Statins abrogate ischemic renal injury in animal studies but whether they are renoprotective in humans is unknown. We conducted a population-based retrospective cohort study that included 213,347 older patients who underwent major elective surgery in the province of Ontario, Canada from 1995 to 2008. During the first 14 postoperative days, 1.9% (4020 patients) developed acute kidney injury and 0.5% (1173 patients) required acute dialysis. The 30-day mortality rate was 2.8% (5974 patients). Prior to surgery, 32% of patients were taking a statin. After statistical adjustment for patient and surgical characteristics, statin use associated with 16% lower odds of acute kidney injury (OR, 0.84; 95% CI, 0.79 to 0.90), 17% lower odds of acute dialysis (OR, 0.83; 95% CI, 0.72 to 0.95), and 21% lower odds of mortality (OR, 0.79; 95% CI, 0.74 to 0.85). Propensity score matching produced similar results. These data suggest that statins may protect against renal complications after major elective surgery and reduce perioperative mortality.

Acute kidney injury (AKI) is a common iatrogenic complication of major elective surgery that impacts morbidity, mortality, and resource use. The predominant mechanism of perioperative AKI is thought to be impaired perfusion, first causing a hypoxic insult, followed by production of reactive oxygen species and activation of inflammatory mechanisms during reperfusion. Although there remains no effective therapy to prevent perioperative AKI, there is emerging evidence to suggest statins may be beneficial. Statins exert anti-inflammatory effects by blocking the infiltration of inflammatory cells and downregulating the expression of inflammatory mediators, such as IL-6 and C-reactive protein. Statins also exert antioxidant effects and improve endothelial function through the increased expression of nitric oxide. Studies using animal models have shown that giving statins before an ischemic event significantly reduces AKI. Whether a similar benefit occurs in humans is uncertain. Some observational studies have shown that statins are associated with less AKI, whereas others have not. Their potential benefit in the perioperative setting has also been shown in some small randomized controlled trials where administration of statins preopera-
tively improved cardiovascular outcomes. To examine the issue further and to inform the conduct of definitive randomized controlled trials, we studied all older patients who underwent major elective surgery in Ontario, the largest province in Canada, over a 14-year period. Our goal was to contrast renal outcomes among patients who were and were not taking a statin before their surgery. We hypothesized that statin use before major elective surgery would associate with less perioperative AKI.

RESULTS

A total of 213,347 patients from 211 hospitals were included in our analysis (patient selection described in Appendix A). The median length of hospitalization was 5 days (interquartile range, 2 to 13 days). A total of 67,941 patients (32%) were statin users. Statin users differed from nonusers on some preoperative characteristics (Table 1). Compared with nonusers, statin users were slightly younger, more likely to be male, on a greater number of medications, and had higher rates of hypertension, cerebrovascular disease, coronary artery disease, and diabetes. Statin users also spent fewer days in hospital in the 3 years before surgery, had a greater number of visits to a cardiologist before surgery, underwent more cardiovascular screening tests, and had more cardiac surgical procedures. Rates of chronic kidney disease were similar between both groups.

Outcomes

The incidence of postoperative AKI was 1.9% (4020 patients), of acute dialysis was 0.5% (1173 patients), and of mortality was 2.8% (5974 patients). After adjustment for patient and surgical characteristics, statin use was associated with less AKI (odds ratio [OR], 0.89; 95% confidence interval [CI], 0.82 to 0.97; high potency adjusted OR, 0.76; 95% CI, 0.70 to 0.78).

Additional Analyses

Other Definitions of Mortality.

Compared with nonusers, statin users had less in hospital mortality (unadjusted OR, 0.75; 95% CI, 0.70 to 0.79; adjusted OR, 0.79; 95% CI, 0.73 to 0.85) and less 90-day mortality (unadjusted OR, 0.63; 95% CI, 0.60 to 0.66; adjusted OR, 0.74; 95% CI, 0.70 to 0.78).

Dialysis 90 to 120 Days after Surgery.

Compared with nonusers, statin users did not differ in an outcome of AKI that resulted in ongoing dialysis 90 to 120 days after surgery (adjusted OR, 0.81; 95% CI, 0.59 to 1.11).

Statin Potency.

Of the 67,941 statin users, 37,627 (55%) were on a low potency statin and 25,454 (37%) were on a high potency statin (potency defined by statin type and dose, see Concise Methods). Compared with nonusers, both low potency and high potency statin users had less AKI (low potency adjusted OR, 0.89; 95% CI, 0.82 to 0.97; high potency adjusted OR, 0.76; 95% CI, 0.70 to 0.78).

Table 1. Characteristics of patients who had major elective surgery

<table>
<thead>
<tr>
<th>Preoperative Statin Use</th>
<th>Yes (n = 67,941)</th>
<th>No (n = 145,406)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics and comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>age, yearsb</td>
<td>73 (69 to 77)</td>
<td>74 (70 to 79)</td>
</tr>
<tr>
<td>age groupsb</td>
<td>66 to 70</td>
<td>23,343 (34.4)</td>
</tr>
<tr>
<td></td>
<td>71 to 75</td>
<td>22,136 (32.6)</td>
</tr>
<tr>
<td></td>
<td>76 to 80</td>
<td>15,066 (22.2)</td>
</tr>
<tr>
<td></td>
<td>81 to 85</td>
<td>6,003 (8.8)</td>
</tr>
<tr>
<td></td>
<td>86 to 90</td>
<td>1,252 (1.8)</td>
</tr>
<tr>
<td></td>
<td>$\geq$91</td>
<td>141 (0.2)</td>
</tr>
<tr>
<td>female genderb</td>
<td>23,935 (35.2)</td>
<td>62,749 (43.2)</td>
</tr>
<tr>
<td>income quintile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 to 5</td>
<td>9,635 (14.2)</td>
<td>44,475 (30.6)</td>
</tr>
<tr>
<td>6 to 10</td>
<td>27,799 (40.9)</td>
<td>56,663 (39.0)</td>
</tr>
<tr>
<td>11 to 15</td>
<td>19,355 (28.5)</td>
<td>29,425 (20.2)</td>
</tr>
<tr>
<td>16 to 20</td>
<td>7,872 (11.6)</td>
<td>10,653 (7.3)</td>
</tr>
<tr>
<td>21 to 26</td>
<td>2,579 (3.8)</td>
<td>3,336 (2.3)</td>
</tr>
<tr>
<td>$\geq$26</td>
<td>701 (1.0)</td>
<td>854 (0.6)</td>
</tr>
<tr>
<td>hypertensionb</td>
<td>42,946 (63.2)</td>
<td>75,546 (52.0)</td>
</tr>
<tr>
<td>cerebrovascular diseaseb</td>
<td>13,502 (19.9)</td>
<td>20,024 (13.8)</td>
</tr>
<tr>
<td>peripheral vascular disease</td>
<td>4,297 (6.3)</td>
<td>7,133 (4.9)</td>
</tr>
<tr>
<td>coronary artery diseaseb</td>
<td>27,732 (40.8)</td>
<td>21,962 (15.1)</td>
</tr>
<tr>
<td>congestive heart failure</td>
<td>13,232 (19.5)</td>
<td>23,612 (16.2)</td>
</tr>
<tr>
<td>diabetesb</td>
<td>19,803 (29.1)</td>
<td>25,930 (17.8)</td>
</tr>
<tr>
<td>chronic kidney diseasec</td>
<td>15,489 (22.8)</td>
<td>32,242 (22.2)</td>
</tr>
<tr>
<td>Medication use in preceding 120 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta$-blockerb</td>
<td>36,660 (54.0)</td>
<td>36,796 (25.3)</td>
</tr>
<tr>
<td>calcium channel blockerb</td>
<td>27,263 (40.1)</td>
<td>37,518 (25.8)</td>
</tr>
<tr>
<td>potassium-sparing diuretic</td>
<td>4,367 (6.4)</td>
<td>9,928 (6.8)</td>
</tr>
<tr>
<td>non-potassium-sparing diureticb</td>
<td>21,152 (31.1)</td>
<td>34,718 (23.9)</td>
</tr>
<tr>
<td>NSAIDsd</td>
<td>7,260 (10.7)</td>
<td>17,206 (11.8)</td>
</tr>
<tr>
<td>Cox-2 inhibitors</td>
<td>2,419 (3.6)</td>
<td>3,727 (2.6)</td>
</tr>
<tr>
<td>ASAAb,d</td>
<td>14,490 (21.3)</td>
<td>21,898 (15.1)</td>
</tr>
<tr>
<td>ARBb</td>
<td>9,012 (13.3)</td>
<td>7,604 (5.2)</td>
</tr>
<tr>
<td>ACEb</td>
<td>34,852 (51.3)</td>
<td>40,284 (27.7)</td>
</tr>
<tr>
<td>anti-platelets other than ASAb</td>
<td>7,833 (11.5)</td>
<td>3,663 (2.5)</td>
</tr>
<tr>
<td>Measures of healthcare access in preceding 3 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>number of primary care visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>20,747 (30.5)</td>
<td>42,163 (29.0)</td>
</tr>
<tr>
<td>1 to 3</td>
<td>40,346 (59.4)</td>
<td>85,508 (58.8)</td>
</tr>
<tr>
<td>4 to 10</td>
<td>6,625 (9.8)</td>
<td>16,728 (11.5)</td>
</tr>
<tr>
<td>$&gt;10$</td>
<td>223 (0.3)</td>
<td>1,007 (0.7)</td>
</tr>
<tr>
<td>number of days in hospitalb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 7</td>
<td>45,549 (67.0)</td>
<td>95,331 (65.6)</td>
</tr>
<tr>
<td>8 to 14</td>
<td>10,593 (15.6)</td>
<td>21,604 (14.9)</td>
</tr>
<tr>
<td>15 to 21</td>
<td>5,026 (7.4)</td>
<td>11,113 (7.6)</td>
</tr>
<tr>
<td>$&gt;21$</td>
<td>6,711 (10.0)</td>
<td>17,358 (11.9)</td>
</tr>
<tr>
<td>number of cardiologist visitsb</td>
<td>1 (0 to 4)</td>
<td>0 (0 to 1)</td>
</tr>
<tr>
<td>number of cholesterol testsb</td>
<td>3 (2 to 5)</td>
<td>1 (0 to 2)</td>
</tr>
</tbody>
</table>
The incidence of AKI among statin nonusers with a remote history of statin use (statin use 365 to 91 days before surgery) was no different than nonusers without such a history (adjusted OR, 1.05; 95% CI, 0.93 to 1.19). Statin users (statin use ≤90 days before surgery) had less AKI than both types of nonusers.

### Duration of Statin Use before Surgery.

Compared with statin nonusers, a similar association of less AKI was seen among statin users who were on a statin for >90 (n = 59,571), 30 to 90 (n = 59,56), and <30 days (n = 2414) before surgery (>90-day adjusted OR, 0.86; 95% CI, 0.79 to 0.93; 30- to 90-day OR, 0.77; 95% CI, 0.64 to 0.93; <30-day OR, 0.61; 95% CI, 0.45 to 0.83).

### Test of Specificity.

No association was expected or observed between statin use and the outcome of perioperative bowel obstruction (adjusted OR, 0.97; 95% CI, 0.90 to 1.04; P = 0.38).

### Propensity Score Matching.

Of the 67,941 statin users included in the primary analysis, 47,307 were matched to 47,307 statin nonusers using propensity scores. Baseline characteristics were no different among matched statin users and nonusers (detailed in Appendix B). Similar to the primary analysis, statin use was associated with less AKI, less acute dialysis, and less 30-day mortality (Table 3).

### Time to Event Analysis.

Repeating the analysis in this way did not change the results (acute dialysis within 14 days of surgery censored for death adjusted hazard ratio, 0.83; 95% CI, 0.73 to 0.95; mortality within 14 days of surgery adjusted hazard ratio, 0.82; 95% CI, 0.76 to 0.89).

### Discussion.

Our data suggest statin use in older persons results in less AKI after major elective surgery and less perioperative mortality. The benefit of statins for the long-term prevention of car-

### Table 2. Association between preoperative statin use and outcomes

<table>
<thead>
<tr>
<th>Event (Statin Use)</th>
<th>No of Patients with Event</th>
<th>No of Events per 10,000 Patients (Statin Use)</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>Unadjusted</td>
<td>Adjusted*</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>2355</td>
<td>1665</td>
<td>1.53 (1.43, 1.63)</td>
</tr>
<tr>
<td>Acute dialysis</td>
<td>681</td>
<td>492</td>
<td>1.55 (1.38, 1.74)</td>
</tr>
<tr>
<td>Death</td>
<td>4448</td>
<td>1526</td>
<td>0.73 (0.69, 0.77)</td>
</tr>
</tbody>
</table>

A total of 67,941 patients were taking a statin before surgery, and 145,406 were not.

*Adjusted for age (per year), gender, rural location, the number of distinct drug products in the preceding year (>5, 6 to 10, 11 to 15, 16 to 20, 21 to 26, >26), socioeconomic status (quintiles of neighborhood income), cerebrovascular disease, chronic kidney disease, diabetes, coronary artery disease, congestive heart failure, angiotensin-converting enzyme inhibitor use, angiotensin receptor blocker use, β-blocker use, non–potassium-sparing diuretic use, calcium channel blocker use, number of primary care visits in the preceding 3 years (0, 1 to 3, 4 to 10, >10), number of cholesterol tests in the preceding 3 years (0, 1, 2, >3), 1 cardiac stress test in the preceding 3 years, 1 echocardiogram in the preceding 3 years, 1 carotid ultrasound in the preceding 3 years, type of surgery (cardiac, thoracic, vascular, abdominal, retroperitoneal), and the year of surgery (per year).

In summary, preoperative statin use was associated with reduced acute kidney injury, acute dialysis, and 30-day mortality in older patients undergoing major elective surgery. These findings suggest that statin use may be a beneficial strategy for preventing AKI in this population.
diovascular events is well established in large randomized controlled trials. More recently, there have been increasing data highlighting the benefit of statins in the perioperative setting. Small randomized trials suggested statins decrease perioperative cardiac events, and in observational studies, statin use was associated with less perioperative mortality. As well, in some observational studies, statin use was associated with fewer renal events (sample sizes of 77 to 2760 patients; renal outcomes were a change in serum creatinine or estimated GFR and acute dialysis). It is biologically plausible that statins decrease renal injury, and a protective effect of statins on the kidney has been shown in several animal studies. To our knowledge, the study is the largest to date to examine the association between statins and perioperative AKI. In our study, there was evidence of a dose-effect, with patients on higher potency statins having less AKI. Statins were beneficial whether they were started >90 or <30 days before surgery. Our results, in conjunction with previously published data, suggest that statins reduce the risk of perioperative AKI. Similar to previous studies, our results also show that statins are associated with a decreased risk of perioperative mortality.

Our large population-based sample of all older persons undergoing major elective surgery in Ontario was free of the screening biases that can arise in the setting of clinical trials and restrictive cohorts. The large number of events (about 1000 dialysis events and 6200 deaths) afforded a unique opportunity to characterize associations between statin use and serious perioperative complications with good precision. However, the allocation of statins was nonrandom. As with all observational studies, the protective association seen between statin use and AKI may not be causal. Information on factors such as nonprescription or in hospital medication use, medication compliance, and cholesterol levels are not recorded in the large Ontario healthcare databases. Confounding by indication could also occur because patients with comorbidities such as diabetes, coronary artery disease, and peripheral vascular disease are more likely to be prescribed a statin, and these comorbidities also increase the likelihood of AKI. This explains the higher rate of AKI observed among statin users in unadjusted analyses. For this reason, we adjusted for a large number of patient and healthcare confounders in the multivariable analysis. We also repeated the analysis using propensity-based matching to confirm the protective association with statins. Another concern is that patients who are adherent to a statin regimen may be inherently healthier than nonusers who in the past proved nonadherent to the regimen. This concept is referred to as a healthy adherer bias and could explain why statin users were observed to have a lower risk of AKI. We reduced concerns about this bias by showing that patients with and without a remote history of statin use had no difference in their incidence of AKI. Finally, a common limitation of research based on healthcare databases is a concern about the accuracy of codes used. The frequency of AKI is under-reported in our study. This is because AKI assessed by database codes has high specificity but poor sensitivity compared with a reference standard established by serum creatinine changes. However, it is hard to conceive that any misclassification of AKI occurred in a differential manner between statin users and nonusers. Furthermore, the definitive renal outcome of acute dialysis is coded with high accuracy in our data sources, as are other key characteristics such as surgical procedures, outpatient statin prescription, and mortality.

Our results support the assertion that preoperative statin use reduces important renal complications after major elective surgery. Given that there are >230 million major elective surgeries performed around the world each year, the hypothesis warrants testing in large multicentered randomized controlled trials. However, conducting trials to prove statins mitigate the renal outcomes most important to patients and their physicians poses many logistical challenges. Feasibility is a concern given the large sample size required to adequately examine a definitive renal outcome such as acute dialysis. In our results, the incidence of acute dialysis was 0.5%; thus, >87,500 similar patients would need to be enrolled to examine a relative risk reduction of 25% with adequate statistical power (α = 0.05, 1 − β = 0.8, no loss to follow-up). The two ongoing trials we know of are each expected to recruit <1000 patients and will therefore have inadequate statistical power, even in meta-analysis, to reliably answer the question of whether statins reduce the need for acute dialysis following major elective surgery. However, should these trials show that statins reduce AKI defined by an increase in serum creatinine (a surrogate outcome) or reduce a host of perioperative complications that include acute dialysis (a composite outcome), it will emphasize that the related improvements in acute dialysis noted in our study are truly caused by statins rather than residual confounding or bias. Furthermore, an ever increasing use of statins in routine care may make enrolling patients into a trial difficult and in some ways may render the renal question mute. A recent perioperative trial terminated early at a sample size of just over

### Table 3. Association between preoperative statin use and outcomes (propensity score matching)

<table>
<thead>
<tr>
<th>Event (Statin Use)</th>
<th>No. of Patients with Event</th>
<th>No. of Events per 10,000 Patients</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute kidney injury</td>
<td>1208 Yes 1039</td>
<td>255 Yes 220</td>
<td>0.86 (0.79, 0.93)</td>
</tr>
<tr>
<td>Acute dialysis</td>
<td>370 Yes 310</td>
<td>78 Yes 66</td>
<td>0.84 (0.72, 0.97)</td>
</tr>
<tr>
<td>Death</td>
<td>1326 Yes 1129</td>
<td>280 Yes 239</td>
<td>0.85 (0.78, 0.92)</td>
</tr>
</tbody>
</table>

Of the 67,941 statin users included in the primary analysis, 47,307 were matched to 47,307 non–statin users using propensity scores.
1000 patients because of slow recruitment, because patients who met inclusion criteria were already on a statin. If the evidence base of statin benefit for perioperative nonrenal complications and mortality continues to grow, withholding statins before surgery may become unethical. For these reasons, our results may endure as persuasive evidence that statins prevent complications of acute dialysis when given in the perioperative setting.

CONCISE METHODS

Setting and Design
Ontario has a universal health insurance program that covers all residents. Currently, there are 12 million residents (38% of the Canadian population); 74% are adults, 13% are ≥65 years of age, 51% are women, and 77% are white. Vital statistics, outpatient health encounters, hospitalizations, drug prescriptions, and procedures are reliably recorded in large healthcare databases. We conducted a retrospective population-based cohort study that used several of these linked healthcare databases. We conducted our study according to a prespecified protocol that was approved by the institutional review board at Sunnybrook Health Sciences Centre, Toronto. The reporting of this study follows guidelines set out in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Data Sources
Records from five databases were linked using encrypted unique identifiers. The Ontario Drug Benefit Plan database contains highly accurate records of all outpatient prescriptions dispensed to patients ≥65 years of age. The Canadian Institute for Health Information Discharge Abstract Database records all hospital admissions and detailed diagnostic and procedural information. The Ontario Health Insurance Plan Database contains all claims for inpatient and outpatient physician services. The Ontario Registered Persons Database contains demographic and vital status information on all residents. All four databases were virtually complete for the variables used in this study and have been used extensively to research health outcomes and health services. For a subset of patients, we also obtained preoperative serum creatinine values from Gamma-Dynacare, a provider of outpatient laboratory services to residents in Southwestern Ontario.

Patients
We included patients ≥66 years of age admitted to hospital for an elective major surgical procedure from January 1, 1995 to November 30, 2008. We included five classes of major surgery: cardiac, thoracic, vascular, intra-abdominal, and retroperitoneal operations (retroperitoneal operations were on the bladder, ureter, or kidney and excluded partial or complete nephrectomy and kidney transplantation). In our analysis, these classes of major surgery were found to carry the highest risk of AKI. We focused on older patients because individuals older than 65 receive universal prescription coverage in Ontario, and all medications dispensed to outpatients are accurately recorded. To ensure patients were in Ontario and accessing the drug plan before surgery, we limited the study to patients who were dispensed at least one prescription in the 90 days preceding surgery. Some patients had multiple eligible surgical hospital admissions during the study period. To avoid clustering in the analysis in such cases, we selected one hospital admission at random. Similarly, if more than one surgical procedure was performed during the same hospital admission, we classified patients according to the first and primary surgery that was performed. This was done to avoid selecting any urgent or emergent surgery performed after an initial elective surgery. To facilitate the assessment of new kidney injury after surgery, we excluded any patient with evidence of dialysis (acute or chronic) or renal transplantation in the 3 years before surgery.

Statin Use
We identified prescriptions filled for statins. Patients were statin users if there was evidence of at least one prescription for a statin in the 90 days before surgery (see Appendix C for statin list). Statin nonusers had no evidence of a statin prescription in the 90 days before surgery. We selected a time frame of 90 days because the drug plan requires that each prescription be renewed in this period.

Other Characteristics
We assessed demographic characteristics, comorbidities, and measures of healthcare access and screening for the 3-year interval preceding each patient’s surgery. We evaluated these characteristics by searching the databases for codes reflecting the conditions of interest. We used database codes with proven accuracy whenever possible (codes and their validity detailed in Appendix D1–3). We assessed concomitant medication use in the 120 days before surgery.

Outcomes
The primary outcome was AKI within 14 days of surgery determined by database codes. Secondary outcomes were acute dialysis (defined by evidence of at least one dialysis treatment within 14 days of surgery) and 30-day mortality. Codes and their validation are detailed in Appendixes D4, and 5, 37–39,41,55

Statistical Analysis
We assessed differences in baseline characteristics between statin users and nonusers using standardized differences. This metric describes differences between group means relative to the pooled SD and is deemed significant if >10%. We used logistic regression to estimate the ORs and 95% CIs for statin use and outcome, with nonstatin users as the referent group. In the multivariable analysis, we adjusted for 22 prespecified characteristics associated with statin use and AKI: age (per year), gender, rural location, the number of distinct drug products in the preceding year (1 to 5, 6 to 10, 11 to 15, 16 to 20, 21 to 26, >26), socioeconomic status (quintiles of neighborhood income), cerebrovascular disease, chronic kidney disease, diabetes, coronary artery disease, congestive heart failure, angiotensin-converting enzyme inhibitor use, angiotensin receptor blocker use, β-blocker use, non–potassium-sparing diuretic use, calcium channel blocker use, number of primary care visits in the preceding 3 years (0, 1 to 3, 4 to 10, >10), number of cholesterol tests in the preceding 3 years (0, 1, 2, ≥3), ≥1 cardiac stress test in the preceding 3 years, ≥1 echocardiogram in the preceding 3 years, ≥1 carotid ultrasound in the preceding 3 years, type of surgery (cardiac, thoracic, vascular, abdominal, retroperitoneal), and the year of surgery.
Additional Analyses

Other Definitions of Mortality.
We repeated the mortality analysis using two alternate definitions of death: (1) death during hospital admission and (2) death within 90 days of surgery.

Dialysis 90 to 120 Days after Surgery.
We examined ongoing dialysis requirements (defined by evidence of at least two dialysis treatments 90 to 120 days after surgery) among patients with AKI.

Statin Potency.
To identify a dose–response relationship, we repeated the primary analysis with statin users separated into low and high potency categories, with statin nonusers serving as the referent group. As done by others, we characterized statin potency based on LDL-lowering capability, with high potency statins lowering LDL cholesterol by ≥45% (statins classified as low and high potency detailed in Appendix C; not all statins were included in this analysis).

Assessment of Healthy Adherer Bias.
Previous investigators have raised concerns about confounding caused by a healthy adherer effect when examining associations between chronic medication use and outcomes in observational studies.34–36 To address this issue, we limited our analysis to statin nonusers (no prescription ≤90 days before surgery) and separated patients into those with and without a history of remote statin use (remote use defined by evidence of at least one prescription 90 to 365 days before surgery). If there was a healthy adherer bias, we hypothesized that patients with a history of remote statin use would have more AKI than those without such a history.

Duration of Statin Use before Surgery.
We repeated the primary analysis with statin users separated into three groups: those who were prescribed a statin >90, 30 to 90, and <30 days before surgery.

Test of Specificity.
To help determine whether any associations we observed were spurious, we re-ran the primary analysis using perioperative bowel obstruction as a tracer outcome (codes detailed in Appendix D4). We expected no association between statin use and perioperative bowel obstruction; observing an association would raise concerns about residual confounding.

Propensity Score Matching.
The primary analysis was repeated using propensity score matching. From the primary cohort, we retained each statin user who could be successfully matched to a statin nonuser on a one-to-one basis using the following matching variables: age (±5 years), gender, coronary artery disease (yes/no), number of cholesterol tests (0, 1, 2, ≥3), year of surgery (±4 years), type of surgery (cardiac, vascular, thoracic, abdominal, retroperitoneal), and logit of a propensity score for statin use (±0.2 SD). The propensity score was derived from 22 variables, and each statin nonuser could be selected only once.

Time to Event Analysis.
We repeated the analysis using Cox proportion hazard models to estimate the adjusted hazard ratio and 95% CIs for statin use and outcome.

ACKNOWLEDGMENTS
We thank three biostatisticians, Dr. Ping Li, Ms. Meaghan Cuerden, and Ms. Heather Thiessen-Philbrook, for help and support. Grant support was provided by the Lawson Health Research Institute. P.J.D. was supported by a New Investigator Award from the Canadian Institutes of Health Research (CIHR). A.J. was supported by a fellowship award from the CIHR. R.W. and M.W. were supported by Randomized Controlled Trial Mentorship Program Awards from the CIHR. A.G. was supported by a Clinician Scientist Award from the CIHR. The Institute for Clinical Evaluative Sciences receives funding from the Ontario Ministry of Health and Long-term Care. The opinions, results, and conclusions reported in this paper are those of the authors, and are independent from the funding sources.

DISCLOSURES
None.

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STATINS MAY PROTECT AGAINST KIDNEY COMPLICATIONS FOLLOWING ELECTIVE SURGERY

The cholesterol-lowering agents may prevent kidney injury and death that can occur soon after procedures

Washington, DC (April 11, 2011) — Taking a statin before having major elective surgery reduces potentially serious kidney complications, according to a study appearing in an upcoming issue of the *Journal of the American Society Nephrology* (JASN).

Each year, more than 230 million major elective surgeries are performed around the world. Unfortunately, many patients who undergo major operations develop kidney injury soon after surgery, often due to decreased blood flow to the kidneys and/or the effects of inflammation.

Animal studies suggest that the cholesterol-lowering drugs called statins protect the kidneys from such damage, but whether a similar benefit occurs in humans is uncertain. To investigate, Amber Molnar, MD (University of Western Ontario and Lawson Health Research Institute, in London, Canada), Amit Garg, MD, PhD (University of Western Ontario and Lawson Health Research Institute, in London; and the Institute for Clinical Evaluative Sciences, in Toronto, Canada) and their colleagues conducted a population-based retrospective study of all older patients who underwent major elective surgery in the province of Ontario, Canada from 1995 to 2008. Surgeries included cardiac, thoracic, vascular, intra-abdominal, and retroperitoneal procedures.

A total of 213,347 patients from 211 hospitals underwent major elective surgery, and 4,020 patients (1.9%) developed postoperative kidney injury within two weeks of surgery. A total of 1,173 patients (0.5%) required dialysis within two weeks of surgery, and 5,974 patients (2.8%) died within a month of surgery.

Prior to surgery, 67,941 patients (32%) were taking a statin. Patients taking a statin were 20% less likely to develop kidney injury, need dialysis, and die compared to patients who were not taking a statin. Also, there was evidence of a dose-effect, with patients on higher potency statins having less kidney injury. In addition, statins were beneficial whether they were started greater than 90 days or less than 30 days prior to surgery.

“Our study suggests that statin use in older persons results in less kidney injury following major elective surgery and reduces the risk of premature death after surgery,” said Dr. Molnar. She added that the results warrant further investigation with more rigorous
studies, but such trials will be difficult to carry out. “Conducting randomized controlled trials to examine whether statins are protective against definitive renal outcomes, such as acute dialysis, will be logistically challenging given that the need for acute dialysis is a relatively rare event,” she said.

Study co-authors include Steven Coca, MD, Chirag Parikh MD, PhD (Yale University School of Medicine); PJ Devereaux, MD, PhD, Michael Walsh, MD (McMaster University, in Hamilton, Canada); Arsh Jain, MD, Abhijat Kitchlu, Nausheen Siddiqui, MD (University of Western Ontario, London, Canada); Jin Luo (Institute for Clinical Evaluative Sciences, Toronto, Canada); J. Michael Paterson (Institute for Clinical Evaluative Sciences, in Toronto, McMaster University, in Hamilton, and the University of Toronto, Canada); and Ron Wald, MD (University of Toronto, Canada).

An accompanying editorial by Sushrut Waikar, MD and Steven Brunelli, MD (Harvard Medical School) entitled, “Statin Use Associates with Less Acute Kidney Injury after Major Elective Surgery” is available upon request.

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