approximately two-thirds of our patients used simvastatin, and one-third used maximal statin doses.

In conclusion, statin use was associated with an increased likelihood of musculoskeletal condition diagnoses, including injuries and pain. Soft-tissue injuries are a lesser known AE of statins and warrant additional research. Further investigations, including randomized clinical studies and larger-scale prospective studies, particularly in physically active individuals, are necessary to obtain a more complete risk-benefit assessment for statin therapy.

### Table 3. Selected Baseline Characteristics of Patients Included in the Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Statin Users (n = 13,626)</th>
<th>Nonusers (n = 32,623)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>60.4 (12.3)</td>
<td>44.8 (11.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>7947 (58.3)</td>
<td>14,263 (43.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Comorbidities in baseline period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>797 (5.8)</td>
<td>120 (0.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>859 (6.3)</td>
<td>189 (0.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>553 (4.0)</td>
<td>226 (0.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4386 (32.2)</td>
<td>858 (2.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes mellitus with complications</td>
<td>1663 (12.2)</td>
<td>178 (0.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Charlson comorbidity total score, mean (SD)</td>
<td>1.2 (1.6)</td>
<td>0.3 (0.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Osteoarthritis at baseline</td>
<td>7469 (54.8)</td>
<td>13,637 (41.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Musculoskeletal injury at baseline</td>
<td>2318 (17.0)</td>
<td>6551 (20.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Obesity</td>
<td>2396 (17.6)</td>
<td>3259 (10.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>1226 (9.0)</td>
<td>1903 (5.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of outpatient visits during baseline period, mean (SD)</td>
<td>40.8 (44.7)</td>
<td>22.8 (31.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of inpatient admission during baseline period, mean (SD)</td>
<td>0.44 (1.0)</td>
<td>0.2 (0.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LDL-C level, mean (SD), mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During baseline period</td>
<td>105.1 (33.9)</td>
<td>111 (27.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>During follow-up period</td>
<td>98 (31.3)</td>
<td>112.5 (27.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>3911 (28.7)</td>
<td>2167 (6.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diuretic</td>
<td>5117 (37.6)</td>
<td>3405 (10.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>7988 (58.6)</td>
<td>3466 (10.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Oral hypoglycemic</td>
<td>2820 (20.7)</td>
<td>383 (1.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NSAID</td>
<td>7568 (55.5)</td>
<td>20,136 (61.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SSRI</td>
<td>2513 (18.4)</td>
<td>4301 (13.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systemic corticosteroid</td>
<td>532 (3.9)</td>
<td>1369 (4.2)</td>
<td>.08</td>
</tr>
</tbody>
</table>

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; LDL-C, low-density lipoprotein cholesterol; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin-reuptake inhibitor.

### Table 4. Outcomes in Statin Users in Comparison With Similar Nonusers in the Propensity Score–Matched Cohort

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. (%)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Msk1, all musculoskeletal diseases</td>
<td>6053 (86.9)</td>
<td>1.19 (1.08-1.30)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Msk1a, osteoarthritis/arthropathies</td>
<td>5127 (73.6)</td>
<td>1.07 (0.99-1.16)</td>
<td>.07</td>
</tr>
<tr>
<td>Msk1b, dislocation/strain/sprain</td>
<td>2452 (35.2)</td>
<td>1.13 (1.05-1.21)</td>
<td>.001</td>
</tr>
<tr>
<td>Msk2, musculoskeletal pain</td>
<td>5113 (73.4)</td>
<td>1.09 (1.02-1.18)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: Msk, musculoskeletal; OR, odds ratio.

* Musculoskeletal disease outcome groups are described in the Outcome Measures subsection of the Methods section.
Table 5. Baseline Characteristics of Statin Users and Nonusers in the No–Charlson Comorbidities Cohorta

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Statin Users (n = 6119)</th>
<th>Nonusers (n = 27 408)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>56.6 (12.1)</td>
<td>43.6 (10.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>3708 (60.6)</td>
<td>12 248 (44.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Comorbidities in baseline period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoarthritis at baseline</td>
<td>3167 (51.8)</td>
<td>10 872 (39.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Musculoskeletal injury at baseline</td>
<td>1092 (17.8)</td>
<td>5456 (19.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Obesity</td>
<td>901 (14.7)</td>
<td>2520 (9.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>477 (7.8)</td>
<td>1401 (5.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Iliac drug use</td>
<td>6 (0.1)</td>
<td>40 (0.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Alcohol abuse/dependence</td>
<td>48 (0.8)</td>
<td>153 (0.6)</td>
<td>.04</td>
</tr>
<tr>
<td>No. of outpatient visits during baseline period, mean (SD)</td>
<td>27.1 (25.4)</td>
<td>19.3 (21.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of inpatient admission during baseline period, mean (SD)</td>
<td>0.2 (0.5)</td>
<td>0.1 (0.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>1386 (22.7)</td>
<td>1500 (5.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diuretic</td>
<td>1749 (28.6)</td>
<td>2306 (8.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>1094 (17.9)</td>
<td>1056 (3.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nonstatin lipid-lowering drug</td>
<td>756 (12.4)</td>
<td>360 (1.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>2372 (38.8)</td>
<td>2266 (8.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Oral hypoglycemic</td>
<td>33 (0.5)</td>
<td>89 (0.3)</td>
<td>&lt;.006</td>
</tr>
<tr>
<td>Cytochrome P450&lt;sup&gt;P&lt;/sup&gt;</td>
<td>467 (7.6)</td>
<td>1113 (4.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Aspirin</td>
<td>2435 (39.8)</td>
<td>1762 (6.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NSAID</td>
<td>3554 (58.1)</td>
<td>16 865 (61.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SSRI</td>
<td>946 (15.4)</td>
<td>3257 (11.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systemic corticosteroid</td>
<td>127 (2.1)</td>
<td>874 (3.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>62 (1.0)</td>
<td>232 (0.8)</td>
<td>.2</td>
</tr>
<tr>
<td>Sedative</td>
<td>1096 (17.9)</td>
<td>4184 (15.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Tricyclic antidepressant</td>
<td>11 (0.2)</td>
<td>42 (0.2)</td>
<td>.4</td>
</tr>
</tbody>
</table>

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin-reuptake inhibitor.

* Based on the Charlson comorbidity score, according to the method of Deyo et al<sup>30</sup>; statin users and nonusers in this cohort had a total Charlson comorbidity score of 0.

* Medications that inhibit the cytochrome P450 system as identified in a recent Food and Drug Administration warning.<sup>31</sup>

ARTICLE INFORMATION

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Author Contributions: Study concept and design: Mansi, Pugh, and Mortensen. Analysis and interpretation of data: All authors. Drafting of the manuscript: Pugh. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Mansi, Frei, and Mortensen. Administrative, technical, and material support: Frei and Pugh. Study supervision: Mansi, Pugh, and Mortensen.

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Disclaimer: The views expressed herein are those of the authors and do not reflect the official policy or position of the Department of the Army, of the Department of Defense, or US government. Drs Mansi, Pugh, Makris, and Mortensen are employees of the US government.

Correction: This article was corrected on July 1, 2013, to fix 1 error each in Tables 4 and 6.

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Table 6. Secondary Analyses and Sensitivity Analyses of Outcomes in Statin Users in Comparison With Nonusers

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Statin Users</th>
<th>Nonusers</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Msks, all musculoskeletal diseases</td>
<td>12 022 (88.1)</td>
<td>26 363 (80.8)</td>
<td>1.13 (1.04-1.22)</td>
<td>.005</td>
</tr>
<tr>
<td>Msks1a, osteoarthritis/arthropathies</td>
<td>10 309 (75.7)</td>
<td>21 287 (65.3)</td>
<td>1.07 (1.01-1.15)</td>
<td>.03</td>
</tr>
<tr>
<td>Msks1b, dislocation/strain/sprain</td>
<td>4572 (33.6)</td>
<td>11 989 (36.8)</td>
<td>1.10 (1.04-1.17)</td>
<td>.002</td>
</tr>
<tr>
<td>Msks2, musculoskeletal pain</td>
<td>10 239 (75.1)</td>
<td>22 019 (67.5)</td>
<td>1.08 (1.01-1.15)</td>
<td>.02</td>
</tr>
</tbody>
</table>

| No-Charlson comorbidities cohort |              |          |                      |         |
| Msks1, all musculoskeletal diseases | 5258 (85.9) | 21 763 (79.4) | 1.12 (1.02-1.24) | .02 |
| Msks1a, osteoarthritis/arthropathies | 4472 (73.1) | 17 392 (63.5) | 1.10 (1.02-1.19) | .01 |
| Msks1b, dislocation/strain/sprain | 2135 (34.9) | 9992 (36.5) | 1.11 (1.03-1.20) | .004 |
| Msks2, musculoskeletal pain | 4415 (72.2) | 18 035 (65.8) | 1.10 (1.02-1.19) | .01 |

| Msks incident cohort |              |          |                      |         |
| Msks1, all musculoskeletal diseases | 4555 (80.0) | 12 159 (72.0) | 1.25 (1.13-1.38) | <.001 |
| Msks1a, osteoarthritis/arthropathies | 3473 (61.0) | 8890 (52.6) | 1.10 (1.01-1.20) | .03 |
| Msks1b, dislocation/strain/sprain | 1435 (25.2) | 4762 (28.2) | 1.19 (1.08-1.31) | <.001 |
| Msks2, musculoskeletal pain | 3580 (62.9) | 9430 (55.8) | 1.13 (1.01-1.27) | .04 |

| 2-y Statin users cohort |              |          |                      |         |
| Msks1, all musculoskeletal diseases | 10 609 (88.4) | 26 363 (80.8) | 1.11 (1.02-1.21) | .02 |
| Msks1a, osteoarthritis/arthropathies | 9128 (76.0) | 21 767 (65.3) | 1.08 (1.005-1.15) | .04 |
| Msks1b, dislocation/strain/sprain | 3966 (33.0) | 11 989 (36.8) | 1.09 (1.03-1.16) | .006 |
| Msks2, musculoskeletal pain | 9050 (75.4) | 22 019 (67.5) | 1.08 (1.007-1.16) | .03 |

Abbreviations: Msks, musculoskeletal; OR, odds ratio.
* Musculoskeletal disease outcome groups are described in the Outcome Measures subsection of the Methods section. ORs were adjusted as described in Table 2.
** The Msks incident cohort consisted of 5692 statin users and 16 888 nonusers.
*** The 2-y statins users cohort consisted of 12 006 statin users and 32 623 nonusers.

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