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Statin Therapy and Risk of Acute Memory Impairment

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Abstract

IMPORTANCE—Reports on the association between statins and memory impairment are inconsistent.

OBJECTIVE—To assess whether statin users show acute decline in memory compared with nonusers and with users of nonstatin lipid-lowering drugs (LLDs).

DESIGN, SETTING, AND PARTICIPANTS—Using The Health Improvement Network database during January 13, 1987, through December 16, 2013, a retrospective cohort study compared 482 543 statin users with 2 control groups: 482 543 matched nonusers of any LLDs and all 26 484 users of nonstatin LLDs. A case-crossover study of 68 028 patients with incident acute memory loss evaluated exposure to statins during the period immediately before the outcome vs 3 earlier periods. Analysis was conducted from July 7, 2013, through January 15, 2015.

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Study concept and design: Strom, Schinnar, Karlawish, Hennessy.
Acquisition, analysis, or interpretation of data: Strom, Schinnar, Hennessy, Teal, Bilker.
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RESULTS—When compared with matched nonusers of any LLDs (using odds ratio [95% CI]), a strong association was present between first exposure to statins and incident acute memory loss diagnosed within 30 days immediately following exposure (fully adjusted, 4.40; 3.01–6.41). This association was not reproduced in the comparison of statins vs nonstatin LLDs (fully adjusted, 1.03; 0.63–1.66) but was also present when comparing nonstatin LLDs with matched nonuser controls (adjusted, 3.60; 1.34–9.70). The case-crossover analysis showed little association.

CONCLUSIONS AND RELEVANCE—Both statin and nonstatin LLDs were strongly associated with acute memory loss in the first 30 days following exposure in users compared with nonusers but not when compared with each other. Thus, either all LLDs cause acute memory loss regardless of drug class or the association is the result of detection bias rather than a causal association.

Although acute memory loss associated with the use of statins has been described in case reports and case series[1–8] as well as studies,[9–11] findings have been inconsistent, and studies of long-term use of statins have found either improved memory or no effect.[12–14] Mechanisms have been postulated both for impairment and improvement of memory with statin therapy. β-Amyloid plaques in the brain are thought to be related to dementia resulting from cholesterol buildup,[2,15–20] and the role of statins in interrupting deposition of plaques might delay the development of dementia.[2,21,22] The lipophilicity of simvastatin and atorvastatin calcium that allows them to cross the blood-brain barrier could either confer protection[2,20] or adversely affect memory if statins interfere with myelin production in the brain.[2,23,24] King et al[2] suggested that inhibition of myelin production could explain memory recovery after discontinuation of statin use because myelin stores can be replenished.

The contradictory findings among the controlled pharmacoepidemiologic studies may be the result of different drugs being studied, limited sample sizes in some studies, differences in how memory was measured, dose, duration of follow-up, choice of controls, and control for confounding.[25–27] The goal of our study was to investigate the association between use of statins and diagnosed acute memory impairment. Our hypothesis was that statin therapy would be associated with acute decline in the memory of patients receiving therapy compared with nonusers as well as users of other lipid-lowering drugs (LLDs).

Methods

Data Source

Data were obtained from The Health Improvement Network (THIN), a database composed of the primary medical records from general practitioners (GPs) in the United Kingdom.[28] THIN consists of the anonymized patient records that are extracted directly from GPs' offices. These data are collected during the routine practice of the GPs and therefore reflect the real-life setting. The patient population in THIN is broadly representative of the UK population. The Health Improvement Network database through December 16, 2013, contained data on nearly 11 million patients from 553 GP practices. The University of Pennsylvania Committee on Studies Involving Human Beings approved the study and certified that informed consent was exempt. The Committee on Scientific Research in the

United Kingdom also approved this study. Analysis was conducted July 7, 2013, through January 15, 2015.

Study Population

All THIN patients eligible for receiving medical care during January 13, 1987, through December 16, 2013, were eligible for the study. In addition, the first study drug had to have been prescribed after the date when Vision (the computerized software used by GPs) was introduced, after the date of Acceptable Mortality Recording (a proxy indicator for adequate data recording),[29] and at least 365 days after a patient's registration with a practice (providing a window to measure baseline variables).

Patients were excluded if they had a history of cognitive dysfunction, such as Alzheimer disease or dementia (as indicated by the presence of a disease code for these conditions before therapy with the study drugs was initiated) or medications used for dementia. Individuals with other dementing illnesses, such as Parkinson disease, or who were taking medications that are used to treat Parkinson disease, Huntington disease, vascular dementia, or frontotemporal dementia were also excluded. Additional exclusion criteria were brain tumors, bacterial meningitis and other brain infections, encephalitis, cerebral degeneration, traumatic brain injury, epilepsy, schizophrenia, history of electroconvulsive therapy, cognitive impairment related to mental retardation, autism, Down syndrome, or delirium. Because we searched for incident cases, patients with diagnosis codes for acute memory loss occurring before the index date (defined below) were excluded.

Study Design

A retrospective cohort study compared new users of statin medications with unexposed individuals (controls). In addition, to help reduce the possibility of confounding by indication and detection bias, users of statins were compared with a second control group of patients receiving nonstatin LLDs (ie, cholestyramine, colestipol hydrochloride, colesevelam, clofibrate, gemfibrozil, fenofibrate, and niacin).

The study group included persons receiving newly prescribed statins (atorvastatin, cerivastatin, fluvastatin, pravastatin, rosuvastatin, or simvastatin; lovastatin, mevastatin, and pitavastatin were not available in the United Kingdom). *Newly prescribed* was defined as having no prescriptions for any statins during at least 1 year of enrollment with the practice before statin therapy was initiated.

The primary control group consisted of a random sample of nonusers of any LLDs (statins and nonstatins), using a propensity score based on sex, age group at the start date of statin therapy (≤40, 41–50, 51–60, 61–70, 71–80, and >80 years), duration of enrollment (1–<3, 3 to <6, and ≥6 years), and GP practice to select 1:1 matched pairs with an optimal matching algorithm. The index date of the primary control group was an assigned date corresponding to the start date of the pair-matched statin user.

A second control group consisted of persons who were receiving newly prescribed nonstatin LLDs without a statin. All were selected without matching because their numbers were smaller compared with the statin group. In this comparison, to keep the cohorts independent,

patients were excluded if they had previously received a statin or if they had prescriptions for both drugs on the same start date. The rationale for including the second comparison group of nonstatin LLDs was to control for detection bias in the comparison between statin users and unexposed individuals since statin users may be more likely to visit their GPs than are nonusers, whereas users of nonstatin LLDs may be more comparable to statin users. The second control group could also determine whether there are differences in risk between drug classes of LLDs. In a separate analysis, this group of users of nonstatin LLDs was compared with its own random sample of nonusers of any LLDs, with propensity score matching as described above.

A secondary case-crossover study[30] was undertaken to eliminate confounding by stable patient factors. A requirement of this design is intermittent exposure, which in the case of statin users occurs during periods of nonuse. All patients with a diagnosis of acute memory loss were selected, comparing in each person the presence or absence of prior exposure to statins during days 0 to 30 immediately preceding the first diagnosis of acute memory loss with the presence of statin exposure during 3 earlier control periods (days 31–60, 150–180, and 270–300 preceding the diagnosis of memory loss).

Study Outcome

The outcome for this study was the onset of acute, reversible memory impairment. Using Read codes Clinical Terms, version 2 (the standard clinical terminology system used by GPs in the United Kingdom), we sought codes with descriptions specifically pertaining to memory loss including amnesia, amnesia symptom, memory loss symptom, temporary loss of memory, short-term memory loss, transient global amnesia, drug-induced amnestic syndrome, nonalcoholic amnestic syndrome, amnesia (retrograde), memory lapses, minor memory lapses, and mild memory disturbance. We avoided codes with descriptions of dementia (eTable 1 in the Supplement includes the codes).

To examine the validity of the diagnosis, we identified a random sample of 100 patients with codes for acute memory loss and mailed a questionnaire to their GPs requesting confirmatory information for the diagnosis of memory loss, disease onset (acute or chronic), and whether it resolved within 3 months. In addition, we requested the GPs' free-text comments from the electronic medical records for 1000 patients with this diagnosis. Our review for acute or chronic memory loss classified the comments as definite, possible, or indeterminate. Reviewers were also asked to look for evidence of reversibility of memory loss.

Confounding Variables

Some potential confounders were controlled for by exclusion (see above). Other confounders (all measured at baseline or before the index date) were controlled for in the analysis.

Statistical Analysis

The outcome was evaluated during several periods (overall after first exposure, during 0 to 30 days following the first exposure, during 0 to 60 days after the first exposure, and at

further cumulative successive intervals). For the primary comparison of statin users vs matched nonusers of any LLDs, we used conditional logistic regression analysis[31] to estimate adjusted odds ratios (ORs) and 95% CIs, taking into account the matched pairs that were created using propensity score matching[32,33] and adjusting for the remaining potential confounding variables as covariates in the models. For the secondary comparison of statin users vs unmatched users of nonstatin LLDs, we used unconditional logistic regression to adjust for all the confounding variables including the demographic variables. For the subanalysis comparing nonstatin LLDs with matched nonuser controls, we again applied conditional logistic regression, controlling in the model for the propensity score used for matching and including all remaining confounding variables not in the propensity score. In a sensitivity analysis conducted after the validation study, we repeated the analyses excluding Read diagnosis codes that belonged to persons classified by the GPs as false cases.

In addition to examining the risk of acute memory loss for the class of statin drugs, we performed subanalyses by individual drugs compared with nonusers since the literature[2,16,21,23,24] suggests that different statins may have different effects. Dose was investigated by classifying the daily dose of the initial statin prescription categorized as low, medium, and high milligrams per day for each (eTable 2 in the Supplement) and fitting a logistic regression model, with the dependent variable being incident acute memory loss occurring within 30 days after the initial prescription. In the case-crossover study,[30,34] we used conditional logistic regression conditioned on each patient to examine the association between acute memory loss and prior statin therapy, evaluating the prevalence of use in the immediately prior 30-day window as the reference period. All analyses were conducted using SAS, version 9.2 (SAS Institute Inc).

Results

Of 928 555 users of statin medications, 482 543 individuals (52.0%) were included in the study after meeting initial screening and eligibility conditions. These patients were compared with 482 543 randomly selected individuals not receiving any LLD. For the second control group, of all 115 297 users of nonstatin LLDs in the THIN database, 26 484 individuals (23.0%) met eligibility criteria.

The distributions of demographic factors for statin users and nonusers were similar because of matching, but statin users were significantly older (305 904 [63.4%] vs 151 162 [57.3%], respectively, were >60 years) and had longer enrollment duration in THIN than the unmatched users of nonstatin LLDs (Table 1). Compared with nonusers of any LLDs, statin users had substantially higher proportions of persons with diagnoses suggesting a medical indication for an LLD as well as higher prevalences of other diseases and drugs. Users of nonstatin LLDs tended to have higher prevalences of diabetes mellitus, hypercholesterolemia, and cardiovascular disease than did statin users (Table 2). The nonstatin LLD cohort also had higher prevalences of liver and kidney disease and use of antihypertensive, antidepressant, anxiolytic, and antihistamine medications compared with statin users.

Comparing statin users with matched nonusers of any LLDs across all time periods, the OR (95% CI) was 1.23 (1.18–1.28). There was a large, statistically significant, increased risk only during the 30-day window immediately following the first exposure (fully adjusted, 4.40; 3.01–6.41) (Table 3). To account for the possibility of delayed reporting of acute memory loss, we looked also at the 60-day window following first exposure (fully adjusted, 2.41; 95% CI, 1.85–3.13); the OR decreased monotonically in each later period (eTable 3 in the Supplement).

Comparing statin users with unmatched users of nonstatin LLDs showed a slightly increased OR (95% CI) overall (fully adjusted, 1.11; 1.03–1.20) but none in the initial 30-day period (fully adjusted, 1.03; 0.63–1.66) (Table 3) or in the 60-day window (fully adjusted, 1.12; 0.74–1.70) (eTable 4 in the Supplement).

In contrast, comparing users of nonstatin LLDs with matched nonusers (26 484 individuals in each group), the overall OR (95% CI) across all time periods was 0.96 (0.79–1.17) (Table 4), and there again was an increased OR in the first 30 days immediately following exposure (3.60; 1.34–9.70, adjusted for the matching variables). In the 60-day window, the adjusted OR was 1.60 (0.84–3.05) (eFigure and eTable 5 in the Supplement).

Both atorvastatin and simvastatin showed an increased OR (95% CI) within the first 30 days after exposure compared with nonusers (2.40; 1.42–4.04, and 3.53; 2.79–4.48, respectively, adjusted for the matching variables). There were fewer patients exposed to the other drugs. In fact, the results of these and all other analyses appear to be driven by simvastatin since it was by far the most prescribed drug with the largest number of patients using it (362 691 of 482 543 statin users [75.2%]). No significant associations were noted when comparing the individual statins with nonstatin LLDs (eTable 6 in the Supplement).

The analysis comparing statins of varying lipophilicity with nonstatins showed the expected trend of increased OR associated with the most lipophilic statin (fully adjusted OR, 4.51; 95% CI, 2.98–6.84 for simvastatin use during the first 30 days after exposure) and a lower OR associated with the lesser lipophilic statins (eTable 7 in the Supplement).

A dose-response relationship was observed (using OR [95% CI]) for all statins combined when comparing medium with low doses (1.34; 1.00–1.79) and high vs low doses (1.59; 1.21–2.09) ($P < .001$ for 3-level linear trend in dose). No interaction by type of statin ($P = .77$) was noted (eTable 8 in the Supplement).

In the case-crossover study, of 119 072 patients with a first diagnosis of acute memory loss, 80 915 remained after screening exclusions; ultimately, only 68 028 remained after excluding patients with preexisting chronic conditions predictive of memory loss. In these patients, the prevalence of statin exposure immediately preceding the first diagnosis of acute memory loss was 18.9%. This prevalence was slightly lower during each of the earlier periods (18.5% during 31–60 days prior, 18.9% during 150–180 days prior, and 17.7% during 270–300 days prior; Fisher exact test, $P = .04$, $P > .99$, and $P < .001$, respectively). Using the immediately prior 30 days as the reference period, the respective OR (95% CI) values were 0.94 (0.91–0.98), 0.93 (0.89–0.97), and 0.82 (0.78–0.85) (eTable 9 in the Supplement).

In the validation study, of the 100 surveys mailed to the GPs, 86 were returned. Of these, 76 patients (88.4%) identified as having acute memory loss by Read codes were confirmed by the GPs to have this diagnosis. The free-text comments available for 5 of the 7 false cases indicated that the patient “thought she might have memory problems but was reassured”; “patient asked to be tested for memory, but then declined”; “patient said short-term memory causing some concerns, started writing lists”; the GP concluded “it didn’t sound like memory loss situation”; or the GP noted “awaiting community psychiatric nurse.” The primary results were essentially unchanged after excluding the 5 codes belonging to false cases. Among confirmed cases, in 29 of the 76 patients (38.2%), the GP confirmed resolution of the memory loss episode; in 37 of 86 patients (43.0%), memory loss was slowly progressing. Thus, acute reversible disease was even less common than the codes indicated.

Review of the free-text comments showed that the GP excluded memory loss in 16 of 1048 cases (1.5%) and that 444 patients (42.4%) had definite memory loss. The available information was too scant for the remaining cases: 34 (3.2%) indeterminate, 386 (36.8%) possible, and 168 (16.0%) unknown. In 7 cases, statins were mentioned by the GP or the patients as a possible cause of memory loss. Regarding onset, only 194 of 1048 patients (18.5%) had definite acute onset, 171 (16.3%) had slowly progressing onset, 667 (63.6%) had unknown onset, and 16 (1.5%) were not applicable because they did not have memory loss.

Discussion

This study revealed a nearly 4-fold increase in the risk of developing acute memory loss in the 30 days immediately following the first statin exposure when comparing statin users with nonusers of LLDs. The dose-response analysis also showed a statistically significant trend. However, the same association was seen when comparing patients receiving nonstatin LLDs with those not receiving any LLD, but the comparison of statin with nonstatin LLDs showed no significant difference between these drugs. There were very few positive cases in a rechallenge analysis (eTable 10 in the Supplement) despite our very large numbers. The case-crossover analysis showed a weak negative association, which would not be clinically meaningful and could simply be the result of delays in reporting the symptom. Thus, overall, these results superficially appeared positive, which is consistent with previously published studies.[1–11] However, the observation that all LLDs were associated with memory loss leads to the conclusion that either all LLDs cause acute memory loss regardless of drug class or that the association is the result of bias (eg, detection bias caused by a higher likelihood of ascertainment of memory loss in patients receiving preventive therapies because of increased physician contact) rather than a causal association. Given the heterogeneity of molecular structures among the LLDs, the latter may be more likely, but we cannot confirm this hypothesis using these data.

We found substantial differences in baseline characteristics between statin users and users of nonstatin LLDs and differences among users of the various statin drugs. Therefore, bias from confounding by indication is the most serious potential problem in this study, even though we attempted to control for indication variables and a large number of other

underlying conditions. The case-crossover analysis was conducted to address this problem because each patient serves as his or her own control.[34] A case-crossover analysis is subject to intraindividual confounding, for example, if what brings them to treatment now instead of earlier is linked in some way to memory loss. Confounding by time-varying indication should be less of a problem for statins than for drugs used for acute conditions. A further analysis that also was intended to help with the problem of confounding by indication was the comparison with users of nonstatin LLDs. Risk of detection bias also exists if patients receiving statins were seeing their physicians more frequently; thus, their memory loss would be more likely to be detected. However, this possibility would not have affected our control groups differentially, as observed.

For a diagnosis of acute memory loss, misclassification of outcome may be problematic. To assess this factor, we validated a random sample of medical records and reviewed GP free-text comments. Still, missed cases may be a problem because patients may not have reported acute memory loss to their physicians.[35] In addition, because of risk that a user could have memory loss after starting treatment with a statin but not report it until after the 30-day case period, we examined later time periods as well, and the OR monotonically decreased. Another limitation is that only one-third of the cases were confirmed to be reversible. Finally, potential confounding could exist for variables not included in the medical record. Strengths of this study include its large sample size, its general population, and the absence of recall bias since assessment of exposure was not dependent on patient recall.

Conclusions

Although we observed a large OR for acute memory loss in the 30-day period immediately following the start of statin use compared with no stain use as did previous studies, subsequent analyses showed an elevated OR for nonstatin LLDs as well. This finding suggests that either all LLDs cause acute memory loss or, perhaps more likely, that the association is the result of a detection bias.

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Table 1

Demographic Distribution of the Study Cohorts After All Screens and Exclusions

Characteristic	New Users of Statins (n = 482 543)	Matched Nonusers of Any LLD (n = 482 543)	*P* Value vs Nonusers	New Users of Nonstatin LLDs (n = 26 484)	*P* Value vs Other LLDs
Male sex, No. (%)	260 091 (53.9)	260 091 (53.9)	>.99	13 424 (50.7)	<.001
Age group at index date, No. (%), y[a]					
0–40	13 709 (2.8)	13 746 (2.8)	.99	2184 (8.2)	<.001
41–50	49 941 (10.3)	49 922 (10.3)		3290 (12.4)	
51–60	112 989 (23.4)	113 082 (23.4)		5848 (22.1)	
61–70	154 188 (32.0)	154 306 (32.0)		7979 (30.1)	
71–80	109 225 (22.6)	109 128 (22.6)		5629 (21.3)	
>80	42 491 (8.8)	42 359 (8.8)		1554 (5.9)	
Age at index date, mean (SD), y[a]	63.8 (12.1)	63.1 (13.8)	<.001	60.8 (13.9)	<.001
Enrollment duration category before index date, No. (%), y[a]					
<3	35 951 (7.5)	35 958 (7.5)	.99	4011 (15.1)	<.001
3 to <6	45 867 (9.5)	45 827 (9.5)		3991 (15.1)	
≥6	400 725 (83.0)	400 758 (83.1)		18 482 (69.8)	
Enrollment duration, mean (SD), y	19.8 (15.3)	19.8 (15.2)	.96	16.4 (15.1)	<.001

Abbreviation: LLD, lipid-lowering drug.

[a]Index date is date of first exposure to an LLD or assigned date for nonuser controls.

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Table 2

Distribution of Potential Confounders in the Study Cohorts

Characteristic	New Users of Statins (n = 482 543)	Matched Nonusers of Any LLD (n = 482 543)	*P* Value vs Nonusers	New Users of Nonstatin LLDs (n = 26 484)	*P* Value vs Other LLDs
Potential indication, No. (%)					
Diabetes mellitus	104 804 (21.7)	15 455 (3.2)	<.001	7357 (27.8)	<.001
Hypercholesterolemia	55 709 (11.5)	11 033 (2.3)	<.001	9375 (35.4)	<.001
Cardiovascular disease	258 522 (53.6)	147 104 (30.5)	<.001	15 518 (58.6)	<.001
Hypertension	241 362 (50.0)	107 316 (22.2)	<.001	13 065 (49.3)	.03
Stroke	45 535 (9.4)	8221 (1.7)	<.001	2147 (8.1)	<.001
Antihypertensive agents	320 470 (66.4)	52 867 (11.0)	<.001	18 928 (71.5)	<.001
Other disease confounders, No. (%)					
Cushing syndrome	134 (0.0)	61 (0.0)	<.001	11 (0.0)	.20
Alcohol abuse	9393 (1.9)	7725 (1.6)	<.001	585 (2.2)	.003
Drug abuse	3079 (0.6)	2622 (0.5)	<.001	242 (0.9)	<.001
Smoking or COPD	49 160 (10.2)	33 535 (6.9)	<.001	2685 (10.1)	.80
Depression/electroconvulsive therapy/anxiety disorder	93 538 (19.4)	71 703 (14.9)	<.001	6084 (23.0)	<.001
Menopausal symptoms	62 550 (13.0)	56 331 (11.7)	<.001	3291 (12.4)	.01
Retinopathy	2778 (0.6)	926 (0.2)	<.001	216 (0.8)	<.001
Myopathy	269 (0.1)	265 (0.1)	.86	27 (0.1)	.002
Vitamin B_{12} deficiency/vitamin B_{12} supplement	30 050 (6.2)	10 016 (2.1)	<.001	2699 (10.2)	<.001
Vitamin D deficiency	670 (0.1)	420 (0.1)	<.001	57 (0.2)	.001
Thiamine deficiency	4 (0.0)	8 (0.0)	.25	0	.64
Mercury exposure	10 (0.0)	12 (0.0)	.67	0	.46
HIV/CMV/herpesvirus	426 (0.1)	246 (0.1)	<.001	49 (0.2)	<.001
Liver disease	25 388 (5.3)	18 574 (3.8)	<.001	3093 (11.7)	<.001
Kidney disease	46 367 (9.6)	27 474 (5.7)	<.001	3822 (14.4)	<.001
Drug confounders, No. (%)					
Antidepressants	145 048 (30.1)	30 123 (6.2)	<.001	9683 (36.6)	<.001

Characteristic	New Users of Statins (n = 482 543)	Matched Nonusers of Any LLD (n = 482 543)	*P* Value vs Nonusers	New Users of Nonstatin LLDs (n = 26 484)	*P* Value vs Other LLDs
Antipsychotics/lithium	94 344 (19.6)	21 041 (4.4)	<.001	5937 (22.4)	<.001
Anxiolytics	76 753 (15.9)	16 758 (3.5)	<.001	5181 (19.6)	<.001
Stimulants	192 (0.0)	28 (0.0)	<.001	24 (0.1)	<.001
Antiepileptics	78 299 (16.2)	16 541 (3.4)	<.001	5463 (20.6)	<.001
Antihistamines	124 932 (25.9)	29 134 (6.0)	<.001	7981 (30.1)	<.001
Chemotherapy	8010 (1.7)	2332 (0.5)	<.001	571 (2.2)	<.001
Corticosteroids	263 914 (54.7)	65 795 (13.6)	<.001	15 186 (57.3)	<.001
Antiretrovirals or HAART	6255 (1.3)	1731 (0.4)	<.001	356 (1.3)	.50
Estrogens	76 327 (15.8)	19 138 (4.0)	<.001	4557 (17.2)	<.001
Barbiturates	152 (0.0)	37 (0.0)	<.001	15 (0.1)	.03
Indomethacin	19 913 (4.1)	4427 (0.9)	<.001	1007 (3.8)	.01

Abbreviations: CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LLD, lipid-lowering drug.

Table 3

Acute Memory Loss Comparing Statin Users With Nonusers of Any LLDs and With Users of Nonstatin LLDs

Time Period	Patients With Incident Acute Memory Loss After First Exposure, No. (%)			Statin vs Nonuse of LLD, Adjusted OR (95% CI)[a,b]		Statin vs Nonstatin LLD, Adjusted OR (95% CI)[b,c]	
	Statin Users (n = 482 543)	Matched Nonusers of Any LLDs (n = 482 543)	Unmatched Users of Nonstatin LLDs (n = 26 484)	Adjusted for Matching Variables[b]	Adjusted for Matching and All Other Confounding Variables[d]	Adjusted for Sex, Age Group, and Enrollment Duration[b]	Adjusted for All Confounding Variables[d]
Any time after first exposure	14 637 (3.03)	11 138 (2.31)	724 (2.73)	1.33 (1.30–1.37)	1.23 (1.18–1.28)	1.00 (0.93–1.08)	1.11 (1.03–1.20)
0–30 d After first exposure	376 (0.08)	114 (0.02)	18 (0.07)	3.30 (2.67–4.07)	4.40 (3.01–6.41)	1.01 (0.63–1.62)	1.03 (0.63–1.66)

Abbreviations: LLD, lipid-lowering drug; OR, odds ratio.

[a] Indicates conditional logistic regression used.

[b] Matching variables were sex, age group, and enrollment duration. The patient's general practitioner was a matching variable but not included in the model because stratifying on 533 practices would have destabilized the model.

[c] Indicates ordinary logistic regression used.

[d] Other confounding variables included indication variables (diabetes mellitus, hypercholesterolemia, cardiovascular disease, hypertension, stroke, and antihypertensive drugs) and other confounders (Cushing syndrome; alcohol abuse; drug abuse; smoking or chronic obstructive pulmonary disease; depression, electroconvulsive therapy, or anxiety disorders; menopausal symptoms; retinopathy; vitamin B_{12} deficiency or supplementation; thiamine deficiency; vitamin D deficiency; mercury exposure; human immunodeficiency virus, cytomegalovirus, or herpesvirus; liver disease; kidney disease; and use of antidepressants, antipsychotics, anxiolytics, stimulants, antiepileptics, antihistamines, chemotherapy, corticosteroids, antiretroviral therapy or highly active retroviral therapy, estrogens, barbiturates, or indomethacin) except for the matching variables.

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Table 4

Acute Memory Loss Comparing Nonstatin LLDs With Their Own Matched Nonusers of Any LLDs

	Patients With Incident Acute Memory Loss After First Exposure, No. (%)		Conditional Logistic Regression, Adjusted OR (95% CI)	
Study Period	Users of Nonstatin LLDs (n = 26 484)	Matched Nonusers of Any LLDs (n = 26484)	Adjusted for Matching Variables[a]	Adjusted for Matching and All Other Confounding Variables[b]
Any time after first exposure	724 (2.73)	488 (1.84)	1.51 (1.34–1.69)	0.96 (0.79–1.17)
0–30 d after first exposure	18 (0.07)	5 (0.02)	3.60 (1.34–9.70)	NA[c]

Abbreviations: LLDs, lipid-lowering drugs; NA, not applicable; OR, odds ratio.

[a]Matching variables were sex, age group, and enrollment duration. The patient's general practitioner was a matching variable but not included in the model because stratifying on 533 practices would have destabilized the model.

[b]Other confounding variables included indication variables (diabetes mellitus, hypercholesterolemia, cardiovascular disease, hypertension, stroke, and antihypertensive drugs) and other confounders (Cushing syndrome; alcohol abuse; drug abuse; smoking or chronic obstructive pulmonary disease; depression, electroconvulsive therapy, or anxiety disorders; menopausal symptoms; retinopathy; vitamin B_{12} deficiency or supplementation; thiamine deficiency; vitamin D deficiency; mercury exposure; human immunodeficiency virus, cytomegalovirus, or herpesvirus; liver disease; kidney disease; and use of antidepressants, antipsychotics, anxiolytics, stimulants, antiepileptics, antihistamines, chemotherapy, corticosteroids, antiretroviral therapy or highly active antiretroviral therapy, estrogens, barbiturates, or indomethacin) except for the matching variables.

[c]The fully adjusted model could not converge owing to small numbers.