Delirium after elective surgery among elderly patients taking statins

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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] 1.19–1.21). 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. In some cases, the delirium never completely disappears, and the patient is left with a degree of permanent disability. 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. 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. 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.

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. 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. 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.

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 time-frame 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.9 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 $\chi^2$ 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.21

### 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 anesthesia 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 | Taking statins | Not taking statins |
| **Age, yr, mean (SD)** | 71.9 (4.7) | 73.9 (6.1) |
| **Sex** | | |
| Female | 10 097 (51.9) | 132 621 (50.1) |
| Male | 9 404 (48.2) | 132 036 (49.9) |
| **Social status** | | |
| Lowest-middle | 11 933 (61.2) | 161 749 (61.1) |
| Next highest–highest | 7 117 (36.5) | 95 217 (36.0) |
| Not available | 451 (2.3) | 7 691 (2.9) |
| **Admissions in prior 3 yr** | | |
| 0 | 13 330 (68.4) | 170 283 (64.3) |
| ≥ 1 | 6 171 (31.6) | 94 374 (35.7) |
| **Prescriptions** | | |
| No. in prior yr, mean (SD) | 7.7 (3.7) | 5.6 (3.8) |
| Neuropsychiatric | | |
| Cholinesterase inhibitor | 29 (0.1) | 170 (0.1) |
| Antipsychotic | 211 (1.1) | 3 889 (1.5) |
| Antidepressant | 1 699 (8.7) | 15 940 (6.0) |
| Benzodiazepine | 3 249 (16.7) | 39 159 (14.8) |
| Cardiac | | |
| ACE inhibitor | 5 549 (28.5) | 36 188 (13.7) |
| ARB blocker | 551 (2.8) | 1 618 (0.6) |
| Thiazide diuretic | 1 963 (10.1) | 15 501 (5.9) |
| Calcium-channel blocker | 5 641 (28.9) | 35 760 (13.5) |
| Furosemide | 1 283 (6.6) | 15 494 (5.9) |
| Digoxin | 1 085 (5.6) | 15 398 (5.8) |
| Spironolactone | 231 (1.2) | 2 956 (1.1) |
| Vascular | | |
| Nonstatin lipid-lowering drug | 387 (2.0) | 3 248 (1.2) |
| Oral anticoagulant | 777 (4.0) | 7 414 (2.8) |
| **Prescriptions** | | |
| Oral anticoagulant | | |
| Oral anticoagulant | | |

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

*Unless stated otherwise.
15% of patients in each case) were benzodiazepines, angio-
tensin-converting-enzyme inhibitors, calcium-channel block-
ers 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 demo-
graphic characteristics, use of neuropsychiatric or common noncardiovascular medications, or the number of non-
cardiovascular 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 pa-
tients \( (11 \text{ per 1000}) \). The risk of delirium was about 30% higher \( (95\% \text{ CI } 15\%–47\%) \) among patients taking statins be-
fore surgery \( (14 \text{ per 1000}) \) than among those not taking statins before surgery \( (11 \text{ per 1000}, p < 0.001) \). After adjusting for demographic characteristics, prior admissions and pre-
scriptions and classes of neuropsychiatric medications, we observed a continued increase \( (OR 1.48, 95\% \text{ CI } 1.38–1.68) \) in risk of delirium among patients prescribed statins than among those not prescribed statins. We observed a similar in-
crease in risk after adjusting for each cardiovascular and non-
cardiovascular 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 \( (95\% \text{ CI } 12\%–46\%, p < 0.001) \).

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 sub-
groups (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 delir-
ium). The relative risk with statins was somewhat higher among patients who had noncardiac surgery than among pa-
tients 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 abso-
late 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, avail-
able online at www.cmaj.ca/cgi/content/full/179/7/645/DC2).

The overall resolution of the multivariable model was rea-
sonable \( (c\text{-index } 0.78, p < 0.001) \). The strongest single predic-
tor of postoperative delirium was the duration of surgery, which yielded about a 44% increase in risk for delirium for each hour of surgery \( (95\% \text{ CI } 41\%–46\%) \). The other statisti-
cally significant predictors were 2 demographic characteristics \( (\text{age and sex}) \), 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.

Non of the other long-term cardiovascular and noncardio-
vascular medications were associated with a statistically sig-
nificant increase in risk of delirium (Table 3).

After comparing patients using different statins and receiv-
ing different doses, we found no major exceptions. Atorva-
statin and simvastatin \( (2 \text{ popular statins with distinct meta-
} \text{bolic pathways and half-lives}) \) were each associated with a significa-
tly increased risk of delirium. The odds ratios were \( 1.68 \) \( (95\% \text{ CI } 1.34–2.09) \) for atorvastatin and \( 1.46 \) \( (95\% \text{ CI } 1.15–1.84) \) for simvastatin. Pravastatin \( (\text{the main non-
lipophilic statin in our study}) \) was associated with a margin-
ally lower risk of delirium \( (OR 1.26, 95\% \text{ CI } 0.96–1.64) \). Pa-

### Table 1: Odds ratio and 95% CI for risk of delirium associated with use of statins

| Comparison                        | Odds ratio (95% CI) | p value |
|----------------------------------|---------------------|---------|
| **Use of statins v. control**    |                     |         |
| Adjusted for age, sex and social status | 1.30 (1.15–1.47)    | < 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**                     |                     |         |
| 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**                     |                     |         |
| 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 1.24, 95% CI 1.11–1.39). We analyzed patients who were prescribed the lowest dose of each statin (20 mg) and found an increase in the risk of delirium 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 the 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...
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.25 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. 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 setting of elderly patients with preexisting cardiovascular disease.

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 posthoc 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.

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.

The implication of our study is that statins, unlike other cardiovascular 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. 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). 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. 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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Contributors: All of the authors participated in the study design, interpretation of results, the drafting of the manuscript and approval of the final version for publication. Donald Redelmeier had full access to all the data, final authority for the decision to submit for publication and ongoing responsibility for accuracy.

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REFERENCES

1. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004;291:1753-62.
2. Thomason JW, Shintani A, Peterson JF, et al. Intensive care unit delirium is an independent predictor of longer hospital stay: a prospective analysis of 261 non-ventilated patients. Crit Care 2005;9:R375-81.
3. Cole MG. Delirium in elderly patients. Am J Geriatr Psychiatry 2004;12:7-21.
4. Roche V. Etiology and management of delirium. Am J Med Sci 2003;325:20-30.
5. Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. Lancet 1998;351:857-61.
6. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons: predictive model and interrelationship with baseline vulnerability. JAMA 1996;275:852-7.
7. Yokota H, Ogawa S, Kurokawa A, et al. Regional cerebral blood flow in delirium patients. Psychiatry Clin Neurosci 2003;57:337-9.
8. Kalisvaart KJ, de Jonghe JF, Bogards MJ. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo controlled study. J Am Geriatr Soc 2005;53:1658-66.
9. Liptzin B, Lakl A, Garb JL, et al. Donepezil in the prevention and treatment of post-surgical delirium. Am J Geriatr Psychiatry 2005;13:1100-6.
10. Leung JM, Sands LP, Vaurio LE, et al. Nitrous oxide does not change the incidence of postoperative delirium or cognitive decline in elderly surgical patients. Br J Anaesth 2006;96:754-60.
11. McGown CC, Brookes ZL. Beneficial effects of statins on the microcirculation during sepsis: the role of nitric oxide. Br J Anaesth 2007;98:163-75.
12. Broek DG, Alochin DN, Riva CE. Investigating the role of nitric oxide in regulating blood flow and oxygen delivery from in vivo electrochemical measurements in eye and brain. Adv Exp Med Biol 2003;530:359-70.
13. Chen J, Zacharek A, Zhang C, et al. Endothelial nitric oxide synthase regulates brain-derived neurotrophic factor expression and neurogenesis after stroke in mice. J Neurosci 2005;25:2366-75.
14. Fong TG, Bogdanski ST Jr, Dalfary A. Cerebral perfusion changes in older delirious patients using 99mTc HMPOA SPECT. J Gerontol A Biol Sci Med Sci 2006;61:1294-9.
15. Redelmeier D. New thinking on postoperative delirium. CMAJ 2007;177:424.
16. Kapoor AS, Kanji H, Buckingham J, et al. Strength of evidence for perioperative use of statins to reduce cardiovascular risk: systematic review of controlled studies. BMJ 2006;333:1149.
17. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med 2004;351:543-51.
18. Tu JV, Penfold SP, McColgan et al. eds. Access to health services in Ontario: ICES Atlas. Toronto: Institute for Clinical Evaluative Sciences; 2005.
19. Horwitz RI, McFarlane JM, Brennan TA, et al. The role of susceptibility bias in epidemiologic research. Arch Intern Med 1985;145:909-12.
20. Levy AR, O’Brien BJ, Sellors C, et al. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. Can J Clin Pharmacol 2003;10:67-71.
21. Redelmeier DA, Thiruchelvam D, Dananman N. Introducing a methodology for estimating duration of surgery in health services research. J Clin Epidemiol 2008;61:882-9.
22. Romano PS, Chan BK, Schembri ME, et al. Can administrative data be used to compare postoperative complication rates across hospitals? Med Care 2002;40:856-67.
23. Dananman N. The epidemiology of surgical site infections [master’s thesis]. Toronto (ON): University of Toronto; 2008.
24. Marcantonio ER, Goldman L, Orav EJ, et al. The association of intraoperative factors with the development of postoperative delirium. Am J Med 1999;105:380-4.
25. Redelmeier DA, Tan SH, Booth GL. The treatment of unrelated disorders in patients with chronic medical diseases. N Engl J Med 1998;338:1516-20.
26. Brookhart MA, Patrick AR, Dormuth C, et al. Adherence to lipid-lowering therapy and the use of preventive health services: an investigation of the healthy user effect. Am J Epidemiol 2007;166:348-54.
27. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age Ageing 2006;35:350-64.
28. Newman S, Stygall J, Hirani S, et al. Postoperative cognitive dysfunction after noncardiac surgery: a systematic review. Anesthesiology 2007;106:572-90.
29. Hering H, Lin CC, Sheng M. Lipid rafts in the maintenance of synapses, dendritic spines, and surface AMPA receptor stability. J Neurosci 2003;23:3262-71.
30. Stang P, Morris L, Kempf J, et al. The co-prescription of contraindicated drugs with statins: continuing potential for increased risk of adverse events. Am J Ther 2007;14:30-40.
31. Cubeddu LX, Seamon MJ. Statin withdrawal: clinical implications and molecular mechanisms. Pharmacotherapy 2006;26:1288-96.
32. Han HS, Suk K. The function and integrity of the neurovascular unit rests upon the integration of the vascular and inflammatory cell systems. Curr Neurovasc Res 2005;2:409-23.
33. Papamikolaou PN, Christidis GD, Ioanidis JP. Comparison of evidence on harms of medical interventions in randomized and nonrandomized studies. CMAJ 2006;174:635-41.
34. Lindenauer PK, Pekow P, Wang K, et al. Lipid-lowering therapy and in-hospital mortality following major noncardiac surgery. JAMA 2004;291:2092-9.
35. Gertz K, Laufs U, Lindauer U, et al. Withdrawal of statin treatment abrogates stroke protection in mice. Stroke 2003;34:551-7.
36. Kapoor AS, Kanji H, Buckingham J, et al. Strength of evidence for perioperative use of statins to reduce cardiovascular risk: systematic review of controlled studies. BMJ 2006;333:1149.
37. Fleisher LA, Poldermans D. Perioperative beta blockade: Where do we go from here? Lancet 2008;371:1813-4.

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