Delirium after elective surgery among elderly patients taking statins

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See related commentary by Marcantonio, page 627

Abstract

Background: Postoperative delirium after elective surgery is frequent and potentially serious. We sought to determine whether the use of statin medications was associated with a higher risk of postoperative delirium than other medications that do not alter microvascular autoregulation.

Methods: We conducted a retrospective cohort analysis of 284 158 consecutive patients in Ontario aged 65 years and older who were admitted for elective surgery. We identified exposure to statins from outpatient pharmacy records before admission. We identified delirium by examining hospital records after surgery.

Results: About 7% (n = 19 501) of the patients were taking statins. Overall, 3195 patients experienced postoperative delirium; the rate was significantly higher among patients taking statins (14 per 1000) than among those not taking statins (11 per 1000) (odds ratio [OR] 1.30, 95% confidence interval [CI] 1.15–1.47, $p < 0.001$). The increased risk of postoperative delirium persisted after we adjusted for multiple demographic, medical and surgical factors (OR 1.28, 95% CI 1.12–1.46) and exceeded the increased risk of delirium associated with prolonging surgery by 30 minutes (OR 1.20, 95% CI 1.19–1.21). The relative risk associated with statin use was somewhat higher among patients who had noncardiac surgery than among those who had cardiac surgery (adjusted OR 1.33, 95% CI 1.16–1.53), and extended to more complicated cases of delirium. We did not observe an increased risk of delirium with 20 other cardiac or noncardiac medications.

Interpretation: The use of statins is associated with an increased risk of postoperative delirium among elderly patients undergoing elective surgery.

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Delirium is an acute change in mental status that is worrisome to patients and families, especially after elective surgery. This condition may contribute to delays in extubation, a prolonged need for intensive care, increased risk of nosocomial infections and about a 1-week rise in total length of stay in hospital for the average patient.[1,2] Delirium also disrupts many specific aspects of care, including the administration of medications, treatment of wounds, physiotherapy, nutrition, hygiene, discharge planning and dignity.[3] The management of delirium is awkward and may lead to a cascade of nonspecific testing and sedation, with an average net increase in hospital costs of $2500 per patient.[4] In some cases, the delirium never completely disappears, and the patient is left with a degree of permanent disability.[5]

The causes of postoperative delirium are not well understood. Hypoglycemia, hypoxemia and hypotension are all possible and correctable, but they rarely have an immediate resolution.[6] Medical imaging studies typically do not show specific changes; however, they may show markers of prior stroke or other lesions. One underlying factor may be cerebral ischemia secondary to inadequate perfusion. Altered cerebral perfusion may result in altered metabolism, an increased predisposition to drug toxicity or other factors during anesthesia and surgery.[7] Cerebral ischemia may also explain commonly observed risk factors for postoperative delirium, including advanced age, baseline cognitive dysfunction and the failure of drug antagonists, major tranquilizers or modern volatile anesthetics to prevent postoperative delirium.[8,9,10]

Statins have pleiotropic properties that alter the tone of smooth muscle in small blood vessels. Experiments on endothelial cells indicate that these changes are mediated by expression of endothelial nitric oxide synthase that is unrelated to cholesterol levels or vascular disease.[11] In turn, activity of endothelial nitric oxide synthase contributes to arteriolar vasodilation by relaxing the surrounding smooth-muscle cells, thereby shifting the distribution of blood flow in the microvasculature of the brain. This can compromise individual neurons even if aggregate blood flow is maintained.[12] These effects can be beneficial for reducing the size of stroke or other long-term neurologic disorders; however, altered cerebral blood flow autoregulation might predispose patients to delirium after anesthesia.[13–15]

We sought to determine whether the use of statins was associated with postoperative delirium among elderly patients undergoing elective surgery.

Methods

Patient selection

Using the Canadian Institutes for Health Information database,

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we identified consecutive patients aged 65 years and older who underwent elective surgery in all Ontario hospitals between Apr. 1, 1992, and Apr. 1, 2002. We selected this timeframe because data for these years were available for analysis. We did not include outpatients, those who had day surgery or patients younger than 65 years because the rate of delirium in such circumstances is generally low. To reduce confounding from pre-existing illness, we initially excluded patients with major vascular disease, as evidenced by long-term use of nitrates or β-blockers; however, we relaxed this restriction in a secondary analysis.[16]

We received institutional review board approval from the Sunnybrook Hospital Ethics Committee and used confidentiality safeguards of the Institute for Clinical Evaluative Sciences.

Hospital records

We gathered population-based data that counted each patient only once. We analyzed only the first admission for patients who had more than 1 elective surgical procedure during the study interval (analyses based on separate admissions yielded more extreme results and are not reported). In cases where patients were transferred to a different hospital, we counted outcomes according to the original hospital admission. All databases have been used extensively in past research.[17,18]

Statin prescriptions

For each patient, we searched prescription records from the Ontario Drug Benefit database for the year before admission, reasoning that statins would customarily be continued perioperatively. We classified people who received 2 or more prescriptions for a statin in the year before surgery (including at least 1 prescription in the 90 days before surgery) as receiving this medication on an ongoing basis. Otherwise, we classified the patient as not receiving a statin. This strategy assured that outcome ascertainment was blind to exposure status, free of reverse-causality bias and conservative in design.[19] The specific statins were atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, rosuvastatin and cerivastatin. A previous validation study indicated that the Ontario Drug Benefit database had an accuracy rate of 99% using pharmacy records as the reference standard.[20]

Risk factors for delirium

We gathered data on patient and surgical factors that could potentially contribute to delirium, since established risk factors are controversial. We derived the patients' age, sex and income quintile at the time of admission from the Ontario Registered Persons Database. We identified patients receiving drug therapy for dementia at baseline by assessing whether they were prescribed a cholinesterase inhibitor (e.g., donepezil) in the year before admission. We determined the use of other important baseline neuropsychiatric treatments with prescriptions for antipsychotics (e.g., risperidone), antidepressants (e.g., citalopram) and benzodiazepines (e.g., lorazepam) in the year before admission. We derived information on additional medical treatments from corresponding long-term medications, in accordance with prior research. We determined operative procedures based on the primary surgical procedures, and we classified them as either cardiac or noncardiac. We further distinguished noncardiac surgeries by anatomic site.

Duration of surgery

An innovative aspect of our study was to develop a method for determining the duration of surgery for each patient. This was necessary because prior research indicated that surgical duration was a risk factor for delirium and could vary substantially among patients undergoing the same primary procedure. Our method relied on anesthesiology billing fees linked to individual patients and reimbursed in 15-minute intervals. This method was analogous to estimating anesthesia and surgical times from Medicare claims (Part B data) in the United States. We examined the reliability and validity of the method and found high correspondence to chart review ($R^2 = 88\%$).[21]

Other medications

We examined other medications prescribed for cardiovascular disease to check whether findings with statins differed from those with other long-term drug therapies that are not known to have pleiotropic properties on the microvasculature. These included nonstatin lipid-lowering medications (e.g., fenofibrate), antihypertensive medications (e.g., hydrochlorothiazide), loop diuretics (e.g., furosemide) and miscellaneous cardiovascular agents (e.g., digoxin). Another set of analyses focused on medications that have indirect effects on the vascular system, including antiplatelet agents (e.g., clopidogrel), orally administered anticoagulants (e.g., coumadin) and other vascular agents (e.g., pentoxifylline). The final set of medications included common drugs that have no major effect on the cardiovascular system (e.g., omeprazole).

Outcome assessment

The primary outcome was the development of delirium during the patient's stay in hospital, based on the International Classification of Diseases codes 293.0–293.9. Surgical complications such as delirium are not always identified by clinicians, recorded in the patient's chart or entered into databases. Hence, the codes are specific (about 98%), but not sensitive (about 35%).[22] A separate chart review of the codes showed a positive predictive value of 100% when compared with doctors' and nurses' progress notes (95% confidence interval [CI] 96%–100%). To check the robustness of our results and to examine the more severe spectrum of postoperative delirium, we considered 7 complex combinations of outcomes: we examined data for patients who experienced postoperative delirium and who also received a computed tomography scan while in hospital, had a wound infection develop during their stay in hospital, experienced a myocardial infarction while in hospital, needed home nursing care after discharge, received ongoing sedatives after discharge, required hospital readmission or died in hospital after surgery.

Statistical analysis

We used the χ^2 test to assess the proportion of patients who experienced delirium, comparing those patients taking statins

with those who were not taking statins. We used logistic regression to adjust this comparison for patient characteristics, since the time of onset of delirium was not recorded (estimates computed with 95% CIs). We tested generalizability by repeating analyses in 3 more patient groups: those excluded because data on the duration of anesthesia were unavailable, those excluded because of pre-existing major vascular disease and those admitted for emergency surgery. We also tested for selection bias through a secondary analysis of patients who had received a statin in the past but not in the 90 days before surgery. In addition, we examined a cohort matched by propensity score to explore whether the main finding was due to hidden confounding.[23]

Results

A total of 541 827 elective surgeries were performed on 454 084 patients during the study interval. The patients were dispersed across 246 hospitals. We observed no major trends over the years. Overall, we excluded 100 832 patients because anesthesiology records were unavailable. We excluded a further 69 094 patients because they had major vascular disease. This left 284 158 patients for analysis. The typical patient took multiple medications on an outpatient basis; underwent an abdominal, musculoskeletal or urogenital procedure; and had a mean duration of surgery of about 115 minutes. The most common outpatient medications (received by about

Table 1: Characteristics of 284 158 patients 65 years and older who underwent elective surgery between Apr. 1, 1992, and Apr. 1, 2002

Characteristic	Group; no. (%) of patients*		Characteristic	Group; no. (%) of patients*	
	Taking statins *n = 19 501*	Not taking statins *n = 264 657*		Taking statins *n = 19 501*	Not taking statins *n = 264 657*
Age, yr, mean (SD)	71.9 (4.7)	73.9 (6.1)	**Prescriptions** (continued)		
Sex			Vascular (continued)		
Female	10 097 (51. 9)	132 621 (50.1)	Oral antiplatelet agent	363 (1.9)	1 112 (0.4)
Male	9 404 (48.2)	132 036 (49.9)	Pentoxifylline	153 (0.8)	1 073 (0.4)
Social status			Oral hypoglycemic agent	2 323 (11.9)	16 165 (6.1)
Lowest–middle	11 933 (61.2)	161 749 (61.1)	Injection insulin	665 (3.4)	5 820 (2.2)
Next highest–highest	7 117 (36.5)	95 217 (36.0)	Miscellaneous		
Not available	451 (2.3)	7 691 (2.9)	Bronchodilator	1 795 (9.2)	22 263 (8.4)
Admissions in prior 3 yr			Allopurinol	795 (4.1)	6 618 (2.5)
0	13 330 (68.4)	170 283 (64.3)	Levothyroxine	2 540 (13.0)	22 490 (8.5)
≥ 1	6 171 (31.6)	94 374 (35.7)	Oral glucocorticoid	469 (2.4)	8 011 (3.0)
Prescriptions			Gastric acid suppressant	4 083 (20.9)	46 432 (17.5)
No. in prior yr, mean (SD)	7.7 (3.7)	5.6 (3.8)	Antiosteoporosis	2 254 (11.6)	20 107 (7.6)
Neuropsychiatric			Glaucoma eye drops	1 184 (6.1)	15 559 (5.9)
Cholinesterase inhibitor	29 (0.1)	170 (0.1)	**Type of surgery**		
Antipsychotic	211 (1.1)	3 889 (1.5)	Cardiac	1 297 (6.7)	7 975 (3.0)
Antidepressant	1 699 (8.7)	15 940 (6.0)	Thoracic	447 (2.3)	6 514 (2.5)
Benzodiazepine	3 249 (16.7)	39 159 (14.8)	Neurosurgical	444 (2.3)	5 069 (1.9)
Cardiac			Vascular	2 293 (11.8)	15 011 (5.7)
ACE inhibitor	5 549 (28.5)	36 188 (13.7)	Musculoskeletal	4 635 (23.8)	60 770 (23.0)
ARB blocker	551 (2.8)	1 618 (0.6)	Abdominal	3 898 (20.0)	64 387 (24.3)
Thiazide diuretic	1 963 (10.1)	15 501 (5.9)	Retroperitoneal	291 (1.5)	3 174 (1.2)
Calcium-channel blocker	5 641 (28.9)	35 760 (13.5)	Lower urogenital	3 859 (19.8)	60 261 (22.8)
Furosemide	1 283 (6.6)	15 494 (5.9)	Breast and skin	1 045 (5.4)	15 013 (5.7)
Digoxin	1 085 (5.6)	15 398 (5.8)	External head and neck	594 (3.0)	9 122 (3.4)
Spironolactone	231 (1.2)	2 956 (1.1)	Ophthalmologic	632 (3.2)	16 803 (6.3)
Vascular			Unclassified	66 (0.3)	558 (0.2)
Nonstatin lipid-lowering drug	387 (2.0)	3 248 (1.2)	**Surgery duration, h, mean (SD)**	2.2 (1.4)	1.9 (1.3)
Oral anticoagulant	777 (4.0)	7 414 (2.8)			

Note: ACE = angiotensin-converting enzyme, ARB = angiotensin receptor II, SD = standard deviation.
*Unless stated otherwise.

15% of patients in each case) were benzodiazepines, angiotensin-converting-enzyme inhibitors, calcium-channel blockers and gastric acid suppressants.

About 7% (n = 19 501) of the patients were taking statins before surgery, compared with about 93% (n = 264 657) who were not taking statins before surgery. There was about a 2-year difference in mean age between the 2 groups, with more younger patients than older patients using statins. Otherwise, we found no major differences between the 2 groups in demographic characteristics, use of neuropsychiatric or common noncardiovascular medications, or the number of noncardiovascular surgeries performed (Table 1). As expected, use of cardiac medications, cardiac surgeries and peripheral vascular surgeries were more common among patients who used statins than among patients who did not use statins.

Overall, postoperative delirium was diagnosed in 3195 patients (11 per 1000). The risk of delirium was about 30% higher (95% CI 15%–47%) among patients taking statins before surgery (14 per 1000) than among those not taking statins before surgery (11 per 1000, $p < 0.001$). After adjusting for demographic characteristics, prior admissions and prescriptions and classes of neuropsychiatric medications, we observed a continued increase (OR 1.48, 95% CI 1.38–1.68) in risk of delirium among patients prescribed statins than among those not prescribed statins. We observed a similar increase in risk after adjusting for each cardiovascular and noncardiovascular medication (Figure 1). The final multivariable model, which adjusted for all the preceding predictors along with the type and duration of surgery, showed a 28% increase in the risk of delirium associated with the use of statins (95% CI 12%–46%, $p < 0.001$).

The increased risk of delirium associated with the use of statins was evident across a variety of clinical settings. In each analysis, the results showed a detrimental association, although the confidence intervals were broad in many subgroups (Figure 2). Increases in risk were highly consistent among patients who did not take selected neuropsychiatric medications (that were associated with delirium) or selected common medications (that were not associated with delirium). The relative risk with statins was somewhat higher among patients who had noncardiac surgery than among patients who had cardiac surgery, although the baseline risk among those who had cardiac surgery was twice as high as that among patients undergoing noncardiac surgery. The absolute risk of delirium associated with the use of statins was highest among patients older than 70 years and among patients whose surgeries lasted longer than 3 hours (Appendix 1, available online at www.cmaj.ca/cgi/content/full/179/7/645/DC2).

The overall resolution of the multivariable model was reasonable (c-index 0.78, $p < 0.001$). The strongest single predictor of postoperative delirium was the duration of surgery, which yielded about a 44% increase in risk for delirium for each hour of surgery (95% CI 41%–46%). The other statistically significant predictors were 2 demographic characteristics (age and sex), use of the 4 neuropsychiatric medications and type of surgery (Table 2). In contrast, use of angiotensin-converting-enzyme inhibitors, calcium-channel blockers or gastric acid suppressors was not associated with delirium. None of the other long-term cardiovascular and noncardiovascular medications were associated with a statistically significant increase in risk of delirium (Table 3).

After comparing patients using different statins and receiving different doses, we found no major exceptions. Atorvastatin and simvastatin (2 popular statins with distinct metabolic pathways and half-lives) were each associated with a significantly increased risk of delirium. The odds ratios were 1.68 (95% CI 1.34–2.09) for atorvastatin and 1.46 (95% CI 1.15–1.84) for simvastatin. Pravastatin (the main nonlipophilic statin in our study) was associated with a marginally lower risk of delirium (OR 1.26, 95% CI 0.96–1.64). Pa-

Comparison	Odds ratio (95% CI)	p value
Use of statins v. control	1.30 (1.15–1.47)	< 0.001
Adjusted for age, sex and social status	1.57 (1.38–1.77)	< 0.001
Adjusted for prior admissions and use of medications	1.24 (1.10–1.41)	< 0.001
Adjusted for use of neuropsychiatric medication	1.26 (1.11–1.42)	< 0.001
Combined	1.48 (1.31–1.68)	< 0.001
Adjusted for use of cardiac medication	1.26 (1.11–1.43)	< 0.001
Adjusted for use of vascular medication	1.28 (1.13–1.45)	< 0.001
Adjusted for use of miscellaneous medications	1.30 (1.15–1.48)	< 0.001
Combined	1.47 (1.30–1.68)	< 0.001
Adjusted for type of surgery	1.12 (0.99–1.27)	0.07
Adjusted for duration of surgery	1.13 (1.02–1.31)	0.02
Adjusted for all of the above*	1.28 (1.12–1.46)	< 0.001

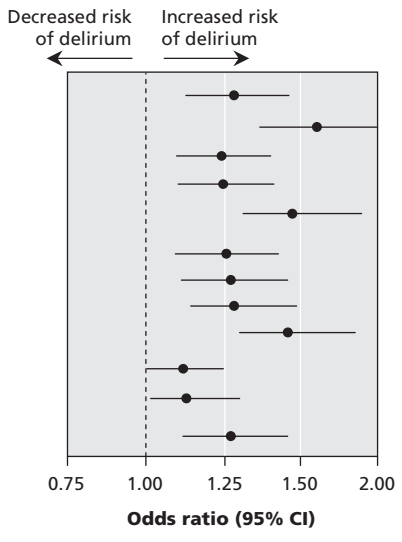

Figure 1: Risk of postoperative delirium with use of statins among elderly patients. *Derived from the full multivariable model after adjustment for age, sex, social status, prior admissions, prior use of medications, each neuropsychiatric, cardiac, vascular and miscellaneous medication, and duration and type of surgery. Note: CI = confidence interval.

tients prescribed the lowest dose of each statin (20 mg) showed a marginally smaller increase in risk of delirium (OR 1.15, 95% CI 0.94–1.40) than patients prescribed higher doses (OR 1.38, 95% CI 1.17–1.63).

We analyzed patients excluded because of pre-existing major vascular disease (n = 69 094) and found about the same increase in delirium risk among those taking statins compared with those not taking statins (OR 1.26, 95% CI 1.10–1.45). We analyzed patients admitted for emergency surgery (n = 222 615) and found an increase in the risk of delirium among those taking statins compared with those not taking statins (OR 1.24, 95% CI 1.11–1.39). We analyzed patients excluded because the duration of anesthesiology was unavailable (n = 100 832), and also found an increase in delirium risk associated with use of statins (OR 1.18, 95% CI 0.92–1.53). In contrast, when we analyzed controls who had received a statin in the past but not in the 90 days before surgery (n = 43 152), we found no increase in the risk of delirium associated with use of statins (OR 0.85, 95% CI 0.76–0.96). Finally, in the cohort matched by propensity scores (n = 25 244), we found about the same increase in delirium risk associated with the use of statins (OR 1.30, 95% CI 0.96–1.70).

We explored 7 combinations of severity to test whether delirium contributed to other postoperative complications and whether delirium associated with the use of statins was any less severe than delirium that was not associated with the use of statins. For example, patients who experienced delirium were 6 times more likely than those who did not experience

Subgroup	No. of patients with delirium / Total no. of patients	Adjusted* odds ratio (95% CI)
All patients	3 195 / 284 158	1.28 (1.12–1.46)
Type of medication†‡		
Cholinesterase inhibitor	3 181 / 283 959	1.28 (1.12–1.46)
Antipsychotic	3 107 / 280 058	1.26 (1.11–1.44)
Antidepressant	2 796 / 266 519	1.24 (1.08–1.44)
Benzodiazepine	2 502 / 241 750	1.20 (1.04–1.40)
ACE inhibitor	2 654 / 242 421	1.27 (1.09–1.48)
Angiotensin receptor II blocker	3 164 / 281 989	1.26 (1.10–1.44)
Thiazide diuretic	3 001 / 266 694	1.31 (1.14–1.50)
Calcium-channel blocker	2 689 / 242 757	1.27 (1.09–1.48)
Furosemide	2 914 / 267 381	1.25 (1.09–1.43)
Digoxin	2 950 / 267 675	1.26 (1.10–1.44)
Spironolactone	3 150 / 280 971	1.26 (1.10–1.44)
Nonstatin lipid-lowering drug	3 163 / 280 523	1.28 (1.12–1.46)
Oral anticoagulant	3 058 / 275 967	1.27 (1.11–1.45)
Oral antiplatelet agent	3 170 / 282 683	1.30 (1.14–1.48)
Pentoxifylline	3 165 / 282 932	1.26 (1.10–1.44)
Oral hypoglycemic agent	2 977 / 265 670	1.30 (1.13–1.49)
Injection insulin	3 129 / 277 673	1.30 (1.14–1.48)
Bronchodilator	2 865 / 260 100	1.20 (1.04–1.38)
Allopurinol	3 107 / 276 745	1.28 (1.12–1.46)
Levothyroxine	2 915 / 259 128	1.24 (1.08–1.43)
Oral glucocorticoid	3 086 / 275 678	1.28 (1.12–1.46)
Gastric acid suppressant	2 528 / 233 643	1.24 (1.07–1.44)
Antiosteoporosis	3 008 / 261 797	1.31 (1.14–1.49)
Glaucoma eye drops	3 007 / 267 415	1.25 (1.09–1.43)
Type of surgery		
Cardiac	207 / 9 272	1.26 (0.86–1.87)
All noncardiac	2 988 / 274 886	1.33 (1.16–1.53)
High-risk noncardiac§	1 618 / 95 183	1.23 (1.03–1.47)
Medium-risk noncardiac¶	854 / 72 374	1.28 (0.98–1.69)
Low-risk noncardiac**	516 / 107 329	1.47 (1.03–2.12)

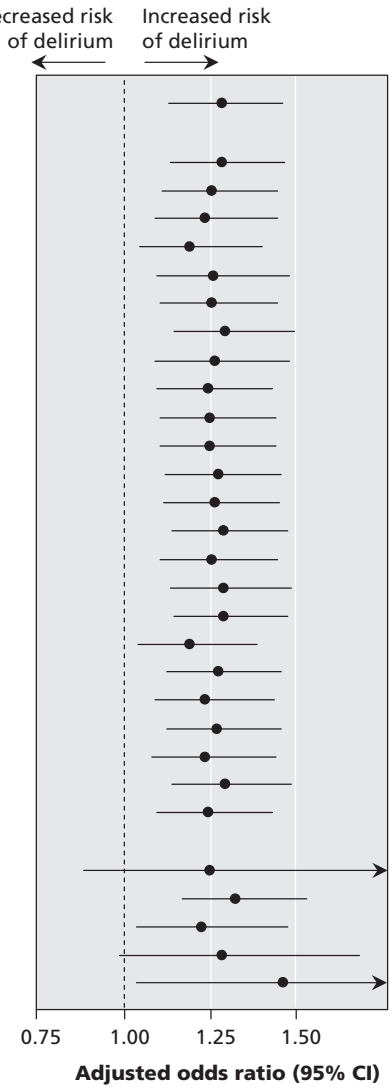

Figure 2: Relative risk of postoperative delirium associated with the use of statins among elderly patients, by type of medication and surgery. *Adjusted for age, sex, duration of surgery and individual medications. †Excludes patients taking corresponding medication. ‡Further adjusted for type of surgery. §Includes thoracic, neurosurgical, vascular and musculoskeletal procedures. ¶Includes abdominal, retroperitoneal and unclassified procedures. **Includes lower urogenital, breast and skin, external head and neck, and ophthalmological procedures. Note: CI = confidence interval.

delirium to receive a computed tomography scan while in hospital (15.7% v. 2.4%, $p < 0.001$). Patients with delirium were 3 times more likely than patients who did not experience delirium to have a wound infection develop while in hospital (17.0% v. 5.5%, $p < 0.001$) and 4 times more likely to experience a myocardial infarction while in hospital (3.1% v. 0.7%, $p < 0.001$). Finally, patients who experienced delirium were 3 times more likely than those who did not experience delirium to die in hospital (3.5% v. 1.0%, $p < 0.001$). The use of statins was associated with an increased risk of all these severe forms of delirium except the combination of delirium followed by death (Table 4). Overall, we observed about a 10-day absolute increase in the length of stay in hospital for all patients who experienced delirium (16.1 days among patients who were taking statins v. 6.3 days among those who were not taking statins, $p < 0.001$). We also observed about a 10% absolute increase in ongoing use of sedatives after discharge (33.9% among patients taking statins v. 23.3% among patients not taking statins, $p < 0.001$).

Interpretation

We found that 1 in 14 elderly patients in our study cohort were taking statins before undergoing elective surgery and about 1 in 90 experienced delirium after elective surgery. Our results suggested that this association was more than a coincidence, particularly among patients who received higher doses of statins and had longer duration noncardiac surgeries. The association between statins and risk of delirium was distinct and was not observed with other lipid-lowering medications, cardiovascular medications or common drugs that reflect underlying chronic diseases but have no major effects on the cardiovascular system. The correlation prevailed among patients in high-risk subgroups and extended to some more complicated combinations of delirium. The magnitude of the association was substantial, but not as substantial as that between risk of delirium and advanced age, baseline neuropsychiatric drug treatment or prolonged surgery.

The most important limitation of our research was that hidden confounding may have biased our results. For example, we were not able to measure intraoperative hypotension or hypoxemia. However, these factors have not been shown to predict postoperative delirium.[24] We were able to measure patient age and duration of surgery, the 2 most established predictors of delirium in this setting. Our multivariable models also adjusted for many other features that could remain

Table 2: Factors associated with increased risk of postoperative delirium among elderly patients undergoing elective surgery

Factor	Odds ratio* (95% CI)	*p* value
Age, per yr increase	1.09 (1.09–1.10)	< 0.001
Sex, male (v. female)	1.71 (1.59–1.86)	< 0.001
Neuropsychiatric drug		
Cholinesterase inhibitor	3.99 (2.26–7.05)	< 0.001
Antipsychotic	1.57 (1.26–1.95)	< 0.001
Antidepressant	2.01 (1.75–2.25)	< 0.001
Benzodiazepine	1.40 (1.28–1.53)	< 0.001
Type of surgery†		
Cardiac	1.12 (0.95–1.31)	0.18
Thoracic	1.54 (1.29–1.84)	< 0.001
Neurosurgical	1.22 (1.00–1.49)	0.049
Vascular	1.20 (1.06–1.36)	0.004
Musculoskeletal	1.19 (1.08–1.31)	< 0.001
Lower urologic and gynecologic	0.55 (0.48–0.62)	< 0.001
Breast and skin	0.46 (0.36–0.59)	< 0.001
External head and neck	0.39 (0.30–0.50)	< 0.001
Ophthalmologic	0.08 (0.05–0.13)	< 0.001
Duration of surgery, per 30-min increase	1.20 (1.19–1.21)	< 0.001

Note: CI = confidence interval.
*From multivariable logistic regression.
†Relative to abdominal, retroperitoneal and unclassified surgery.

Table 3: Risk of postoperative delirium associated with other medications*

Medication	Odds ratio† (95% CI)	*p* value
Cardiac		
Angiotensin-converting-enzyme inhibitor	0.96 (0.87–1.06)	0.43
Angiotensin II receptor blocker	1.05 (0.73–1.52)	0.77
Thiazide diuretic	0.92 (0.79–1.07)	0.29
Calcium-channel blocker	0.94 (0.85–1.04)	0.21
Furosemide	1.03 (0.89–1.18)	0.71
Digoxin	0.96 (0.83–1.11)	0.60
Spironolactone	1.09 (0.80–1.47)	0.59
Vascular		
Nonstatin lipid-lowering drug	0.80 (0.56–1.14)	0.21
Oral anticoagulant	1.14 (0.95–1.38)	0.16
Oral antiplatelet agent	1.01 (0.68–1.52)	0.95
Pentoxifylline	1.16 (0.80–1.69)	0.44
Oral hypoglycemic agent	0.96 (0.83–1.11)	0.57
Insulin	0.93 (0.73–1.20)	0.59
Miscellaneous		
Bronchodilator	1.06 (0.94–1.20)	0.34
Allopurinol	0.83 (0.67–1.03)	0.10
Levothyroxine	1.00 (0.88–1.14)	0.99
Oral glucocorticoid	0.94 (0.77–1.15)	0.56
Gastric acid suppressant	0.99 (0.90–1.08)	0.80
Antiosteoporosis	1.01 (0.86–1.18)	0.89
Glaucoma eye drops	0.94 (0.80–1.09)	0.39

Note: CI = confidence interval.
*Each analysis compares those receiving agent to those not receiving agent.
†Adjusted for age, sex, neuropsychiatric medication, surgery type and surgery duration.

imbalanced in small trials. Our analysis of selection bias suggested that patients taking statins were healthier than patients who were not taking statins. In addition, prior research indicated that unmeasured comorbidities tended to be biased in a manner favouring patients taking statins.[25,26] Hidden confounding would not explain why our results showed the association between postoperative delirium and the use of statins to be distinct, or why we found no association between delirium and the use of other medications.

Another important limitation of our analysis was outcome definition. That is, the database analyses provided a specific, but insensitive, indicator for postoperative delirium. As such, our study detected extreme cases and underestimated the overall incidence of postoperative delirium, particularly in our analyses that focused on severe combinations of delirium. Consequently, all estimates were biased conservatively, and the absolute increase in risk associated with statin use was understated (assuming no systematic coding bias). If the true incidence of delirium were 10%,[27] for example, an observed odds ratio of 1.28 might amount to a number needed to harm of about 35. The true incidence may be impossible to determine with certainty given the vagaries of distinguishing delirium from other forms of postoperative cognitive dysfunction.[28]

Shifts in the distribution of capillary blood flow leading to neuronal ischemia scattered throughout the brain could explain postoperative delirium. However, results of our goodness-of-fit test suggested that other mechanisms also contributed. These mechanisms merit research because delirium could be associated with many of them, including altered isoprenoid metabolism in neurons, inhibition of membrane receptors, toxicity at synaptic clefts, blood–brain barrier dysfunction or drug interactions if such statin pleiotropic effects are tolerated under normal circumstances but not during anesthesia.[29,30] Our findings are not easily explained as drug withdrawal, because statin cessation generally led to a decreased effect (not rebound harm) and because the observed risk was no lower for the statin with the longest half-life (atorvastatin).[31] The endothelial nitric oxide synthase mechanism emphasized the role of microvascular blood flow autoregulation for preserving neuronal function.[32]

Table 4: Association of severe forms of postoperative delirium with use of statins among elderly patients undergoing elective surgery*

Variable	Adjusted odds ratio (95% CI)†	*p* value
Any delirium	1.28 (1.12–1.46)	< 0.001
Delirium combined with computed tomography scan	1.22 (0.89–1.68)	0.21
Delirium combined with wound infection	1.33 (0.99–1.79)	0.06
Delirium combined with myocardial infarction	3.24 (1.97–5.33)	< 0.001
Delirium combined with subsequent home care nursing‡	1.59 (1.27–1.99)	< 0.001
Delirium combined with ongoing sedative prescription§	1.38 (1.12–1.71)	0.011
Delirium combined with hospital readmission¶	1.24 (0.98–1.55)	0.09
Delirium combined with death	0.39 (0.12–1.22)	0.10

Note: CI = confidence interval.
*Each analysis compares patients who took statins with those who did not take statins.
†Adjusted for age, neuropsychiatric drug, duration of surgery and type of surgery.
‡From hospital database, as ordered on day of discharge.
§From outpatient pharmacy database within 90 days after discharge.
¶From hospital emergency department database within 1 yr after discharge.

Our results are not readily attributable to unmeasured underlying severity of vascular disease for several reasons. First, we observed no adverse association with 20 other medications, each a marker of vascular disease. Second, the analyses adjusted for 30 measured factors and yielded stable results. Hence, a postulated underlying disease would need to be unrelated to all these factors to extinguish the finding. Third, the adverse association was no more or less substantial in our post-hoc analysis of patients who had major vascular disease. Fourth, no risk was observed in earlier studies correlating statin use with postoperative myocardial infarction. Hence, the adverse association between the use of statins and postoperative delirium is distinct. Conducting a randomized trial would be a different way to check for bias due to severity of disease. However, randomized trials are generally an unreliable method for studying adverse drug effects, whereas nonrandomized studies are a powerful method for identifying potential toxicity.[33]

We caution that our findings do not imply that statins are harmful under normal circumstances. On the contrary, trials involving outpatients show many benefits from long-term statin therapy in cardiovascular care. Furthermore, our primary analysis was restricted to patients who did not have major vascular disease; therefore, we did not assess their potential benefits in preventing myocardial infarction.[34]

The implication of our study is that statins, unlike other cardiac medications, might contribute to delirium after elective surgery and can be discontinued temporarily before surgery. Studies suggest that expression of endothelial nitric oxide synthase returns to normal within 2–4 days after interrupting statin therapy.[35] If needed, statin therapy can be reinstated on the first postoperative day, which would re-establish activity of endothelial nitric oxide synthase within 1–2 days (the interval most common for a postoperative myocardial infarction).[36] Such a strategy would have the additional advantage of reducing the risk of inadvertent drug interactions during the hospital stay and reducing the risk of postoperative hepatitis.

Further research could be designed as either a discontinuation trial or a prophylaxis trial, depending on the feasibility of recruitment. We applaud recent calls for more clinical trials in perioperative medicine to directly determine whether medications that are beneficial in the outpatient setting are equally safe in the perioperative setting.[37] The results of our study should inform the design of future studies, bolster recruitment in trials that are currently underway and underscore the need to carefully assess both cardiac and adverse neurologic out-

comes after surgery. Until more data are available, a recommendation to temporarily interrupt the use of statins before surgery may be a reasonable compromise.

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