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Psychological Disorders and Statin Use: A Propensity Score-Matched Analysis

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Abstract

Study Objective—To evaluate the association between statin therapy and risk of psychological disorders including schizophrenia, psychosis, major depression, and bipolar disorder in a military population.

Design—Retrospective, observational, population-based, propensity score-matched, cohort study.

Setting—Database of a patient population enrolled in the San Antonio Military Multi-Market Area as Tricare Prime or Plus.

Patients—Medical records were reviewed from 46249 patients aged 30 to 85 years who were continuously enrolled in the San Antonio Military Multi-Market Area as Tricare Prime or Plus from October 1, 2003 to March 1, 2010. Data were obtained from the Military Health System Management Analysis and Reporting Tool (M2). Based on medication fills during fiscal year 2005, patients were stratified as statin users (N=13626 who received at least 90-days supply of statin) or non-users (N=32623 who never received a statin during the study period). A propensity score-matched cohort of 6972 statin users and 6972 non-users from this population was created.

Measurements and Main Results—The occurrence of psychological disorders between October 1, 2005 and March 1, 2010 was determined using pre-specified groups of International Classification of Diseases, 9th Revision, Clinical Modification codes: 1) Psych1: schizophrenia, schizoaffective disorders, and other psychosis; 2) Psych2: major depression and bipolar disorder; 3) Psych3: all psychological disorders as identified by the Agency for Health Research and

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Quality-Clinical Classifications (except for categories of childhood or developmental psychiatric disorders). Among matched pairs of statin users and non-users, the odds ratios and 95% confidence intervals (OR, 95%CI) were as follows: Psych1 (0.9, 0.75–1.05), Psych2 (1.02, 0.94–1.11), and Psych3 (1.02, 0.96–1.1).

Conclusion—The risk of developing psychological disorders was similar in this cohort of propensity score-matched statin users and non-users.

Keywords

Statin; schizophrenia; depression; adverse events; psychological injury; observational study

Introduction

Despite their effectiveness in lowering cardiovascular morbidity and mortality, hydroxyl methyl glutaryl coenzyme A reductase inhibitors (statins) have been associated with an extremely wide variety of adverse events.[1–6] Pharmacovigilance groups from different parts of the world have implicated statins as a potential cause of severe psychological adverse events. The New Zealand Center for Adverse Reaction Monitoring (CARM) reported the association of 285 cases of psychological adverse events with statins.[5] Another review of spontaneous adverse events in an Italian database identified 71 psychological adverse events.[7] Adverse events included insomnia, somnolence, agitation, confusion, hallucinations, mood disorders, cognitive disorders, and perception disorders.[5, 7] Case reports, case series, and small randomized controlled studies have linked statin use to the increased risk of psychological disorders, such as violence or depression.[8–11] The recent FDA warning of cognitive disorders associated with statins has raised additional concerns.[12]

The objective of this study was to determine if statins were associated with an increased risk of psychological disorders, including schizophrenia, psychosis, major depression, and bipolar disorder in a military population that requires a high degree of psychological preparedness.

Methods

This study was approved by the Institutional Review Board at the Brooke Army Medical Center (BAMC), San Antonio, Texas and the University of Texas Health Science Center, San Antonio, Texas.

This was a retrospective cohort study of patients aged 30 to 85 years who were enrolled in the San Antonio Military Multi-Market Area as Tricare Prime or Plus from October 1, 2003 to March 1, 2010. Using the Military Health System Management Analysis and Reporting Tool (M2), we retrieved all inpatient and outpatient medical encounters, diagnoses, and medication fill histories. M2 is a powerful tool that has been used in administrative and leadership decision making as well as in research.[13–17]

The M2 database encompasses the full spectrum of clinical care: 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. The inpatient electronic medical record is used to document all inpatient service activities. Medical benefit claims data contain services and medications from providers outside the military facilities. Laboratory data include all laboratory investigation results performed within the military system. Finally, pharmacy data include the medication issue date, product strength, quantity dispensed, and days supply for all medications dispensed at military facilities.

Patient selection

The study duration was divided into a baseline period and a follow-up period. The baseline period started on October 1, 2003 and concluded on September 30, 2005 and was used to identify patients' baseline characteristics. The follow-up period began on October 1, 2005 and ended on March 1, 2010 and was used to identify the occurrence of outcome events. All patients were continuously enrolled in the system throughout the study period. We identified two groups of patients. Statin users were patients who received and filled a prescription for a statin medication for at least 90 days between October 1, 2004 and September 30, 2005. Non-users were patients who did not receive a statin at any time from October 1, 2003 to March 1, 2010.

Inclusion criteria—All patients aged 30 to 85 years in the M2 database enrolled in Tricare Prime or Plus in the San Antonio Multi-Market Area were eligible. Tricare is the health care program serving active duty service members, National Guard and Reserve members, retirees, and their families. Eligible patients had at least one outpatient medical encounter during the baseline period (from October 1, 2003 to September 30, 2005), one outpatient medical encounter during the follow-up period (October 1, 2005 to March 1, 2010), and had received at least one prescription medication during the study baseline period.

Exclusion criteria—Burn patients as identified by the Agency for Health Research (AHRQ) Quality-Clinical Classifications Software (category 240) [18] and trauma patients as identified by International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] codes compiled from the ICD-9 manual and previous publications were not included.[19, 20] Due to the mechanism of injury, trauma and burn patients may have comorbidities and outcomes different from the general population,[21, 22] and the value of statins is unclear for these patients.[23–26] Patients who were newly started on statins after September 30, 2005 (end of baseline period) were not eligible because the follow-up period would fall short of 4.5 years.

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 utilized pre-specified diagnosis groups to define psychological disorders (Appendix 1). Briefly, these diagnostic groups were Psych1 (schizophrenia/other psychosis), Psych2 (depression/bipolar disorder/post-traumatic stress disorder [PTSD]), and Psych3 (all psychological disorders). The Psych1 group included patients with schizophrenia, schizoaffective disorders, and other psychosis as identified in VACS (Veterans Aging Cohort Study)[27], except for the codes of "developmental diseases and psychosis with origin specific to childhood" because this group is unlikely to be related to statin use. The Psych2 group included patients with major depression, bipolar disorder, and post-traumatic stress disorder (PTSD) as identified in VACS.[27] The Psych3 group consisted of patients with psychological disorders as identified by AHRQ-Clinical Classifications Software, except for categories of childhood or developmental psychiatric disorders (categories 654 and 655). Patients in the Psych3 group had diagnoses of adjustment disorder (category 650), anxiety disorder (category 651), attention-deficit, conduct, or disruptive behavior disorder (category 652), impulse control disorder (category 656), mood disorder (category 657), personality disorder (category 658), schizophrenia or other psychotic disorders (category 659), and miscellaneous disorders (category 670).

Data Analysis

Comorbidities were characterized using the Charlson comorbidity score (CCS) described by Deyo et al.[28] We created a propensity score-matched cohort of statin users and non-users using age, gender, comorbidities (as defined by the Deyo method[28]), total CCS score, and histories of obesity, alcohol dependence/abuse, illicit drug use, cigarette smoking, glaucoma, vision defects/blindness, healthcare utilization (number of outpatient and inpatient medical encounters during the baseline and follow-up periods), and medication use (e.g., beta-blockers, diuretics, calcium channel blockers, non-statin lipid lowering drugs, angiotensin-receptor blockers/angiotensin converting enzyme inhibitors, oral hypoglycemic agents, medications that inhibit the Cytochrome P450 system as identified in a recent FDA warning,[29] aspirin, non-steroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, systemic corticosteroids, antipsychotics, sedatives, and tricyclic antidepressants).

The primary analysis compared the occurrence of psychological disorders in the statin user group to the non-user group in the propensity score-matched cohort. Two sets of secondary analyses were conducted using different patient cohorts and different durations of statin use. For the cohort analysis, we adjusted for potential confounders and assessed the risk of psychological disorders for the all-patients cohort (all patients that met the study criteria), the primary prevention cohort (patients with no CCS comorbidity [CCS = 0]; statins in this subgroup were presumably used for primary prevention), and the no baseline psychological comorbidity cohort (patients who did not have one of the psychological disorders of interest during the baseline period). For the duration of statin use analysis, we assessed the risk of psychological disorders in statin users who continued using statins for ≥1 year and statin users who continued using statins for ≥2 years in comparison to non-users.

Statistical analysis

Baseline characteristics of statin users and non-users were compared using appropriate two-way tests (i.e., chi-square for categorical variables and Student's t test for continuous variables). Continuous variables were summarized by mean and standard deviation. Comparisons were considered statistically significant if the calculated p-value was less than an alpha level of 0.05.

Propensity score matching—Logistic regression was used to create the propensity scores and test the balance of covariates in our models using the routines developed by Becker and Ichino.[30] Using the technique developed by Leuven and Sianesi, we conducted nearest number matching with a caliper of 0.001.[31]

Finally, outcomes among statin users and non-users were compared using logistic regression analysis. Covariates for the secondary analyses are listed in Table 4. Statistical analyses were performed using STATA 12 (StataCorp. 2011. *Stata Statistical Software: Release 12.* College Station, TX: StataCorp.) and SPSS statistical software version 19 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows. Version 19.0. Armonk, NY: IBM Corp).

Results

Of the 60891 patients who met the inclusion criteria, 14642 were excluded (2124 were burn or trauma patients, 10476 received statins after September 30, 2005, and 2042 did not receive a medication during the baseline period). The study population consisted of 46249 patients who were statin users (n=13626) and 32623 non-users (n=32623).

The mean ± standard deviation (SD) cumulative duration of statin use among statin users was 1695 ± 662 days, with a median (interquartile range) of 1860 (1260–2220) days.

Approximately, 34% of statin users had been prescribed intensive statin therapy, defined as simvastatin 80 mg, atorvastatin 80 mg, pravastatin 80 mg, or rosuvastatin 40 mg. During the study period, 73.5% of statin prescriptions were simvastatin, 17.4% atorvastatin, 7% pravastatin, 1.7% rosuvastatin, and 0.24% fluvastatin or lovastatin.

Table 1 describes characteristics of the all-patients cohort. Statin users were older, more likely to be male, had more comorbidities, were prescribed more medications, and used the healthcare system more frequently than non-users. Importantly, there were no significant differences in baseline characteristics between statin users and non-users after the propensity score matching (primary analysis) (Table 2).

For the secondary analysis, the primary prevention cohort included 33513 patients (6113 statin users and 27400 non-users). Statin users in the primary prevention cohort (Table 3) were older, more likely to be male, had higher rates of obesity, smoking, and alcohol abuse/dependence, were prescribed more medications, and used the healthcare system more frequently than non-users. Lastly, patients in the no baseline psychological comorbidity cohort (Table 4) were similar to the all-patients cohort in terms of differences between statin users and non-users.

Outcome measures

Table 5 compares the psychological diagnoses made during the follow-up period for statin users and non-users. In the propensity score-matched cohort (primary analysis), statin users and non-users had similar risks of Psych1, Psych2, and Psych3 diagnoses.

In the secondary analyses, after adjusting for potential confounders in the all-patients cohort, the primary prevention cohort, and the no baseline psychological comorbidity cohort, statin users and non-users had similar risks of Psych1, Psych2, and Psych3 diagnoses. The secondary analyses were repeated for sub-groups of patients on statins for different durations (Tables 6, 7). Once again, statin users and non-users had similar risks of Psych1, Psych2, and Psych3 diagnoses across all 3 cohorts.

Discussion

The risk of developing psychological disorders was similar after 4.5 years of follow-up in this cohort of propensity score-matched statin users and non-users. These results were consistent for all pre-specified psychological disorder groups and all patient cohorts. To our knowledge, this is the largest observational study to investigate the relationship between statin therapy and the risk of psychological disorders. In a prospective observational study, Young-Xu et al. used a validated questionnaire to assess for anxiety, depression, and hostility in 590 patients recruited from a cardiology clinic.[32] The patients were followed for an average of 4 years. The authors created a propensity score for statin use and used that score in their final regression model. It is noteworthy that the investigators initially screened 2598 patients, and identified 761 patients who met study inclusion criteria, yet they only included 590 patients in their final analysis.

In a secondary analysis of the LIPID (Long-term Intervention with Pravastatin in Ischemic Disease study) trial, a representative sample of 1222 patients were followed using a standard self-administered questionnaire at baseline and on repeated follow-up intervals over a 4-year period.[33] The LIPID trial randomized patients to pravastatin 40 mg or placebo. A total of 1130 participants returned the questionnaire. The questionnaire assessed anxiety, anger, depression, impulsiveness, alcohol consumption, and adverse life events. This study found no significant association between pravastatin and psychological adverse events. In another prospective observational analysis from the Singapore Longitudinal Aging Study, 1083

individuals (out of 2084 eligible individuals) responded to several validated questionnaires; medical comorbidities and functional status were self-reported.[34] This study found no association between statin use and depression. In another cross-sectional analysis of the same patient cohort, statin users had fewer depressive symptoms than non-users (OR: 0.71; 95%CI: 0.52–0.97).[35] Finally, a recent prospective observational study of 965 patients with coronary artery disease found that statin use was associated with a 48% reduction in the odds of developing depression during follow up.[36]

It is important to note that each of these studies collected data using patient surveys or questionnaires, which are subject to selection bias. Compared to patients who elect to complete the surveys or questionnaires, non-responders are more likely to experience significant physical illness, be unmarried, have lower education, perform more poorly on cognitive testing, and have a history of psychological illness.[37] Therefore, our use of ICD-9 codes as a method of identifying psychological disorders avoids potential selection bias and adds to the existing literature.

Contrary to the studies discussed above, several small, randomized controlled trials (RCT) have reported adverse outcomes with statin use. In a RCT of 80 elderly volunteers, simvastatin was associated with more depressive symptoms and a decrease in positive affect.[8] In another crossover RCT (placebo vs. simvastatin) of 120 patients, simvastatin resulted in a statistically significant increase in depression and somatization but no change in anxiety, hostility, or aggression scores.[9] Statins were also associated with minimal decline in testosterone levels. Data from a small RCT of 12 patients randomized to atorvastatin 20 mg (9 patients) or lovastatin 20 mg (3 patients) and followed by standardized psychological tests at 4 weeks and 52 weeks demonstrated a statistically significant increase in impulsivity at 4 weeks. However, treatment-emergent impulsivity resolved over time, and depression rating scale scores improved at 52 weeks.[11]

The largest body of evidence supporting an association between statins and psychological disorders comes from case reports, case series, and pharmacovigilance reviews.[38–40] Golomb et al. reported 6 cases of severe irritability associated with statins that resolved after stopping the drug, but recurred upon re-challenge in 4 patients.[10] A review of reports from the New Zealand Center for Adverse Reaction Monitoring (CARM) showed that 285 out of 364 psychological adverse drug reactions were associated with statins.[5] The psychological conditions included mood disorders, cognitive disorders, sleep disorders, perception, and psychotic disorders. In a review of an Italian database of spontaneous adverse drug reaction reporting, the investigators compared statin adverse events with other drugs.[7] Out of 35314 adverse event reports, 71 psychological adverse events in 60 reports were associated with statin use; 14 reports noted a positive re-challenge. The five most frequent adverse events were insomnia, somnolence, agitation, confusion, and hallucination. Adjusted and unadjusted ORs for statin-associated psychological adverse events were similar to other medications. Only insomnia was higher with statins as compared with all other drugs (OR: 3.3; 95%CI: 1.9–5.7).[7]

Despite the value of pharmacovigilance reports and case series, their passive surveillance approaches are limited because there is no control group; therefore, we cannot calculate a relative risk or odds ratio. Furthermore, those types of data lack generalizability, because of the patients self-select for participation. Hence, our study offers a unique opportunity to assess the risk of psychological adverse events in a large, well-described patient population. The lack of an association between statin use and psychological disorders in our study is reassuring; however, it does not preclude the possibility of rare adverse effects.

Changes in the serotonin system have been suggested as a mechanism underlying psychological adverse events related to statins. One study measured serotonin transporter (SERT) activity in 17 hyperlipidemic patients treated with simvastatin.[41] In this group of patients, SERT activity increased significantly and cell membrane cholesterol content decreased following 1 month of therapy, but both showed a tendency to normalize after about 1 year of therapy. Increased SERT activity may be linked to impulsiveness,[41] and may lead to a decrease in serotonin neurotransmitter activity, which has been associated with increased impulsivity.[42] Data from an animal model of serotonin$_{1A}$ receptor activity suggested that chronic cholesterol depletion by mevastatin reduces the level of specific ligand binding and G-protein coupling to serotonin$_{1A}$ receptors. [43]

Coenzyme Q10 (CoQ10) may provide another plausible mechanism for a relationship between statins and depression. Statins lower plasma CoQ10 levels, which were significantly lower in 35 patients with depression in comparison to control subjects.[44] In addition, studies on hypercholesterolemic, but otherwise healthy subjects, demonstrated that higher levels of ω-3 polyunsatutrated fatty acids were associated with lower scores on a standardized depression scales.[45]

There are some limitations to our study. First, we cannot exclude the presence of infrequent adverse events, such as those reported in case series and pharmacovigilance reports. Future observational studies may focus on studying patients who discontinued statins, not only those who continued statins. Additionally, as in any retrospective observational study, unaccounted for confounders may still be present even after propensity score matching. The use of an administrative database has its own inherent weaknesses, because diagnosis codes may lack accuracy when compared to actual patient medical charts.[46] Some psychological disorders may not be adequately diagnosed by healthcare professionals. We also did not account for ethnicity, which may affect diagnosis rates of psychological disorders.[47] Some of the current non-users may represent a group of patients who experienced statin-related severe adverse events prior to the date of our study (2003). Our study did not address the risk of suicide, which has been a concern in lipid-lowering interventions, nor did it account for mortality as a cause of competing outcome. However, it is unlikely that such events occur in the absence of any ICD-9-CM code suggestive of psychological illness. We also did not study the effect of statin use on drug dependence; however, we are not aware of any study that has identified an association between statin use and drug or alcohol dependence.

In conclusion, in this cohort of propensity score-matched statin users and non-users, the risk of developing psychological disorders was similar after 4.5 years of follow-up. In contrast, other reports have suggested the presence of such an association; therefore, this topic warrants further study.

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Appendix 1. Groups of psychiatric comorbidity and their definitions

Group Name (Reference)	Definitions/ICD-9-CM codes
Psychiatric diseases at Baseline (Skanderson) [21]	Schizophrenia
	Other psychosis
	Schizoaffective disorders
	Bipolar disorder
	Major depression
	Other depression (formerly mild depression)
	PTSD (post-traumatic stress disorder)
	Developmental diseases and psychosis with origin specific to childhood
Psych1 (Skanderson) [21] *	Schizophrenia
	Other psychosis
	Schizoaffective disorders
Psych2 (Skanderson) [21] †	Bipolar disorder
	Major depression
	Other depression (formerly mild depression)
	PTSD (post-traumatic stress disorder)
Psych 3 (AHRQ)[18]	Anxiety disorders: 29384 30000 30001 30002 30009 30010 30020 30021 30022 30023 30029 3003 3005 30089 3009 3080 3081 3082 3083 3084 3089 30981 3130 3131 31321 31322 3133 31382 31383
	Adjustment disorders: 3090 3091 30922 30923 30924 30928 30929 3093 3094 30982 30983 30989 3099
	Attention-deficit, conduct, and disruptive behavior disorders: 31200 31201 31202 31203 31210 31211 31212 31213 31220 31221 31222 31223 3124 3128 31281 31282 31289 3129 31381 31400 31401 3141 3142 3148 3149
	Impulse control disorders, NEC: 31230 31231 31232 31233 31234 31235 31239
	Mood disorders: 29383 29600 29601 29602 29603 29604 29605 29606 29610 29611 29612 29613 29614 29615 29616 29620 29621 29622 29623 29624 29625 29626 29630 29631 29632 29633 29634 29635 29636 29640 29641 29642 29643 29644 29645 29646 29650 29651 29652 29653 29654 29655 29656 29660 29661 29662 29663 29664 29665 29666 2967 29680 29681 29682 29689 29690 29699 3004 311
	Personality disorders: 3010 30110 30111 30112 30113 30120 30121 30122 3013 3014 30150 30151 30159 3016 3017 30181 30182 30183 30184 30189 3019
	Schizophrenia and other psychotic disorders: 29381 29382 29500 29501 29502 29503 29504 29505 29510 29511 29512 29513 29514 29515 29520 29521 29522 29523 29524 29525 29530 29531 29532 29533 29534 29535 29540 29541 29542 29543 29544 29545 29550 29551 29552 29553 29554 29555 29560 29561 29562 29563 29564 29565 29570 29571 29572 29573 29574 29575 29580 29581 29582 29583 29584 29585 29590 29591 29592 29593 29594 29595 2970 2971 2972 2973 2978 2979 2980 2981 2982 2983 2984 2988 2989
	Miscellaneous disorders (670): 293.89, 293.9, 3001.1, 3001.2, 3001.3, 300.14, 300.15, 300.16, 300.19, 300.6, 300.7, 300.81, 300.82, 302.1, 302.2, 302.3, 302.4, 302.50, 302.51,, 302.52, 302.53, 302.6, 302.70, 302.71, 302.72, 302.73, 302.74, 302.75, 302.76, 302.79, 302.81, 302.82, 302.83, 302.84, 302.85, 302.89, 302.9, 306.0, 306.1, 306.2, 306.3, 306.4, 306.50, 306.51, 306.52, 306.53, 306.59, 306.6, 306.7, 306.8, 306.9, 307.1, 307.40, 307.41, 307.42, 307.43, 307.44, 307.45, 307.46, 307.47, 307.48, 307.49, 307.50, 307.51, 307.52, 307.53, 3075.4, 307.59,

Group Name (Reference)	Definitions/ICD-9-CM codes
	307..80, 307.81, 307.89, 310.1, 316, 648.40, 648.41, 648.42, 648.43, 648.44, V402, V403, V403.1, V403.9, V409, V673

* In difference with the VACS, we did not include codes 299.x (pervasive developmental disorder), and code V11.0 (personal history of schizophrenia), which are not in consideration as a complication for statin-associated side effects.

† In difference with the VACS, we did not include codes code V11.1 (personal history of manic-depressive psychosis), which is not in consideration as a complication for statin-associated side effects.

Table 1

Baseline demographic features, disease characteristics, and outcomes

	Statin users (n = 13626)	Non-users (n = 32623)	p-value
Age in years: mean ± SD	60.4 ±12.3	44.8 ± 11.3	< 0.0001
Male gender: n (%)	7947 (58.3)	14263 (43.7)	< 0.0001
Comorbidities in baseline period:			
Acute myocardial infarction *: n (%)	797 (5.8)	120 (0.4)	< 0.0001
Congestive heart failure *: n (%)	746 (5.5)	163 (0.5)	< 0.0001
Peripheral vascular disease *: n (%)	859 (6.3)	189 (0.6)	< 0.0001
Cerebrovascular disease *: n (%)	553 (4)	226 (0.7)	< 0.0001
Dementia *: n (%)	58 (0.4)	44 (0.1)	< 0.0001
Chronic obstructive lung disease *: n (%)	2065 (15.2)	2464 (7.6)	< 0.0001
Rheumatologic diseases *: n (%)	290 (2.1)	471 (1.4)	< 0.0001
Peptic ulcer disease *: n (%)	220 (1.6)	263 (0.8)	< 0.0001
Mild liver disease *: n (%)	48 (0.4)	117 (0.4)	0.5
Diabetes mellitus *: n (%)	4386 (32.2)	858 (2.6)	< 0.0001
Diabetes mellitus with complications *: n (%)	1663 (12.2)	178 (0.5)	< 0.0001
Hemiplegia/paraplegia *: n (%)	49 (0.4)	27 (0.1)	< 0.0001
Renal disease *: n (%)	471 (3.5)	117 (0.4)	< 0.0001
Malignancy *: n (%)	1010 (7.4)	1101 (3.4)	< 0.0001
Liver disease (moderate/severe) *: n (%)	8 (0.1)	41 (0.1)	0.03
Metastatic neoplasm *: n (%)	48 (0.4)	95 (0.3)	0.17
HIV *: n (%)	13 (0.1)	39 (0.1)	0.3
Charlson Comorbidity total score: mean ±SD	1.2 ±1.6	0.3 ±0.8	< 0.0001
Psychological disorders at baseline **: n (%)	2168 (15.9)	3762 (11.5)	< 0.0001
Illicit drug use: n (%)	20 (0.1)	62 (0.2)	0.35
Alcohol abuse/dependence: n (%)	133 (1)	237 (0.7)	.007
Smoking: n (%)	1226 (9.0)	1903 (5.8)	< 0.0001
Obesity: n (%)	2396 (17.6)	3259 (10.0)	< 0.0001
Vision defects/blindness	6247 (45.8)	13318 (40.8)	< 0.0001
Mean HDL-C in baseline period: mean ± SD†	52.5 ±14.5	58.5 ±17.8	< 0.0001
Mean HDL-C in follow-up period : mean ± SD†	51.1 ±13.6	57 ±16.5	< 0.0001
Mean LDL-C in baseline period: mean ± SD†	105.1 ±33.9	111 ±27.9	< 0.0001
Mean LDL-C in follow-up period: mean ± SD†	98 ±31.3	112.5 ±27.4	< 0.0001
Mean TG in baseline period: mean ± SD†	156.2 ±97.6	120.1±84.2	< 0.0001
Mean TG in follow-up period: mean ± SD†	143.3 ±78.7	114.7 ±74	< 0.0001
Number of outpatient medical encounters during baseline period: mean ± SD	40.9 ±44.7	23 ±31.8	< 0.0001

	Statin users (n = 13626)	Non-users (n = 32623)	p-value
Number of inpatient admissions during baseline period: mean ± SD	0.44 ±1.0	0.18 ±0.6	< 0.0001
Number of outpatient medical encounters during follow-up period: mean ± SD	118.8 ±149	63.5 ±79	< 0.0001
Number of inpatient admissions during follow-up period: mean ± SD	2.87 ±3.06	1.87 ± 1.94	< 0.0001
Medications:			
Beta-blocker: n (%)	3911 (28.7)	2167 (6.6)	< 0.0001
Diuretic: n (%)	5117 (37.6)	3405 (10.4)	< 0.0001
Calcium channel Blocker: n (%)	3514 (25.8)	1643 (5.0)	< 0.0001
Non-statin lipid lowering drugs: n (%)	2321 (17.0)	573 (1.8)	< 0.0001
ACE/ARB: n (%)	7982 (58.6)	3466 (10.6)	< 0.0001
Oral Hypoglycemic: n (%)	2820 (20.7)	383 (1.2)	< 0.0001
Cytochrome p 450: n (%)	1464 (10.7)	1404 (4.3)	< 0.0001
Aspirin: n (%)	7274 (53.4)	2659 (8.2)	< 0.0001
NSAID: n (%)	7568 (55.5)	20136(61.7)	< 0.0001
SSRI: n (%)	2513 (18.4)	4301 (13.2)	< 0.0001
Systemic corticosteroid: n (%)	532 (3.9)	1369 (4.2)	0.08
Antipsychotic: n (%)	180 (1.3)	322 (1.0)	0.002
Sedatives: n (%)	2862 (21.0)	5430(16.6)	< 0.0001
Tricyclic antidepressants: n (%)	35 (0.3)	58 (0.2)	0.09
Outcomes			
Psych1 (schizophrenia/other psychosis): n (%)	767 (1.7)	533 (1.2)	< 0.0001
Psych2 (depression / bipolar disorder): n (%)	3105 (6.7)	6375 (13.8)	< 0.0001
Psych3 (all psychological disorders): n (%)	11933 (25.8)	5691 (12.3)	< 0.0001

ACE/ARB: Angiotensin-receptor blockers & angiotensin converting enzyme inhibitors; Cytochrome p 450: medications that inhibit the Cytochrome p450 system as identified in a recent FDA warning;[29] HDL-C: High-density lipoprotein cholesterol in mg/dL; LDL-C: Low-density lipoprotein cholesterol in mg/dL; NSAID: non-steroidal anti-inflammatory drugs; SSRI: Selective serotonin reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TG: Triglycerides in mg/dL.

*Diagnosis is based on ICD-9-CM codes as identified in Deyo method for applying the Charlson comorbidity score.[28]

**Definition is detailed in Appendix 1.

†Lipid measurements represent the mean value for each patient throughout the baseline or follow-up periods; these laboratory measurements were missing in 8647–7520 patients in statin-users and 26546 – 18619 patients in the non-users.

Table 2

Baseline characteristics and outcomes of propensity score-matched statin users and non-users.

	Statin Users (n =6972)	Non-users (n =6972)	*p*
Age in years: mean ±SD	56.5 ±12.5	56.8 ±12.2	0.2
Male gender: n (%)	3769 (54.1)	3778 (54.2)	0.9
Comorbidities in baseline period:			
Acute myocardial infarction*: n (%)	59 (0.8)	66 (0.9)	0.5
Congestive heart failure*: n (%)	130 (1.9)	130 (1.9)	1.0
Peripheral vascular disease*: n (%)	136 (2)	142 (2)	0.8
Cerebrovascular disease*: n (%)	153 (2.2)	146 (2.1)	0.7
Dementia*: n (%)	29 (0.4)	29 (0.4)	1.0
Chronic obstructive lung disease*: n (%)	817 (11.7)	835 (12)	0.7
Rheumatologic diseases*: n (%)	157 (2.3)	170 (2.4)	0.8
Peptic ulcer disease*: n (%)	99 (1.4)	102 (1.5)	0.9
Mild liver disease*: n (%)	30 (0.4)	30 (0.4)	1.0
Diabetes mellitus*: n (%)	699 (10)	680 (9.8)	0.6
Diabetes mellitus with complications*: n (%)	182 (2.6)	162 (2.3)	0.3
Hemiplegia/paraplegia*: n (%)	9 (0.1)	9 (0.1)	1.0
Renal disease*: n (%)	96 (1.4)	91 (1.32)	0.8
Malignancy*: n (%)	438 (6.3)	435 (6.2)	0.9
Liver disease (moderate/severe)*: n (%)	4 (0.1)	4 (0.1)	1.0
Metastatic neoplasm*: n (%)	24 (0.3)	20 (0.3)	0.6
HIV *: n (%)	7 (0.2)	9 (0.1)	0.6
Charlson Comorbidity total score: mean ± SD	0.59 ± 1.1	0.57 ± 1.15	0.4
Psychological disorders at baseline **: n (%)	980 (7)	1010 (7.2)	0.5
Illicit drug use: n (%)	11 (0.2)	10 (0.1)	0.8
Alcohol abuse/dependence: n (%)	72 (1)	60 (0.9)	0.3
Smoking: n (%)	565 (8.1)	581 (8.3)	0.6
Obesity	1066 (15.3)	1059 (15.2)	0.9
Vision defects/blindness	3073 (44.1)	3096 (44.4)	0.7
Number of outpatient medical encounters during baseline period: mean ± SD	32.3 ±31.8	32.2 ± 51.3	0.7
Number of inpatient admission during baseline period: mean ± SD	0.27 ± 0.8	0.27 ± 0.7	0.9
Number of outpatient medical encounters during follow-up period: mean ± SD	89.5 ± 84.2	88.4 ± 115	0.5
Number of inpatient admission during follow- up period: mean ± SD	0.8 ± 1.8	0.8 ± 1.9	0.8
Medications:			
Beta-blocker: n (%)	1274 (18.3)	1275 (18.3)	1.0
Diuretic: n (%)	1934 (27.7)	1950 (28)	0.8
Calcium channel Blocker: n (%)	1105 (15.8)	1086 (15.6)	0.7
Non-statin lipid lowering drugs: n (%)	520 (7.5)	483 (6.9)	0.2

	Statin Users (n =6972)	Non-users (n =6972)	*p*
ACE/ARB: n (%)	2444 (35.1)	2427 (34.8)	0.8
Oral hypoglycemic: n (%)	321 (4.6)	297 (4.3)	0.3
Cytochrome p 450: n (%)	465 (6.7)	461 (6.6)	0.9
Aspirin: n (%)	2169 (31.1)	2147 (30.8)	0.7
NSAID: n (%)	3998 (57.3)	3993 (57.3)	0.9
SSRI: n (%)	1167 (16.7)	1191 (17.1)	0.6
Systemic corticosteroid: n (%)	272 (3.9)	270 (3.9)	1.0
Antipsychotic: n (%)	89 (1.3)	94 (1.3)	0.7
Sedatives: n (%)	1377 (19.8)	1370 (19.7)	0.9
Tricyclic antidepressants: n (%)	13 (0.2)	20 (0.3)	0.2
Outcomes			
Psych1 (schizophrenia/other psychosis): n (%)	265 (1.9)	297 (2.1)	0.2
Psych2 (depression / bipolar disorder): n (%)	1490 (21.4)	1462 (21)	0.6
Psych3 (all psychological disorders): n (%)	2828 (40.6)	2784 (39.9)	0.5

ACE/ARB: Angiotensin-receptor blockers & angiotensin converting enzyme inhibitors;

NSAID: non-steroidal anti-inflammatory drugs; Cytochrome p 450: medications that inhibit the Cytochrome p450 system as identified in a recent FDA warning; [29] SSRI: selective serotonin reuptake inhibitors

* Diagnosis is based on ICD-9-CM codes as identified in Deyo method for applying the Charlson comorbidity score[28]

** Definition is detailed in Appendix 1

Table 3

Baseline characteristics of statin users and non-users in patients with no comorbidity (based on Charlson Comorbidity Score[28])

	Statinusers (n =6113)	Non-users (n =27400)	p-value
Age in years: mean ± SD	56.6 ± 12.1	43.6 ± 10.3	< 0.0001
Male gender: n (%)	3707 (60.6)	12246 (44.7)	< 0.0001
Charlson Comorbidity total score: mean ± SD	0 ± 0	0 ± 0	
Psychological disorders at baseline *: n (%)	789 (12.9)	2802 (10.2)	< 0.0001
Illicit drug use: n (%)	6 (0.1)	40 (0.1)	0.45
Alcohol abuse/dependence: n (%)	48 (0.8)	153 (0.6)	0.04
Smoking: n (%)	477 (7.8)	1401 (5.1)	< 0.0001
Obesity: n (%)	901 (14.7)	2520 (9.2)	< 0.0001
Vision defects/blindness	2613 (42.7)	11048 (40.3)	0.001
Number of outpatient medical encounters during baseline period: mean ± SD	27.2 ± 25.4	19.4 ± 21	< 0.0001
Number of inpatient admissions during baseline period: mean ± SD	0.18 ± 0.5	0.13 ± 0.4	< 0.0001
Number of outpatient medical encounters during follow-up period: mean ± SD	81.1 ± 78.3	55.6 ± 59.6	< 0.0001
Number of inpatient admissions during follow-up period: mean ± SD	2.1 ± 1.9	1.7 ± 1.5	< 0.0001
Medications:			
Beta-blocker: n (%)	1385 (22.7)	1500 (5.5)	< 0.0001
Diuretic: n (%)	1748 (28.6)	2305 (8.4)	< 0.0001
Calcium channel Blocker: n (%)	1092 (17.9)	1064 (3.9)	< 0.0001
Non-statin lipid lowering drugs: n (%)	755(12.4)	360 (1.3)	< 0.0001
ACE/ARB: n (%)	2371 (38.8)	2265 (8.3)	< 0.0001
Oral hypoglycemic: n (%)	32 (0.5)	89 (0.3)	0.02
Cytochrome p 450: n (%)	465 (7.6)	1113 (4.1)	< 0.0001
Aspirin: n (%)	2434 (39.8)	1761 (6.4)	< 0.0001
NSAID: n (%)	3550 (58.1)	16860 (61.5)	< 0.0001
SSRI: n (%)	944 (15.4)	3256 (11.9)	< 0.0001
Systemic corticosteroid: n (%)	127 (2.1)	873 (3.2)	< 0.0001
Antipsychotic: n (%)	62 (1.0)	232 (0.8)	0.2
Sedatives: n (%)	1094 (17.9)	4182 (15.3)	< 0.0001
Tricyclic antidepressants: n (%)	11 (0.2)	42 (0.2)	0.4

ACE/ARB: Angiotensin-receptor blockers & angiotensin converting enzyme inhibitors; NSAID: non-steroidal anti-inflammatory drugs; Cytochrome p 450: medications that inhibit the Cytochrome p450 system as identified in a recent FDA warning; [29] SSRI: selective serotonin reuptake inhibitors

*Schizophrenia/other psychosis, mood disorders, depression, and bipolar disorder as detailed in Appendix 1

Table 4

Baseline characteristics of statin users and non-users in patients with no psychological disorders* during the baseline period

	Statin-users (n =11458)	Non-users (n =28861)	p-value
Age in years: mean ± SD	60.3 ±12.2	44.7 ±11.2	< 0.0001
Male gender: n (%)	7077 (61.8)	13419 (46.5)	< 0.0001
Comorbidities in baseline period:			
Acute myocardial infarction*: n (%)	616 (5.4)	90 (0.3)	< 0.0001
Congestive heart failure*: n (%)	560 (4.9)	119 (0.4)	< 0.0001
Peripheral vascular disease*: n (%)	723 (6.3)	151 (0.5)	< 0.0001
Cerebrovascular disease*: n (%)	390 (3.4)	148 (0.5)	< 0.0001
Dementia*: n (%)	12 (0.1)	10 (<0.01)	< 0.009
Chronic obstructive lung disease*: n (%)	1583 (13.8)	2026 (7)	< 0.0001
Rheumatologic diseases*: n (%)	233 (2)	362 (1.3)	< 0.0001
Peptic ulcer disease*: n (%)	163 (0.4)	211 (0.7)	< 0.0001
Mild liver disease*: n (%)	34 (0.3)	81 (0.2)	< 0.4
Diabetes mellitus*: n (%)	3641 (31.8)	690 (2.4)	< 0.0001
Diabetes mellitus with complications*: n (%)	1374 (12)	147 (0.5)	< 0.0001
Hemiplegia/paraplegia*: n (%)	27 (0.2)	15 (0.1)	< 0.0001
Renal disease*: n (%)	388 (3.4)	88 (0.3)	< 0.0001
Malignancy*: n (%)	829 (7.2)	917 (3.2)	< 0.0001
Liver disease (moderate/severe)*: n (%)	7 (0.1)	28 (0.1)	0.2
Metastatic neoplasm*: n (%)	32 (0.3)	75 (0.3)	0.4
HIV *: n (%)	11 (0.1)	31 (0.1)	0.4
Charlson Comorbidity Total Score: mean ± SD	1.18 ± 1.58	0.24 ± 0.76	< 0.0001
Illicit drug use: n (%)	17 (0.1)	5 (<0.01)	0.4
Alcohol abuse/dependence: n (%)	96 (0.8)	142 (0.5)	< 0.0001
Smoking: n (%)	966 (8.4)	1554 (5.4)	< 0.0001
Obesity: n (%)	1919 (16.7)	2641 (9.2)	< 0.0001
Vision defects/blindness	5198 (45.4)	11725 (40.6)	0.001
Number of outpatient medical encounters during baseline period: mean ± SD	36.9 ± 39.7	20.4 ± 23.3	< 0.0001
Number of inpatient admissions during baseline period: mean ± SD	0.37 ± 0.89	0.15 ± 0.49	< 0.0001
Medications:			
Beta-blocker: n (%)	3241 (28.3)	1766 (6.1)	< 0.0001
Diuretic: n (%)	4238 (37)	2880 (10)	< 0.0001
Calcium channel Blocker: n (%)	2892 (25.2)	1387 (4.8)	< 0.0001
Non-statin lipid lowering drugs: n (%)	1952 (17)	485 (1.7)	< 0.0001
ACE/ARB: n (%)	6682 (58.3)	2943 (10.2)	< 0.0001
Oral Hypoglycemic: n (%)	2317 20.2)	299 (1)	< 0.0001

	Statin-users (n =11458)	Non-users (n =28861)	p-value
Cytochrome p 450: n (%)	1205 (10.5)	1216 (4.2)	< 0.0001
Aspirin: n (%)	6091 (53.2)	2244 (7.8)	< 0.0001
NSAID: n (%)	6220 (54.3 5)	17642 (61.1)	< 0.0001
SSRI: n (%)	934 (8.2)	1722 (6)	< 0.0001
Systemic corticosteroid: n (%)	409 (3.6)	1100 (3.8)	< 0.1
Antipsychotic: n (%)	29 (0.3)	44 (0.2)	0.02
Sedatives: n (%)	1890 (16.5)	3853 (13.4)	< 0.0001
Tricyclic antidepressants: n (%)	26 (0.2)	39 (0.1)	0.02

ACE/ARB: Angiotensin-receptor blockers & angiotensin converting enzyme inhibitors; NSAID: non-steroidal anti-inflammatory drugs; Cytochrome p 450: medications that inhibit the Cytochrome p450 system as identified in a recent FDA warning; [29] SSRI: selective serotonin reuptake inhibitors

* Schizophrenia/other psychosis, mood disorders, depression, and bipolar disorder as detailed in Appendix 1

Table 5

Comparison of psychological disorders during follow-up in statin users and non-users

	OR	95%CI		p-value
Propensity-matched patients				
Psych1 (schizophrenia/other psychosis)	0.9	0.75	1.05	0.2
Psych2 (depression / bipolar disorder)	1.02	0.94	1.11	0.6
Psych3 (all psychological disorders)	1.02	0.96	1.1	0.5
All patients cohort *				
Psych1 (schizophrenia/other psychosis)	0.9	0.78	1.06	0.2
Psych2 (depression / bipolar disorder)	1.03	0.95	1.11	0.5
Psych3 (all psychological disorders)	1.05	0.99	1.12	0.1
Patients with no Charlson comorbidity †				
Psych1 (schizophrenia/other psychosis)	0.95	0.76	1.19	0.7
Psych2 (depression / bipolar disorder)	1.01	0.9	1.12	0.8
Psych3 (all psychological disorders)	1.03	0.95	1.05	0.5
Patients with no psychological disorders at baseline ‡				
Psych1 (schizophrenia/other psychosis)	0.88	0.72	1.08	0.2
Psych2 (depression / bipolar disorder)	0.97	0.89	1.07	0.6
Psych3 (all psychological disorders)	1.02	0.96	1.09	0.6

*Adjusting for age, gender, statin use, all comorbid conditions as in table 2, total Charlson comorbidity score, obesity, smoking, alcohol use, illicit drug use, Psychological disorders at baseline, vision defects/blindness, number of all admissions in baseline period, number of all outpatients medical encounters in the baseline period, and use of different classes of medications as listed in table 1.

†adjusting for the same factors mentioned earlier except for Charlson comorbidity total score and its components.

‡adjusting for the same factors mentioned in “all patients cohort” except for “psychological disorders at baseline” covariate.

Table 6

Comparison of psychological disorders during follow-up in statin users (≥ = 1 year) and non-users

	OR	95%CI		p-value
All patients cohort [*] (statin users = 12883 patients, non-users = 32623 patients)				
Psych1 (schizophrenia/other psychosis)	0.89	0.76	1.04	0.1
Psych2 (depression / bipolar disorder)	1.05	0.96	1.14	0.3
Psych3 (all psychological disorders)	1.06	0.998	1.132	0.06
Patients with no Charlson comorbidity [†] (statin users = 5646 patients, non-users = 27400 patients)				
Psych1 (schizophrenia/other psychosis)	0.94	0.74	1.18	0.6
Psych2 (depression / bipolar disorder)	1.03	0.93	1.14	0.6
Psych3 (all psychological disorders)	1.05	0.97	1.14	0.2
Patients with no psychological disorders at baseline [‡] (statin users = 10826 patients, non- users = 28861 patients)				
Psych1 (schizophrenia/other psychosis)	0.89	0.73	1.08	0.2
Psych2 (depression / bipolar disorder)	1.0	0.9	1.1	0.9
Psych3 (all psychological disorders)	1.06	0.99	1.13	0.1

[*] Adjusting for age, gender, statin use, all comorbid conditions as in table 2, total Charlson comorbidity score, obesity, smoking, alcohol use, illicit drug use, psychological disorders at baseline, vision defects/blindness, number of all admissions in baseline period, number of all outpatients medical encounters in the baseline period, and use of different classes of medications as listed in table 1.

[†] adjusting for the same factors mentioned earlier except for Charlson comorbidity total score and its components.

[‡] adjusting for the same factors mentioned in “all patients cohort” except for “psychological disorders at baseline” covariate.

Table 7

Comparison of psychological disorders during follow-up in statin users (≥ = 2 years) and non-users

	OR	95%CI		p-value
All patients cohort [*] (statin users = 12006 patients, non-users = 32623 patients)				
Psych1 (schizophrenia/other psychosis)	0.87	0.76	1.02	0.09
Psych2 (depression / bipolar disorder)	1.15	1.05	0.97	0.2
Psych3 (all psychological disorders)	1.06	0.99	1.13	0.1
Patients with no Charlson comorbidity [†] (statin users = 5172 patients, non-users = 27400 patients)				
Psych1 (schizophrenia/other psychosis)	0.88	0.69	1.12	0.3
Psych2 (depression / bipolar disorder)	1.03	0.93	1.15	0.5
Psych3 (all psychological disorders)	1.04	0.96	1.13	0.4
Patients with no psychological disorders at baseline [‡] (statin users = 10095 patients, non- users = 28861 patients)				
Psych1 (schizophrenia/other psychosis)	0.85	0.7	1.03	0.1
Psych2 (depression / bipolar disorder)	1.01	0.9	1.11	0.9
Psych3 (all psychological disorders)	1.05	0.98	1.12	0.2

[*] Adjusting for age, gender, statin use, all comorbid conditions as in table 2, total Charlson comorbidity score, obesity, smoking, alcohol use, illicit drug use, psychological disorders at baseline, vision defects/blindness, number of all admissions in baseline period, number of all outpatients medical encounters in the baseline period, and use of different classes of medications as listed in table 1.

[†] adjusting for the same factors mentioned earlier except for Charlson comorbidity total score and its components.

[‡] adjusting for the same factors mentioned in “all patients cohort” except for “psychological disorders at baseline” covariate.