RESEARCH ARTICLE

Statin use and the risk of acute kidney injury in older adults

Marcello Tonelli\textsuperscript{1,*}, Anita M. Lloyd\textsuperscript{2}, Aminu K. Bello\textsuperscript{2}, Matthew T. James\textsuperscript{1}, Scott W. Klarenbach\textsuperscript{2}, Finlay A. McAlister\textsuperscript{2}, Braden J. Manns\textsuperscript{1}, Ross T. Tsuyuki\textsuperscript{1}, Brenda R. Hemmelgarn\textsuperscript{1} and for the Alberta Kidney Disease Network

Abstract

Background: As more patients at lower cardiovascular (CV) risk are treated with statins, the balance between cardiovascular benefits and the risk of adverse events becomes increasingly important.

Methods: We did a population-based cohort study (May 1, 2002 to March 30, 2013) using province-wide laboratory and administrative data in Alberta. We studied new statin users aged 66 years of age and older who were not receiving renal replacement therapy at baseline. We assessed statin use at 30-day intervals to allow time-varying assessment of statin exposure in Cox proportional hazards models that examined the relation between statin use and hospitalization with acute kidney injury (AKI).

Results: Of the 128,140 new statin users, 47 and 46\% were prescribed high- and medium-intensity regimens at the index date. During median follow-up of 4.6 years (interquartile range 2.2, 7.4), 9118 individuals were hospitalized for AKI. Compared to non-use, the use of high- and medium-intensity statin regimens was associated with significant increases in the adjusted risks of hospitalization with AKI: hazard ratios 1.16 [95\% confidence interval (CI) 1.10, 1.23] and 1.07 (95\% CI 1.01, 1.13), respectively. Risks of AKI were higher among women than men, and among users of angiotensin converting enzyme inhibitors/angiotensin receptor blockers than non-users, and among diuretic users (p for interaction 0.002, 0.01, and 0.04 respectively).

Conclusions: We found a graded, independent association between the intensity of statin use and the risk of hospitalization with AKI, although the absolute magnitude of the excess risk was small.

Keywords: Statins, Kidney injury-acute, Older adults

Background

Randomized controlled trials (RCTs) demonstrate that statins reduce cardiovascular (CV) risk in diverse clinical populations – including reductions in all-cause mortality, myocardial infarction, stroke, and the need for coronary revascularization [1]. Although statins are undoubtedly beneficial for people at risk of CV events, they also have side effects that may partially offset their benefits [2, 3]. As the prevalence of statin use increases among patients at lower CV risk [4], the risk of adverse events becomes increasingly important for accurately assessing net clinical benefit.

Acute kidney injury (AKI) is associated with adverse clinical outcomes and high healthcare costs [5, 6]. Even mild forms of AKI (increases in serum creatinine of 26 μmol/L) are associated with excess mortality, prolonged length of hospital stay, and high healthcare costs [7]. Earlier studies done with less potent statin regimens (pravastatin 40 mg daily or equivalent) suggested that statin treatment might decrease the risk of AKI in people at high CV risk [8]. More recent studies in which more intensive statin treatment were more frequently used suggest that statins actually increase the risk of AKI [9, 10]. However, factors that influence any excess risk associated with statin use have not been conclusively determined.

We used a unique population-based dataset with data on clinical information, medication use, laboratory
results and health outcomes to test the hypothesis that the risk of AKI due to statin treatment is regimen-specific, with the highest risk observed for higher doses and for high potency statins. An important secondary hypothesis was that any apparent excess risk of AKI associated with statin use was confounded by concomitant use of angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) or diuretics.

**Methods**

**Alberta Kidney Disease Network (AKDN) database**

We used a previously described population-based database [11], which incorporates data from Alberta Health (AH; the provincial health ministry) such as demographics, physician claims, hospitalizations, ambulatory care utilization and Alberta Blue Cross Coverage for Seniors drug data; the Northern and Southern Alberta Renal Programs and the clinical laboratories in Alberta. All people registered with the Alberta Health Care Insurance Plan (AHCIP) were included in the database; all Alberta residents are eligible for the AHCIP and > 99% participate in coverage. For eligible individuals aged 65 years and older, prescription drugs dispensed from community pharmacies are adjudicated through Alberta Blue Cross. There are no premiums for this coverage and the individual shares the cost of the prescription with AH by paying 30% to a maximum of $25 for each prescription dispensed. We used the database to assemble a cohort of individuals 66 years of age and older with an incident statin prescription between 2002 and 2013. Participants entered the cohort on the date of their first statin prescription (i.e., index date) on or after their 66th birthday between May 1, 2002 and March 30, 2013. Prescriptions for any of atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, or simvastatin were considered. By limiting entry to occur at least one year after eligibility for Alberta Blue Cross Coverage for Seniors commenced, we could properly assess previous statin use, using a one-year washout period. We excluded individuals who had ≥1 statin prescription during the one year period prior to their first statin prescription; we considered the remaining participants as incident statin users and included them in the main analyses (Additional file 1: Figure S1).

**Assessment of exposure to statins**

We deemed exposure to statins to have commenced on the date of the first statin prescription and reassessed exposure every 30 days of follow-up. We considered individuals as statin users for the entire 30-day period if they were dispensed at least one statin tablet. Incident statin users were grouped according to the intensity of statin [12] they were receiving and could move back and forth between statin use and non-use as well as between different types of statins. The non-use periods of the time-varying statin exposure variable formed the reference group in analyses. We classified statin intensity as high, medium or low according to the National Institute for Health and Clinical Excellence (NICE) clinical guidelines on lipid modification [12] (Additional file 1: Table S1). If a non-use period was ≤90 days and was followed by a period of statin use, we assumed that these individuals were statin users during this “non-use” period. We assumed individuals were adherent with statin prescriptions if they continued to have prescriptions for statins dispensed. If in a 30-day period an individual was dispensed more than one type of statin, we classified that individual as receiving on one agent for the entire period (the agent which accounted for the majority of tablets during that period). Usage was based on dispensing events and number of days supplied (Additional file 1: Figure S2).

**Definitions**

We used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [13] and a standardized serum creatinine assay to estimate the baseline estimated glomerular filtration rate (eGFR) for each participant. The most recent outpatient serum creatinine on or within 1 year prior to the index date was selected if available. We assessed albuminuria using the most recent outpatient measurement (or the median of all multiple measurements available) on or within 1 year prior to the index date and categorized it as: normal [albumin:creatinine ratio (ACR)< 3 mg/mmol, protein:creatinine ratio (PCR) < 15 mg/mmol or urine dipstick negative], moderately increased (ACR 3–30 mg/mmol, PCR 15–50 mg/mmol or urine dipstick trace or 1+), severely increased (ACR >30 mg/mmol, PCR > 50 mg/mmol or urine dipstick ≥2+), or not measured/available. We used ACR as the primary measure of albuminuria; if ACR was unavailable we used PCR; if PCR was unavailable we used dipstick urinalysis. We used validated algorithms based on claims and hospitalization data to classify participants regarding the baseline presence of 30 comorbidities [14]. We also classified individuals with respect to any use of ACEI, ARB or loop diuretics (oral furosemide or ethacrynic acid; as captured through dispensing events) within 1 year of the index date.

**Ascertainment of outcomes**

We followed participants from their index date until the outcome of interest, date of death, initiation of chronic
renal replacement, outmigration from the province or the study end (March 31, 2013). The primary study outcome was hospitalization with acute kidney injury (AKI) based on International Classification of Diseases (ICD9 or ICD10) codes obtained from Alberta Health data [15] (Additional file 1: Table S2).

**Statistical analyses**
We reported baseline descriptive statistics as percentages or medians and interquartile ranges (IQR) as appropriate. We used Cox proportional hazards models to assess the relationship between statin intensity and the primary outcome of interest. We treated statin use categorized by intensity as a time-varying exposure. Covariates (eGFR, albuminuria, comorbidities, medication use) were also time-varying; they were updated for each 30-day interval and defined in the same manner as at baseline. We tested the proportional hazards assumption by assessing log-log plots.

To test our secondary hypothesis, we examined whether the relationship between statin exposure and hospitalization with AKI was modified by a) ACEI/ARB use at baseline; or b) loop diuretic use at baseline. We also examined other potential dichotomous effect modifiers as follows: c) age 66–75 years versus age > 75 years; d) sex; e) diabetic status at index; f) chronic kidney disease (CKD) status at index (where individuals were classified as having CKD if either their baseline eGFR was less than 60 ml/min/1.73 m² or they had “moderately increased” or worse albuminuria); and g) albuminuria status at baseline (where individuals had albuminuria if they had “moderately increased” or worse albuminuria). Finally, to test whether AKI apparently due to statin use was actually due to cardiovascular events or interventions that were associated with both initiation of statins and hospitalization with AKI, we stratified on the presence of i) cardiovascular events. Cardiovascular events of interest included cerebrovascular vascular accident (CVA), myocardial infarction (MI), coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), or coronary angiogram. The presence or absence of these cardiovascular events was classified during the entire follow-up period. Analyses a) to i) were done by including an interaction term between the stratification variable and statin exposure in each model.

We did several sensitivity analyses, including a) repeating the primary analyses in individuals without previous cardiovascular disease as of the index date; and b) assessing the relation between statin intensity and hospitalization for AKI requiring dialysis (based on ICD 9 or ICD 10 codes in Additional file 1: Table S2); and c) repeating the primary analyses based on defining statin exposure in terms of medication possession ratio [16].

We defined cardiovascular disease as any of: acute myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, coronary catheterization, heart failure or stroke/transient ischemic attack. We assessed medication possession ratio (MPR) as a percentage at each 30-day interval and was defined as the “number of tablets” divided by “days in period”. We categorized MPR into three categories as follows: MPR ≥ 75%, MPR 1 to 75%, and non-use (where as before, these were the periods where no tablets were taken). If a non-use period was ≤ 90 days and was followed by a period of statin use, the last available MPR value was carried forward into this period.

We also compared the characteristics of statin users to an age- and sex-matched cohort of randomly selected non-users. First, random index dates were generated for the non-users according to the distribution of index dates of the statin users; the statin users were each matched to a non-user (if a match was available) based on age (in 5 year increments) and sex. Characteristics between statin users and non-users were compared using standardized differences [17].

We did statistical analyses using Stata 13.1 MP software (www.stata.com). The institutional review boards at the Universities of Calgary and Alberta approved the study (REB14–0884, Pro00053469) with a waiver of consent granted.

**Results**
There were 128,140 incident statin users; the characteristics of statin users are compared to an age- and sex-matched cohort of randomly selected non-users is presented in Additional file 1: Table S3. As expected, non-users were significantly less likely than users to have prior vascular disease. Baseline characteristics of the statin users that were the focus of analysis are presented according to the intensity of statin use (which reflects potency and dose) at the index date (Table 1). The statin regimens were 47% high-intensity and 46% medium-intensity; < 7% of individuals were initially prescribed a low-intensity regimen. Individuals taking a high-intensity regimen were similar in age and diabetic status but there were more males in comparison to those taking medium- or low-intensity regimens. The former generally had similar levels of baseline comorbidities in comparison to the latter groups except for acute myocardial infarction and chronic kidney disease which were all more common in the high intensity group. During a median follow-up of 4.6 years (IQR 2.2, 7.4), total follow-up time approximately 624,000 person-years, 9118 individuals were hospitalized for AKI. The rates of hospitalization for AKI (per 1000 person years) were 17.1 [95% confidence interval (CI) 16.6, 17.7] for high-intensity statin use, 13.8 (95% CI 13.3, 14.4) for medium-intensity statin use, 13.3 (95% CI 12.1, 14.7) for
| Table 1 Baseline characteristics at index date | High-intensity | Medium-intensity | Low-intensity |
|---------------------------------------------|----------------|------------------|---------------|
| **n** | 60,625 | 58,919 | 8,596 |
| Age, years | 72.7 (68.6, 78.1) | 73.1 (69, 78.5) | 73.4 (68.9, 78.8) |
| Female | 45 | 53 | 55 |
| Hypertension | 73 | 71 | 70 |
| Diabetes | 27 | 29 | 27 |
| Statin | | | |
| Rosuvastatin | ≥10 mg: 44 | < 10 mg: 19 | 0 |
| Atorvastatin | ≥20 mg: 55 | < 20 mg: 62 | 0 |
| Simvastatin | ≥80 mg: 0.3 | 20–40 mg: 20 | < 20 mg: 40 |
| Lovastatin | 0 | 40 mg: 0.2 | < 40 mg: 4 |
| Pravastatin | 0 | 0 | ≤40 mg: 52 |
| Fluvastatin | 0 | 80 mg: 0.1 | ≤40 mg: 4 |
| Comorbidities | | | |
| Alcohol misuse | 2 | 2 | 2 |
| Asthma | 4 | 3 | 3 |
| Atrial fibrillation | 12 | 10 | 10 |
| Cancer, lymphoma | 1 | 1 | 1 |
| Cancer, metastatic | 1 | 1 | 1 |
| Cancer, non-metastatic | 7 | 6 | 6 |
| Chronic heart failure | 14 | 11 | 12 |
| Chronic kidney disease | 43 | 39 | 34 |
| Chronic pain | 17 | 18 | 18 |
| Chronic pulmonary disease | 21 | 19 | 18 |
| Chronic viral hepatitis B | 0.02 | 0.04 | 0.05 |
| Cirrhosis | 0.2 | 0.2 | 0.3 |
| Dementia | 4 | 3 | 3 |
| Depression | 9 | 9 | 9 |
| Epilepsy | 1 | 1 | 1 |
| Hypothyroidism | 14 | 14 | 14 |
| Inflammatory bowel disease | 1 | 1 | 1 |
| Irritable bowel syndrome | 2 | 2 | 2 |
| Multiple sclerosis | 0.4 | 0.4 | 0.4 |
| Myocardial infarction | 17 | 8 | 7 |
| Parkinson’s disease | 1 | 1 | 2 |
| Peptic ulcer disease | 1 | 1 | 1 |
| Peripheral vascular disease | 3 | 3 | 2 |
| Psoriasis | 1 | 1 | 1 |
| Rheumatoid Arthritis | 4 | 4 | 3 |
| Schizophrenia | 1 | 1 | 1 |
| Severe constipation | 2 | 2 | 2 |
| Stroke or TIA | 18 | 17 | 16 |
| Proteinuria | | | |
| Not measured | 42 | 41 | 51 |
| Normal | 46 | 47 | 39 |
low-intensity statin use, and 12.7 (95% CI 12.2, 13.2) for no statin use.

**Association between statin use, statin regimen intensity, statin potency, and the risk of AKI**

Compared to non-use, use of any statin (all types; all doses) was associated with a significant increase in the unadjusted and adjusted risks of hospitalization with AKI [hazard ratio (HR) 1.22 (95% confidence interval CI 1.16, 1.28), and HR 1.11 (95% CI 1.06, 1.17)], respectively.

High-intensity regimens were associated with a significantly increased unadjusted risk of hospitalization with AKI [HR 1.35 (95% CI, 1.28, 1.43) vs non-use]. Similarly, the unadjusted HR for the risk of hospitalization with AKI for medium-intensity users versus non-use was also significant [HR 1.09 (95% CI 1.03, 1.16)] (Table 2). After adjustment, the adjusted hazard ratios (aHR) for the risk of hospitalization with AKI were attenuated but remained significantly increased (high-intensity versus non-use aHR 1.16 (95% CI 1.10, 1.23); medium-intensity versus non-use aHR 1.07 (95% CI 1.01, 1.13). There were no differences in the risk of hospitalization with AKI between low-intensity users and non-use (Table 2).

**Effect modification**

In sensitivity analyses, we searched for clinical characteristics that might modify the association between statin regimen intensity and the risk of hospitalization with AKI. Of 8 characteristics considered, sex, ACEI/ARB use and loop diuretic use significantly modified these associations (Fig. 1). Specifically, the dose-adjusted risk of hospitalization with AKI associated with statin use was substantially greater in women than in men (p for interaction 0.002). While the absolute risk of hospitalization for AKI in women was smaller than in men, compared with non-use, the risk of hospitalization with AKI associated with high-intensity statin use among women was 1.29 (95% CI 1.19, 1.39) but only 1.07 (95% CI 0.99, 1.14) in men. Similarly, the increased risk of hospitalization with AKI associated with high-intensity statin use was 1.26 (95% CI 1.19, 1.34) among those using ACEI or ARB, but only 1.10 (95% CI 0.99, 1.22) among those not using the latter (p for interaction 0.01). There was also a significant interaction between diuretic use and the risk of hospitalization with AKI associated with statin use (p for interaction 0.04). Among those using a diuretic at the index date, the risk of hospitalization with AKI were attenuated but remained significantly increased (high-intensity versus non-use aHR 1.16 (95% CI 1.10, 1.23); medium-intensity versus non-use aHR 1.07 (95% CI 1.01, 1.13). There were no differences in the risk of hospitalization with AKI between low-intensity users and non-use (Table 2).

**Table 1** Baseline characteristics at index date (Continued)

|               | High-intensity n = 60,625 | Medium-intensity n = 58,919 | Low-intensity n = 8596 |
|---------------|---------------------------|-----------------------------|------------------------|
| Moderately increased | 10                        | 10                          | 8                      |
| Severely increased  | 2                         | 2                           | 2                      |
| **Medications**   |                           |                             |                        |
| ACEI/ARB        | 65                        | 58                          | 56                     |
| Loop diuretics  | 13                        | 11                          | 11                     |
| eGFR ml/min/1.73m² |                           |                             |                        |
| Not measured   | 25                        | 27                          | 37                     |
| < 15            | 0.2                       | 0.2                         | 0.3                    |
| 15–29           | 2                         | 2                           | 2                      |
| 30–44           | 6                         | 6                           | 6                      |
| 45–59           | 15                        | 15                          | 13                     |
| 60–89           | 45                        | 44                          | 37                     |
| ≥ 90            | 7                         | 6                           | 5                      |

Data expressed as %, except *median (interquartile range). Totals do not always add to 100% because of rounding. See Additional file 1: Table S1 for statin intensity groupings.

Proteinuria categories: Normal (ACR < 3 mg/mmol, PCR < 15 mg/mmol or urine dipstick negative), moderately increased (ACR 3–30 mg/mmol, PCR 15–50 mg/mmol or urine dipstick trace or 1+), severely increased (ACR > 30 mg/mmol, PCR > 50 mg/mmol or urine dipstick ≥2+)

ACEI angiotensin converting enzyme inhibitors, ACR albumin creatinine ratio, ARB angiotensin receptor blockers, eGFR estimated glomerular filtration rate, PCR protein:creatinine ratio, TIA transient ischemic attack

**Table 2** Hazard ratios (95% CI) for the risk of hospitalization with acute kidney injury

|               | Unadjusted HR (95% CI) | Fully-adjusted* HR (95% CI) |
|---------------|------------------------|-------------------------------|
| High-intensity| 1.35 (1.28, 1.43)      | 1.16 (1.10, 1.23)             |
| Medium-intensity| 1.09 (1.03, 1.16)      | 1.07 (1.01, 1.13)             |
| Low-intensity | 1.04 (0.93, 1.15)      | 1.03 (0.93, 1.15)             |
| Non-use       | 1 (referent)           | 1 (referent)                  |
| P for trend   | < 0.001                | < 0.001                       |

CI confidence interval, HR hazard ratio

*Adjusted for covariates in Table 1
### Effect Modification Adjusted Analyses

**Fig. 1**

The figure illustrates effect modification adjusted analyses. *ACEI* angiotensin converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *CI* confidence interval, *CKD* chronic kidney disease, *HR* hazard ratio, *NICE* National Institute of Clinical Excellence

| Stratification                                      | NICE Exposure | HR (95% CI) | p for interaction |
|-----------------------------------------------------|---------------|-------------|-------------------|
| **Age at baseline**                                |               |             |                   |
| Age 66-75                                           | Non-use (ref) | 1.00 (0.85, 1.18) | 0.19              |
|                                                     | Low-intensity | 1.04 (0.86, 1.23) |                   |
|                                                     | Medium-intensity | 1.04 (0.91, 1.18) |                   |
|                                                     | High-intensity  | 1.04 (0.86, 1.23) |                   |
| Age>=75                                             | Non-use (ref) | 1.06 (0.91, 1.21) |                   |
|                                                     | Low-intensity | 1.06 (0.91, 1.21) |                   |
|                                                     | Medium-intensity | 1.06 (0.91, 1.21) |                   |
|                                                     | High-intensity  | 1.12 (1.14, 1.31) |                   |
| **Sex**                                             |               |             |                   |
| Males                                               | Non-use (ref) | 1.00 (0.85, 1.18) | 0.002             |
|                                                     | Low-intensity | 1.03 (0.89, 1.16) |                   |
|                                                     | Medium-intensity | 1.03 (0.89, 1.16) |                   |
|                                                     | High-intensity  | 1.03 (0.89, 1.16) |                   |
| Females                                             | Non-use (ref) | 1.03 (0.89, 1.16) |                   |
|                                                     | Low-intensity | 1.03 (0.89, 1.16) |                   |
|                                                     | Medium-intensity | 1.03 (0.89, 1.16) |                   |
|                                                     | High-intensity  | 1.03 (0.89, 1.16) |                   |
| **Diabetic status at baseline**                     |               |             |                   |
| No diabetes                                         | Non-use (ref) | 1.01 (0.87, 1.16) | 0.06              |
|                                                     | Low-intensity | 1.01 (0.87, 1.16) |                   |
|                                                     | Medium-intensity | 1.01 (0.87, 1.16) |                   |
|                                                     | High-intensity  | 1.01 (0.87, 1.16) |                   |
| Diabetes                                            | Non-use (ref) | 1.07 (0.93, 1.25) |                   |
|                                                     | Low-intensity | 1.07 (0.93, 1.25) |                   |
|                                                     | Medium-intensity | 1.07 (0.93, 1.25) |                   |
|                                                     | High-intensity  | 1.07 (0.93, 1.25) |                   |
| **CKD status at baseline**                          |               |             |                   |
| No CKD                                              | Non-use (ref) | 1.00 (0.85, 1.18) | 0.53              |
|                                                     | Low-intensity | 1.04 (0.86, 1.23) |                   |
|                                                     | Medium-intensity | 1.04 (0.86, 1.23) |                   |
|                                                     | High-intensity  | 1.04 (0.86, 1.23) |                   |
| CHD                                                 | Non-use (ref) | 1.08 (0.93, 1.24) |                   |
|                                                     | Low-intensity | 1.08 (0.93, 1.24) |                   |
|                                                     | Medium-intensity | 1.08 (0.93, 1.24) |                   |
|                                                     | High-intensity  | 1.08 (0.93, 1.24) |                   |
| **Albuminuria at baseline**                         |               |             |                   |
| No albuminuria                                      | Non-use (ref) | 1.04 (0.89, 1.21) | 0.62              |
|                                                     | Low-intensity | 1.04 (0.89, 1.21) |                   |
|                                                     | Medium-intensity | 1.04 (0.89, 1.21) |                   |
|                                                     | High-intensity  | 1.04 (0.89, 1.21) |                   |
| Albuminuria                                         | Non-use (ref) | 1.07 (0.94, 1.23) |                   |
|                                                     | Low-intensity | 1.07 (0.94, 1.23) |                   |
|                                                     | Medium-intensity | 1.07 (0.94, 1.23) |                   |
|                                                     | High-intensity  | 1.07 (0.94, 1.23) |                   |
| **ACE/ARB use at baseline**                         |               |             |                   |
| No ACE/ARB use                                      | Non-use (ref) | 1.07 (0.93, 1.24) | 0.01              |
|                                                     | Low-intensity | 1.07 (0.93, 1.24) |                   |
|                                                     | Medium-intensity | 1.07 (0.93, 1.24) |                   |
|                                                     | High-intensity  | 1.07 (0.93, 1.24) |                   |
| ACE/ARB use                                         | Non-use (ref) | 1.10 (0.99, 1.22) |                   |
|                                                     | Low-intensity | 1.10 (0.99, 1.22) |                   |
|                                                     | Medium-intensity | 1.10 (0.99, 1.22) |                   |
|                                                     | High-intensity  | 1.10 (0.99, 1.22) |                   |
| **Diuretic use at baseline**                        |               |             |                   |
| No diuretic use                                     | Non-use (ref) | 1.04 (0.89, 1.14) | 0.04              |
|                                                     | Low-intensity | 1.04 (0.89, 1.14) |                   |
|                                                     | Medium-intensity | 1.04 (0.89, 1.14) |                   |
|                                                     | High-intensity  | 1.04 (0.89, 1.14) |                   |
| Diuretic use                                         | Non-use (ref) | 1.22 (1.09, 1.37) |                   |
|                                                     | Low-intensity | 1.22 (1.09, 1.37) |                   |
|                                                     | Medium-intensity | 1.22 (1.09, 1.37) |                   |
|                                                     | High-intensity  | 1.22 (1.09, 1.37) |                   |
| **Coronary event during follow-up**                 |               |             |                   |
| No event                                            | Non-use (ref) | 1.02 (0.88, 1.17) | 0.85              |
|                                                     | Low-intensity | 1.02 (0.88, 1.17) |                   |
|                                                     | Medium-intensity | 1.02 (0.88, 1.17) |                   |
|                                                     | High-intensity  | 1.02 (0.88, 1.17) |                   |
| Event                                               | Non-use (ref) | 1.09 (0.89, 1.33) |                   |
|                                                     | Low-intensity | 1.09 (0.89, 1.33) |                   |
|                                                     | Medium-intensity | 1.09 (0.89, 1.33) |                   |
|                                                     | High-intensity  | 1.09 (0.89, 1.33) |                   |
| No stratification Overall                           | Non-use (ref) | 1.03 (0.93, 1.15) |                   |
|                                                     | Low-intensity | 1.03 (0.93, 1.15) |                   |
|                                                     | Medium-intensity | 1.03 (0.93, 1.15) |                   |
|                                                     | High-intensity  | 1.03 (0.93, 1.15) |                   |
hospitalization with AKI with high-intensity statin use was 1.35 (95% CI 1.22, 1.49) and only 1.16 (95% CI 1.09, 1.23) among those not using a diuretic.

Other sensitivity analyses
Compared to non-use, use of any statin (all types; all doses) was associated with a significant increase in the unadjusted risk of hospitalization with AKI requiring dialysis but not the adjusted risk [hazard ratio (HR) 1.45 (95% confidence interval CI 1.06, 1.98), and HR 1.15 (95% CI 0.83, 1.59)], respectively. Neither low-, medium- nor high-intensity statin use were associated with adjusted risk of AKI requiring dialysis (data not shown). Compared to non-use periods, MPR of statins between 1 to 75% and ≥75% were both associated with a significantly increased adjusted risk of hospitalization with AKI [HR 1.23 (95% CI 1.15, 1.33)] and [HR 1.09 (95% CI 1.04, 1.15), respectively. Analyses examining the risk of hospitalization with AKI in the subgroup of individuals without cardiovascular disease at baseline were similar in findings to the main analyses that did not make this exclusion (data not shown).

Discussion
In this population-based study of 128,140 older incident statin users treated in a single Canadian province, we found a graded, independent association between the intensity of statin treatment and the risk of hospitalization with AKI. In addition, we found that both female sex and baseline use of ACEI or ARB or loop diuretics may modify the relation between statin treatment and the risk of hospitalization with AKI.

We speculate that the observed effect modification by sex may be due to higher blood levels of statin at a given dose among women than in men, due to the generally lower body size of women. Although we adjusted for baseline use of ACEI or ARB in all analyses, the finding that the risk of statin-associated hospitalization with AKI is substantially higher in people also using ACEI or ARB suggests the possibility that the former (and not statin use per se) may have contributed to the apparently increased risk of AKI among statin users. We also found evidence that the risk of AKI associated with statin use was modified by baseline use of diuretics.

A previous large multinational observational study (N = 2,008,003) found an excess risk of AKI within two years of statin initiation among high potency statin users (defined by daily doses of ≥10 mg rosuvastatin, ≥20 mg atorvastatin, or ≥40 mg simvastatin) compared to users of statin at lower potency, but only among people without CKD at baseline [9]. In that study, claims data rather than eGFR was used to define CKD, which may have led to inaccuracies in assessing the presence or absence of pre-existing kidney disease. Also, that study did not evaluate for effect modification by characteristics such as sex or ACEI/ARB use. These differences in study design may account for the slightly different findings between that and our study. An earlier population-based cohort study in England and Wales (N = 2,004,692) that used different methods to ascertain statin exposure and clinical outcomes also found an excess risk of acute kidney injury among statin users than non-users [10]. That study also reported a higher risk among users of higher doses than users of lower doses, although potential effect modifiers such as sex and concomitant medication use were again not evaluated. A third study done in the U. S suggested that higher doses of simvastatin were associated with a higher risk of claims for AKI during follow-up [18], although there was no association between AKI and statin use as compared to non-use. Thus, on balance, available data from observational studies suggest that more intensive exposure to statins may lead to slightly increased risk of AKI, as compared to milder exposure or no exposure.

In contrast, previous RCTs have not found a significant association between statin treatment and the risk of AKI, or an excess risk of AKI for high potency vs moderate/low potency regimens [19–21]. A recent RCT examined the risk of AKI associated with a short course of atorvastatin 40–80 mg daily during the perioperative period among adult patients receiving cardiac surgery, and found no significant effect overall (HR associated with atorvastatin 1.06 (95% CI 0.78, 1.46)) or among those who were naïve to statin treatment at baseline (HR 1.61, 95% CI 0.86, 3.81)) [22]. Although they are more methodologically robust, these RCTs had much lower statistical power than the current study, and tended to study highly selected populations. Plans to pool adverse event rates across multiple large RCTs will help to offset the latter limitation [23], and may help to resolve the apparently conflicting results between RCTs and observational studies.

Our results should be placed in the context of what is known about the cardiovascular benefits of statins: higher doses of these medications clearly lead to important reductions in clinically relevant outcomes including death, stroke, and myocardial infarction [1]. While the dose-dependent increase we observed in the risk of hospitalization with AKI for statin users was statistically significant, its magnitude was clinically small: only 107 excess AKI hospitalizations (compared to non-use) would be expected in a population of 10,000 people aged >65 years who received high intensity statin treatment for approximately 5 years, as compared with no statin use. Put differently, the number needed to harm (NNH) for one case of AKI over 5 years is approximately 93. In comparison, assuming a conservative 20% relative risk reduction, high intensity statin use in the same 10,000
people would be expected to prevent 135 myocardial infarctions during the same period, as compared with no statin use (number needed to treat, 74).

Strengths and limitations
Our study has important strengths, including its use of a large population-based database from a setting with universal health care coverage, its use of validated algorithms for ascertaining the presence or absence of hospitalization with AKI as well as baseline comorbidity, and its rigorous analytical methods. However, our study also has several potential limitations that should be considered when interpreting results. First, like all studies using administrative data, residual confounding is possible by unmeasured characteristics including use of over-the-counter medications such as non-steroidal anti-inflammatory medications, intercurrent illness or the underlying risk of AKI among study participants. Confounding by indication is a particular concern, but the similar findings in a sensitivity limited to individuals with known cardiovascular disease at baseline should increase confidence in our findings. Second, not all individuals had baseline eGFR or albuminuria measurement available to assess CKD status. This would not have been expected to affect our key findings regarding the association between statin use and AKI, although it might have reduced statistical power to show effect modification by baseline CKD status. It is worth noting that low eGFR does not affect blood statin levels appreciably, since these medications primarily undergo hepatic metabolism rather than renal excretion [24]. Third, we studied only people older than 66 years. Although such people account for most statin users in Alberta, whether our findings apply to younger people requires confirmation. Fourth, our algorithm for identifying AKI has limitations, including a sensitivity of approximately 35%, although it is approximately 98% specific [15], as compared with a clinical gold standard. On balance, these limitations may have led to under-recognition of milder forms of AKI (perhaps reducing statistical power), although they are unlikely to have led to bias. Fifth, we were not able to identify the cause of AKI, although it is unlikely to have been due to rhabdomyolysis, given how infrequently this event occurs [1]. Sixth, like most pharmacoepidemiological studies, our data source captured dispensing of medications from pharmacies and not actual medication use. Participants may not have taken medications that were dispensed, and dates of dispensing may not correspond to actual doses taken during each 30-day interval. Finally, we studied people from a single Canadian province and our findings may not apply to other settings.

Conclusions
In conclusion, we found a graded, independent association between the intensity of statin use and the risk of hospitalization with AKI, although the absolute magnitude of the excess risk was small. Our findings suggest that higher dose statin use could be considered as a contributing factor to AKI in older people, especially in females or those receiving ACEI, ARB or loop diuretics. This slight increase in risk should be weighed against the known and clinically relevant benefits of statins for preventing death and significant morbidity from cardiovascular disease.

Additional files

Additional file 1: Figure S1. Flow Diagram. Figure S2. Assessment of exposure to statins. Table S1. Classification of statin intensity. Table S2. Algorithm for identifying acute kidney injury from administrative data. Table S3. Baseline characteristics of statin users and non-users. (DOCX 104 kb)

Abbreviations
ACEI: Angiotensin converting enzyme inhibitors; ACR: Albumin:creatinine ratio; AH: Alberta Health; AHCIP: Alberta Health Care Insurance Plan; aHR: Adjusted hazard ratios; AKDN: Alberta Kidney Disease Network; AKI: Acute kidney injury; ARB: Angiotensin receptor blockers; CABG: Coronary artery bypass grafting; CI: Confidence interval; CKD: Chronic kidney disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CV: Cardiovascular; CVA: Cerebrovascular vascular accident; eGFR: Estimated glomerular filtration rate; HR: Hazard ratio; ICD: International Classification of Diseases; IQR: Interquartile ranges; MI: Myocardial infarction; MPR: Medication possession ratio; NICE: National Institute for Health and Clinical Excellence; NNH: Number needed to harm; PCI: Percutaneous coronary intervention; PCR: Protein:creatinine ratio; RCTs: Randomized controlled trials

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Availability of data and materials
The datasets used in this analysis are not publicly available.

Disclaimer
This study is based in part on data provided by Alberta Health. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views of the Government of Alberta. Neither the Government of Alberta nor Alberta Health express any opinion in relation to this study.

Authors’ contributions
MT and AB conceived the study; AL performed the analyses; MT and AL had access to all the data in the study and take responsibility for the integrity and the accuracy of the data analysis; MT and AL drafted the paper; AB, MJ, SK, FA, BM, RT and BH made substantial contributions in manuscript revision; MT, AL, AB, MJ, SK, FA, BM, RT and BH approved the final version.
Ethics approval and consent to participate
The institutional review boards at the Universities of Calgary and Alberta approved the study (REB14-0884, Pro00053469) with a waiver of consent granted.

Consent for publication
Not applicable.

Competing interests
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Author details
1Department of Medicine, University of Calgary, 7th Floor, TRW Building, 3280 Hospital Drive NW, Calgary, Alberta T2N 4G6, Canada. 2Department of Medicine, University of Alberta, Edmonton, Canada.

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References
1. Cholesterol Treatment Trials C, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R, de Lemos J, Braunwald E, Blazing M, Murphy S, Downs JR, Gotto A, Cefaled M, Holdaas H, Gordon D, Davis B, Koren M, Dahlof B, Poulter N, Sever P, Knopp RH, Follistom B, Holdaas H, Jardine A, Schmieder R, Zannad F, Goldbourt U, Kaplinsky E, Colhoun HM, Betteridge DJ, Durandt PN, Hittman GA, Fuller J, Neil A, Wanner C, Krane V, Sachs F, Moyle L, Pfeiffer M, Hawkins CM, Braunwald E, Barter P, Keech A, Tavazzi L, Maggioni A, Marchioli R, Tognoni G, Franzosi MG, Maggioni A, Bloomfield H, Robins S, Collins R, Armitage J, Keech A, Parish S, Peto R, Sleight P, Pedersen TR, Ridker PM, Holman R, Meade T, Simes J, Keech A, MacManus S, Marschner I, Tonkin A, Shaw J, Serruyas PW, Nakamura H, Katterud G, Furberg C, Byington R, Macfarlane P, Cobbe S, Ford I, Murphy M, Blauw GJ, Packard C, Shepherd J, Kjekshus J, Jardine A, Pedersen TR, Wilhelmsen L, Braunwald E, Cannon CP, and Cholesterol Treatment Tr.
2. Thompson PD. What to believe and do about statin-associated adverse effects. J Am Coll Cardiol. 2016;67:2395–410.
3. Hennessy DA, Tanuseputro P, Tuna M, Bennett C, Perez R, Shields M, Ko DT, Tu J, Manuel DG. Population health impact of statin treatment in Canada. J Am Coll Cardiol. 2016;67:2395–410.
4. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-associated side effects. J Am Coll Cardiol. 2016;67:2395–410.
5. Hemmelgarn BR, Wiebe N, Fortin M, Guthrie B, Hemmelgarn BR, James MT, Klaenbach SW, Lewanzuck M, Manns BJ, Rosenblatt P, Sargios P, Staus S, Quan H, Alberts Kidney Disease N. Methods for identifying 30 chronic conditions: Application to administrative data. BMC Med Inform Decis Mak. 2015;15:53.
6. Billings FT, Hendricks PA, Schildcrout JS, Shi Y, Petracek MR, Byrne JG, Brown NJ. High-dose perioperative atorvastatin and acute kidney injury following cardiac surgery: a randomized clinical trial. JAMA. 2016;315:877–88.
7. Holman RR, Ridker PM, Meade T, Simes J, Keech A, MacMahon S, Marschner I, Newby DE, Scholzen R, Zannad F, Goldbourt U, Kaplinsky E, Colhoun HM, Betteridge DJ, Durandt PN, Hittman GA, Fuller J, Neil A, Wanner C, Krane V, Sachs F, Moyle L, Pfeiffer M, Hawkins CM, Braunwald E, Barter P, Keech A, Tavazzi L, Maggioni A, Marchioli R, Tognoni G, Franzosi MG, Maggioni A, Bloomfield H, Robins S, Collins R, Armitage J, Keech A, Parish S, Peto R, Sleight P, Pedersen TR, Ridker PM, Holman R, Meade T, Simes J, Keech A, MacManus S, Marschner I, Tonkin A, Shaw J, Serruyas PW, Nakamura H, Katterud G, Furberg C, Byington R, Macfarlane P, Cobbe S, Ford I, Murphy M, Blauw GJ, Packard C, Shepherd J, Kjekshus J, Jardine A, Pedersen TR, Wilhelmsen L, Braunwald E, Cannon CP, and Cholesterol Treatment Tr.
8. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-associated side effects. J Am Coll Cardiol. 2016;67:2395–410.
9. Hemmelgarn BR, Wiebe N, Fortin M, Guthrie B, Hemmelgarn BR, James MT, Klaenbach SW, Lewanzuck M, Manns BJ, Rosenblatt P, Sargios P, Staus S, Quan H, Alberts Kidney Disease N. Methods for identifying 30 chronic conditions: Application to administrative data. BMC Med Inform Decis Mak. 2015;15:53.
10. Billings FT, Hendricks PA, Schildcrout JS, Shi Y, Petracek MR, Byrne JG, Brown NJ. High-dose perioperative atorvastatin and acute kidney injury following cardiac surgery: a randomized clinical trial. JAMA. 2016;315:877–88.
11. Hemmelgarn BR, Clement F, Manns BJ, Klarenbach S, James MT, Ravani P, Pannu N, Ahmed SB, MacRae J, Scott-Douglas N, Jindal K, Quinn R, Cullerton BF, Wiebe N, Krause R, Thorlarsdottir L, Tonelli M. Overview of the Alberta kidney disease network. BMC Nephrol. 2009;10:30.
12. National Institute for Health and Clinical Excellence. Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. 2014.