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RESEARCH

Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases


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Abstract

Objective To quantify an association between acute kidney injury and use of high potency statins versus low potency statins.

Design Retrospective observational analysis of administrative databases, using nine population based cohort studies and meta-analysis. We performed as treated analyses in each database with a nested case-control design. Rate ratios for different durations of current and past statin exposure to high potency or low potency statins were estimated using conditional logistic regression. Ratios were adjusted for confounding by high dimensional propensity scores. Meta-analytic methods estimated overall effects across participating sites.

Setting Seven Canadian provinces and two databases in the United Kingdom and the United States.

Participants 2 067 639 patients aged 40 years or older and newly treated with statins between 1 January 1997 and 30 April 2008. Each person hospitalized for acute kidney injury was matched with ten controls.

Intervention A dispensing event was new if no cholesterol lowering drug or niacin prescription was dispensed in the previous year. High potency statin treatment was defined as ≥10 mg rosuvastatin, ≥20 mg atorvastatin, and ≥40 mg simvastatin; all other statin treatments were defined as low potency. Statin potency groups were further divided into cohorts with or without chronic kidney disease.

Main outcome measure Relative hospitalization rates for acute kidney injury.

Results Of more than two million statin users (2 008 003 with non-chronic kidney disease; 59 636 with chronic kidney disease), patients with similar propensity scores were comparable on measured characteristics. Within 120 days of current treatment, there were 4691 hospitalizations for acute kidney injury in patients with non-chronic kidney injury, and 1896 hospitalizations in those with chronic kidney injury. In patients with non-chronic kidney disease, current users of high potency statins were 34% more likely to be hospitalized with acute kidney injury within 120 days after starting treatment (fixed effect rate ratio 1.34, 95% confidence interval 1.25 to 1.43). Users of high potency statins with chronic kidney disease did not have as large an increase in admission rate (1.10, 0.99 to 1.23). χ^2 tests for heterogeneity confirmed that the observed association was robust across participating sites.

Conclusions Use of high potency statins is associated with an increased rate of diagnosis for acute kidney injury in hospital admissions compared with low potency statins. The effect seems to be strongest in the first 120 days after initiation of statin treatment.

Introduction

Evidence has indicated that statin use could lead to unintended adverse renal effects.[1-3] A large scale, randomized controlled

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Web appendix: Disease definitions
Web figure: Fixed cohort analysis of hospitalization for acute kidney injury 6 months after cohort entry

trial—JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin)—compared high dose (20 mg) rosuvastatin with placebo in almost 18 000 patients.[4] Data subsequently reported to the United States Food and Drug Administration (FDA) showed a non-significant increase of 19% in acute renal failure (risk ratio 1.19, 95% confidence interval 0.61 to 2.31).[5] The non-significant risk increased further to 35% (1.35, 0.81 to 2.23) when the endpoint also included doubling of serum creatinine. A large, population based cohort study of over two million patients also reported that statin use was associated with a greater than 50% increase in risk of acute renal failure, with evidence of raised risk within the first year of statin use, and a dose-response effect.[3] In a Canadian product monograph for rosuvastatin, the most potent statin, the manufacturer also reported renal impairment in some patients who received 80 mg of the drug in investigational clinical trials.[6]

It remains unclear whether statin therapy is specifically associated with greater adverse renal effects. In the light of data alluding to a possible dose response, we aimed to explore a possible association between statins and kidney injury by comparing patients who were prescribed high potency statins with those prescribed low potency statins. The main advantage of using exposure to lower potency statins as a reference group was an expectation that a substantial amount of unmeasured confounding by indication would thus be eliminated. A comparison of high versus low potency might also be informative for treatment where statin use is clearly supported by evidence of total mortality benefit (for example, in patients who have had myocardial infarction), but where evidence of incremental benefit for high potency statins versus low potency statins is questionable.[7]

In the inaugural study of the Canadian Network for Observational Drug Effect Studies (CNODES),[8] we used the administrative healthcare records of two million people to assess the association between treatment with high versus low potency statins and hospitalization for acute kidney injury in patients with and without chronic kidney disease. CNODES is part of the new Canadian Drug Safety and Effectiveness Network, initiated by Health Canada and administered by the Canadian Institutes of Health Research. The principal aim of CNODES is to collaboratively analyze existing healthcare databases using observational research methods, to provide rapid answers to questions on drug safety and effectiveness.

Methods

Setting and source population

We used a common analytical protocol to conduct studies of statins in acute kidney injury in seven Canadian provinces (Alberta, British Columbia, Manitoba, Nova Scotia, Ontario, Quebec, and Saskatchewan; source population 33 million in 2011), as well as in two international databases in the United Kingdom (General Practice Research Database (GPRD), 11.6 million) and the US (Caremark-Medicare database, 1.2 million). The study populations were patients aged 40 years or older, newly treated with statins between 1 January 1997 and 30 April 2008. In three provinces, only patients aged 65 years and older were available, and four of the databases were established after 1997.

Data sources

All participating jurisdictions contributed data from their respective administrative healthcare databases. Prescription data included, at a minimum, patient level records specifying the drug dispensed, the quantity or days' supply of treatment, and the date of dispensation. The GPRD was an exception in that written prescriptions were recorded rather than actual drugs dispensed. Physician claims and hospitalizations databases included date of service encounter or hospital admission, up to 25 ICD-9 or ICD-10 (international classification of disease, 9th or 10th revisions) diagnosis codes, and procedure and billing codes. The Saskatchewan databases and GPRD included laboratory test data. The GPRD also included body mass index and smoking status. All databases have been used extensively in observational research.

Cohorts of patients according to statin use

Our analytical approach was to conduct as treated analyses using nested case-control methodology. This design is a good alternative to cohort analysis when studying time dependent exposures, and its computational efficiency is well suited to analyzing rare events in large databases.[9] In each jurisdiction, patients from the source population were included in cohorts of chronic or non-chronic kidney disease if they were newly dispensed a statin between 1 January 1997 (or one year after the beginning of data availability) and 30 April 2008.

We defined a dispensing event as new if no cholesterol lowering drug (World Health Organization Anatomical Therapeutic Class C10) or prescription for niacin was dispensed in the previous 365 days. The date of the new statin prescription was defined as the cohort entry date. Daily statin doses were categorized according to their potency in lowering serum concentrations of low density lipoprotein (LDL) cholesterol.

High potency statin treatment was defined as at least 10 mg rosuvastatin, at least 20 mg atorvastatin, and at least 40 mg simvastatin; all other statin treatments were defined as having low potency. Our categorization was derived from a systematic review and meta-analysis of randomized controlled trials that quantified the effects of statins on LDL cholesterol concentration.[10] The analysis showed that statins clustered around three levels of LDL reduction. One group (defined as low potency) produced a reduction of about 35%, another (defined as high potency) reduced concentrations by about 45%; 80 mg rosuvastatin lowered concentrations by 60%. This classification is similar to ones used elsewhere.[11-13] We grouped 80 mg rosuvastatin with the middle group, owing to relatively few of such prescriptions. Therefore, statins were categorized as high or low in our study, according to whether they would produce a theoretical reduction in LDL cholesterol concentration of less than 45%, or at least 45%.[12]

Patients were excluded if they were younger than 40 years (<66 years in jurisdictions that only had drug data for senior citizens), had less than one year of enrolment in their medical system, or received any cholesterol lowering drug or underwent dialysis in the previous year. Finally, we assigned eligible patients to cohorts of chronic and non-chronic kidney disease according to whether they had at least one hospitalization or physician medical encounter for non-dialysis dependent, chronic kidney disease in the previous three years. The web appendix lists definitions of chronic kidney disease.

Acute kidney injury endpoint

The primary endpoint was hospitalization for acute kidney injury, defined using a validated algorithm (diagnosis code for acute kidney injury in any of the following listed diagnoses: ICD-9 584, 584.5, 584.6, 584.7, 584.8, or 584.9; ICD-10 N17, N17.0, N17.1, N17.2, N17.8, or N17.9).[14 15]

High dimensional propensity scores

High dimensional propensity scores (hdPS) were estimated for all patients in the cohorts. The hdPS algorithm is available as downloadable SAS software files from the Brigham and Women's Hospital.[16] As described in detail elsewhere,[17] hdPS is an empirically driven, multistep process to adjust for confounding bias in observational studies. The hdPS algorithm prioritizes thousands of variables at the drug, diagnostic, procedural, and demographic level according to their potential to cause multiplicative bias in the estimate of an exposure-outcome association (for example, rate ratio). Typically, the 500 variables most likely to cause bias are included in a propensity score model. We used logistic regression to estimate the predicted probability (as measured by the propensity score) of exposure to high potency statins versus low potency statins, conditional on all of the included covariates.

In addition to the 500 covariates empirically selected for the propensity score models, we also included the following prespecified covariates: year of cohort entry, hospitalization, order for a laboratory test, greater than four distinct drugs dispensed, greater than four physician visits, hypertensive disease, hypercholesterolemia, peripheral vascular disease, congestive heart failure, and injury or poisoning, all within the year prior to cohort entry (web appendix). Propensity score models were estimated using logistic regression.

As treated analysis

In each cohort described above, we defined a follow-up end date for each patient as the earliest occurrence of an acute kidney injury endpoint, date of death, date of emigration, 24 months after initiation on statin treatment, a dispensing for cerivastatin, or 31 March 2010. Cerivastatin was not among the statins included in the analysis. We identified all cases of the endpoint occurring within patients' follow-up windows and defined the date of admission for acute kidney injury as the index date. For each case, we randomly selected ten controls from a matched risk set comprising patients of the same sex and age within one year (if no controls were available, within five years), who also entered the cohort within 90 days before or after the case's cohort entry date.

We used conditional logistic regression to estimate matched odds ratios for three mutually exclusive durations of current exposure (≤120, 121-365, and 366-730 days) and past exposure (no exposure within 120 days of the index date). Patients who received both a high and low potency statin in the same current exposure category or as past exposures were categorized as receiving high potency statins in that particular category. Adjusted matched odds ratios were estimated by including the tenth of the propensity score (nine binary indicator variables); diagnosis of diabetes; and prior use of angiotensin II converting enzyme inhibitors or receptor blockers, non-steroidal anti-inflammatory drugs, thiazide diuretics, and loop diuretics. In addition, we assessed potential drug-drug interactions with statins by including main effect variables and interaction variables for three types of compounds: macrolide antibiotics, fibrates, and calcium channel blockers.

Fixed cohort analysis

We also conducted fixed cohort analyses on the cohorts in each jurisdiction, where the statin exposure category was defined by the initial prescription at cohort entry. We expected that fixed cohort estimates would be biased towards the null hypothesis, mostly because of dilution of risk due to treatment non-adherence and dose escalation. The hdPS model used in this analysis was the same as the model in the as treated analysis, but it estimated effects for 180 days of follow-up after cohort entry instead of two years. For patients with non-chronic or chronic kidney disease, we used logistic regression to estimate odds ratios for statin potency and acute kidney injury. Odds ratio estimates were reported as relative risks, and the logistic regressions included tenth of propensity score (nine binary indicator variables); category of age (in five year groups); diagnosis of diabetes; and prior use of angiotensin II converting enzyme inhibitors or receptor blockers, non-steroidal anti-inflammatory drugs, thiazide diuretics, and loop diuretics.

Meta-analysis

All analyses were undertaken independently at each site, which were kept blind to results from the other sites until the meta-analysis was conducted. For the meta-analysis, we pooled the studies from each site using either fixed effect or random effects models according to results of χ^2 tests for heterogeneity.[18] Matched odds ratios were reported as rate ratios. Inverse variance weighted odds ratios and 95% confidence intervals were calculated to estimate the total effect across all study populations.

Results

Study populations

Overall, 2 067 639 patients in participating databases were newly exposed to statins during the study period, of which 673 410 (33%) received high potency statins (table⇓); the sizes of the source populations varied broadly. We recorded 59 636 patients with chronic kidney injury using statins within three years before cohort entry. The table also shows baseline characteristics of the overall study population, matched and unmatched on propensity score, which demonstrates the comparability of patients using high potency and low potency statins on measured factors conditional on their propensity scores. The mean age of study participants was 68 years, although in jurisdictions with younger patients the mean age was between 61 and 65 years. Fifty percent of patients were women.

Rates of acute kidney injury

In the Canadian jurisdictions with patients younger than 65 years, the risk of hospitalization for acute kidney injury at six months in patients with non-chronic kidney disease receiving low dose statins (that is, the reference group) ranged from 1.2-1.4 per 1000 patients (in British Columbia, Manitoba, and Saskatchewan) to 3.5 per 1000 patients (in Quebec). The corresponding risk was 1.0 per 1000 patients in the GPRD. In the remaining jurisdictions with data for adults aged 65 years and older only, the corresponding risk was 3.1 per 1000 patients thousand in Ontario, Nova Scotia, and Alberta, and 4.0 per 1000 patients in the US Medicare Caremark database. Rates were substantially higher in patients with a history of chronic kidney disease: 23-45 per 1000 patients in first six months after statin initiation in Canada, 10 per 1000 patients in the GPRD, and 63 per 1000 patients in the US Medicare Caremark database.

As treated analysis

Patients who started high potency statins were 34% more likely to be hospitalized for acute kidney injury than those who started low potency statins in the first 120 days of treatment (fixed effect rate ratio 1.34, 95% confidence interval 1.25 to 1.43; fig 1⇓). The elevated effect was attenuated with longer durations

of current exposure. The rate of hospitalization for acute kidney injury did not increase significantly in patients with chronic kidney disease (1.10, 0.99 to 1.23; fig 2⇓).

The χ^2 tests for heterogeneity were not significant for all meta-analyses except for past use in patients with chronic kidney disease. In that analysis, a random effects estimate of the total effect was reported. We checked for effect modification of statin potency by macrolide antibiotics, calcium channel blockers, and fibrates, but did not find any significant interactions. The fixed cohort analysis also showed a significantly increased risk for acute kidney injury within six months of treatment initiation in both groups of patients with non-chronic and chronic kidney disease (web fig).

Discussion

In this study of over two million patients newly treated with a statin, we found a significant relative increase of 34% in the rate of hospitalization for acute kidney injury within 120 days of initiation for patients receiving high potency statins versus low potency statins. Our as treated analysis was based on an expectation that less than perfect treatment persistence and a high tendency for subsequent switching to higher doses might cause a fixed cohort analysis to underestimate the risk while actually on treatment. Loss of some patients to follow-up and competing risks also could have contributed to an underestimation of the effect. The as treated analysis, which allowed quantification of risk from different durations of current exposure, indicated that risk remained elevated for at least two years.

Although we used multiplicative models to answer our study questions, it is the subsequent translation of relative risks into numbers needed to treat to harm that provides the most useful metric for prescribers, regulators, and decision makers. In this regard, we estimate that 1700 patients with non-chronic kidney disease need to be treated with a high potency statin instead of a low potency statin for 120 days to cause one additional hospitalization for acute kidney injury. A number of 1700 patients is sufficiently large for there not to be enough patients enrolled in randomized trials to find an association between acute kidney injury and statin use with high precision. However, our definition of acute kidney injury was chosen to be highly specific and thus probably excluded a number of patients with real but milder cases, which could have underestimated the absolute risk.

Further studies are necessary to determine the biological mechanism linking statins to kidney injury. The elevated risk in patients using high potency statins could be related to an increased risk of rhabdomyolysis. Another mechanism could be the statin induced suppression of coenzyme Q10, a fat soluble enzyme with antioxidant properties. Statins have been shown to block the production of coenzyme Q10,[19 20] and placebo controlled trials of coenzyme Q10 treatment in humans and animals with kidney disease have shown improvements in renal function within 28 days of use.[20 21] Other studies have shown an association between statin treatment and proteinuria.[5 22] Pleiotrophic statin effects should also be contemplated.

Comparison with existing evidence

According to data from the JUPITER trial, as published by the FDA,[5] the maximum likelihood estimate of the relative risk was 1.11 for any renal event over a median follow-up duration of 1.9 years, and 1.19 for acute renal failure. Our rate ratio estimate was 1.15 for acute kidney injury for patients treated for one to two years. Over all treatment durations in our analysis, the average rate ratio was 1.17, or 1.20 if past treatment was excluded. The compatibility of these results with our hypothesis, their agreement with the maximum likelihood estimate observed in the large JUPITER trial, and the high degree of precision obtained from our study population, together lend meaningful support for this increased risk.

Similarity between our results and other epidemiologic studies is mixed. One multicenter study of statin use and acute kidney injury in patients with community acquired pneumonia (CAP) reported an odds ratio of 1.32 for acute kidney injury in patients with CAP who received statins compared with statin naive patients.[23] By contrast, a meta-analysis of four observational studies of rosuvastatin, designed to study multiple outcomes but which included renal failure, reported no difference between rosuvatstain and other statins.[24] This meta-analysis is impossible to interpret from a statin potency perspective, because the control patients received other statins of all different potencies.

It is also important to note that most statin treatment in randomized trials was of low potency. The JUPITER trial showed that about 450 patients needed to be treated with 20 mg rosuvastatin per day instead of placebo for two years to prevent one death from myocardial infarction, stroke, or cardiovascular disease (combined endpoint).[4] It remains to be shown whether the number needed to treat to benefit with high potency statins instead of low potency statins (versus placebo) would outweigh the combined risk of acute kidney injury, rhabdomyolysis, and diabetes.

Implications

In a meta-analysis of clinical trials of statins, the Cholesterol Treatment Trialists (CTT) reported that more intensive statin treatment in secondary prevention was associated with a 0.3% reduction in absolute risk in major coronary events per year of treatment, compared with less intensive statin treatment over a mean of five years.[25] Some have argued that an absolute risk reduction of 0.3% per year overstates what could be expected in typical clinical practice.[7] Importantly, the trials comparing more intensive treatment with less intensive treatment included in the CTT meta-analysis were mostly comparisons of a low dose of a particular statin versus the highest possible dose of that same statin. In reality, clinicians would not choose between, for example, 10 mg of atorvastatin and 80 mg of atorvastatin. Given what is likely to be a small magnitude of incremental cardiovascular benefit of high potency statins over low potency statins in reality, a pressing question is how to identify patients for whom the risk-benefit balance for high potency statin treatment is unfavourable.

Methodological considerations

Chronic kidney disease status could have been misclassified at cohort entry using ICD codes from administrative data. However, in view of the specificity of these definitions (99%),[26] we do not believe that any potential misclassification (that is, in relation to the small number of participants with chronic kidney disease being misclassified as having non-chronic kidney disease) would be substantial enough to have influenced the estimate of effect in the patients with non-chronic kidney disease.

Our outcome of acute kidney injury was defined using a validated algorithm with high specificity but low sensitivity. Thus, the absolute rates of acute kidney injury identified in hospitalization records would underestimate the true incidence based on changes in serum creatinine. However, we do not expect that our definition of acute kidney injury would have

resulted in differential misclassification of patients during the study period. Acute kidney injury would have been an unexpected outcome of treatment, and patients with true injuries misclassified as non-injuries would have been those not hospitalized for the disease, and were probably less clinically relevant than those captured by our specified definition.

Although our results are much more compatible with the maximum likelihood estimates of renal harm in the JUPITER trial than with a null hypothesis, confounding by indication remains a possible threat to the validity of our results. To minimize this bias, the reference group consisted of patients who also received statin treatment. We adjusted for a broad spectrum of possible confounders using hdPS scores. There was probably a non-significant trend over time towards increasing use of high potency statins, which necessitated the inclusion of calendar year of cohort entry as a covariate in the models.

There was also a small imbalance after propensity score matching between patients using high potency and low potency statins in the proportion that had congestive heart failure (table), which is a known independent risk factor for acute kidney injury. In view of the difference between and the relative numbers of patients exposed to high potency statins versus low potency statins, we estimate that at least a 25-fold independent relative increase in the risk of acute kidney injury associated with congestive heart failure would be needed to spuriously produce our risk estimate of 1.34 in our population (that is, association between acute kidney injury with statin potency). A 2.0 risk of acute kidney injury associated with congestive heart failure would produce a spurious association between statin potency and acute kidney injury of about 1.01. Diagnosis of congestive heart failure was included in the propensity score models, and outcome models were adjusted for use of loop diuretics in the year before cohort entry.

This study was made possible through data sharing agreements between CNODES member research centres and the respective provincial governments of Alberta, British Columbia, Manitoba, Nova Scotia, Ontario, Quebec and Saskatchewan. We thank Sebastian Schneeweiss and Jun Liu of the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital for their expertise and assistance in analyzing the US Medicare data and use of the high-dimensional propensity score method; and James M Wright for sharing expert knowledge of pharmacology and clinical trial evidence for statins.

CNODES investigators: Samy Suissa (principal investigator, McGill University); David Henry and Michael Paterson (Ontario); Colin Dormuth (British Columbia); Brenda Hemmelgarn (Alberta); Gary Teare (Saskatchewan); Patricia Martens and Patricia Caetano (Manitoba); Pierre Ernst, Jacques LeLorier, and Robert Platt (Québec); and Adrian Levy (Nova Scotia).

Contributors: CRD was responsible for overseeing the development of the study protocol and the creation of a data analysis plan that was adapted for use in each jurisdiction and each data set. All variables and all outcomes were specified in that protocol and any deviations from this were for technical reasons only (for example, variable coding of administrative data in certain jurisdictions). Except where prevented by insufficient data or small cell size limitations, all prespecified outcomes in the protocol are reported. A copy of the study protocol is available on request. All coauthors contributed to roundtable discussions on protocol development and all provided critical revisions to the manuscript. BRH, MTJ, J-PL, and AXG were instrumental in defining the acute kidney injury outcome and identifying patients with chronic kidney disease. CBR assisted with exposure definitions. JMP, GFT, AL, and PE contributed to numerous study design issues and critical revision of the manuscript. CRD was responsible for drafting the manuscript and incorporating suggestions of coauthors and he is the guarantor of the manuscript. The final manuscript was approved by the publications subcommittee of CNODES.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from Health Canada, the Drug Safety and Effectiveness Network, and the Canadian Institutes for Health Research for the submitted work; PE receives consultancy and speaker's fees from Astra Zeneca, Boehringer Ingelheim, Merck, and Nycomed, and a research grant from Boehringer Ingelheim; AL receives consultancy fees from Oxford Outcomes (now Icon), a company that carries out contracted work for pharmaceutical companies; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Ethics approval for each study was obtained from the respective academic institutions in each province.

Data sharing: CNODES is not permitted to release individual level data or aggregated data with small cell sizes. The analytical protocol for this analysis is available on request.

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What is already known on this topic

Various data sources have pointed to a possible harmful effect of statins on the kidney, although previous analyses have not specifically looked at acute kidney injury

What this study adds

Prescription of high potency statins (≥10 mg rosuvastatin, ≥20 mg atorvastatin, ≥40 mg simvastatin) is associated with an increased rate of hospital admission for acute kidney injury, compared with lower potency statins

Increased risk of admission occurs early after starting statin treatment and remains elevated for at least two years

Prescribers should consider this potential risk when contemplating use of high potency statins in clinical practice, particularly when treatment with a low potency statin is an option

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Table

Table 1| Baseline characteristics of patients receiving high potency and low potency statins (1997-2008)

	Patients without chronic kidney disease				Patients with chronic kidney disease			
	Subset with matched propensity score*		Full cohort		Subset with matched propensity score*		Full cohort	
	High potency statins (n=633 054)	Low potency statins (n=633 054)	High potency statins (n=651 069)	Low potency statins (n=1 356 934)	High potency statins (n=20 511)	Low potency statins (n=20 511)	High potency statins (n=22 341)	Low potency statins (n=37 295)
Age (years)								
40-49	53 063 (8.4)	53 043 (8.4)	54 588 (8.4)	98 040 (7.2)	479 (2.3)	477 (2.3)	521 (2.3)	1172 (3.1)
50-59	103 608 (16.4)	102 999 (16.3)	105 892 (16.3)	205 985 (15.2)	1118 (5.4)	1116 (5.4)	1220 (5.5)	2249 (6.0)
60-64	62 598 (9.9)	62 663 (9.9)	63 753 (9.8)	131 137 (9.7)	911 (4.4)	921 (4.5)	994 (4.4)	1813 (4.9)
65-69	133 890 (21.2)	134 037 (21.2)	137 811 (21.2)	287 547 (21.2)	2783 (13.6)	2782 (13.6)	3099 (13.9)	5487 (14.7)
70-74	119 624 (18.9)	120 076 (19.0)	123 221 (18.9)	279 905 (20.6)	3986 (19.4)	3990 (19.5)	4337 (19.4)	7797 (20.9)
75-79	87 110 (13.8)	87 113 (13.8)	89 903 (13.8)	201 711 (14.9)	4493 (21.9)	4472 (21.8)	4820 (21.6)	8189 (22.0)
≥80+	73 161 (11.6)	73 123 (11.6)	75 901 (11.7)	152 609 (11.2)	6741 (32.9)	6753 (32.9)	7350 (32.9)	10 588 (28.4)
Sex								
Women	291 877 (46.1)	291 861 (46.1)	302 883 (46.5)	706 318 (52.1)	8827 (43.0)	8814 (43.0)	9741 (43.6)	17 230 (46.2)
Men	341 177 (53.9)	341 193 (53.9)	348 186 (53.5)	650 616 (47.9)	11 684 (57.0)	11 697 (57.0)	12 600 (56.4)	20 065 (53.8)
Diagnoses								
Hypertensive disease	245 372 (38.8)	239 908 (37.9)	255 282 (39.2)	536 985 (39.6)	13 442 (65.5)	13 029 (63.5)	14 137 (63.3)	22 437 (60.2)
Hypercholesterolemia	170 979 (27.0)	178 730 (28.2)	177 377 (27.2)	438 124 (32.3)	4700 (22.9)	4619 (22.5)	4865 (21.8)	8373 (22.5)
Peripheral vascular disease	15 144 (2.4)	14 250 (2.3)	15 740 (2.4)	33 528 (2.5)	1385 (6.8)	1328 (6.5)	1768 (7.9)	2939 (7.9)
Congestive heart failure	38 036 (6.0)	29 107 (4.6)	40 317 (6.2)	61 699 (4.5)	5938 (28.9)	4834 (23.6)	6984 (31.3)	9073 (24.3)
Diabetes	134 289 (21.2)	139 806 (22.1)	138 702 (21.3)	296 000 (21.8)	7116 (34.7)	7044 (34.3)	7797 (34.9)	13 041 (35.0)
Injury or poisoning	72 122 (11.4)	68 889 (10.9)	76 574 (11.8)	171 879 (12.7)	2807 (13.7)	2489 (12.1)	2875 (12.9)	4242 (11.4)
No of hospitalizations								
None	418 648 (66.1)	453 553 (71.6)	459 485 (70.6)	1 057 112 (77.9)	7559 (36.9)	9512 (46.4)	7950 (35.6)	18 084 (48.5)
1	85 508 (13.5)	71 387 (11.3)	103 286 (15.9)	170 078 (12.5)	6135 (29.9)	5411 (26.4)	6683 (29.9)	9126 (24.5)
2	36 995 (5.8)	27 415 (4.3)	44 882 (6.9)	64 843 (4.8)	3204 (15.6)	2694 (13.1)	3620 (16.2)	4590 (12.3)
≥3	38 481 (6.1)	27 199 (4.3)	43 599 (6.7)	64 867 (4.8)	3613 (17.6)	2896 (14.1)	4087 (18.3)	5496 (14.7)
Drugs								
Prescription acetaminophen	64 042 (10.1)	61 515 (9.7)	65 545 (10.1)	148 468 (10.9)	5070 (24.7)	4784 (23.3)	5268 (23.6)	8420 (22.6)
Prescription NSAID	147 029 (23.2)	144 000 (22.7)	150 810 (23.2)	328 350 (24.2)	4940 (24.1)	4701 (22.9)	5370 (24.0)	8799 (23.6)
ACE inhibitor	236 534 (37.4)	214 661 (33.9)	242 816 (37.3)	436 912 (32.2)	12 013 (58.6)	11 444 (55.8)	12 950 (58.0)	20 602 (55.2)
Angiotensin II receptor blocker	84 527 (13.4)	80 889 (12.8)	88 255 (13.6)	135 863 (10.0)	4996 (24.4)	4958 (24.2)	5622 (25.2)	8036 (21.5)
Thiazide diuretics	110 216 (17.4)	112 030 (17.7)	113 738 (17.5)	240 556 (17.7)	5738 (28.0)	5795 (28.3)	6234 (27.9)	9749 (26.1)
Loop diuretics	53 896 (8.5)	45 664 (7.2)	55 777 (8.6)	102 710 (7.6)	8073 (39.4)	7347 (35.8)	8748 (39.2)	13 712 (36.8)
Potassium sparing diuretics	37 514 (5.9)	35 419 (5.6)	39 717 (6.1)	87 843 (6.5)	2895 (14.1)	2699 (13.2)	3462 (15.5)	5160 (13.8)
β blockers	195 998 (31.0)	164 369 (26.0)	201 952 (31.0)	360 234 (26.5)	11 105 (54.1)	9738 (47.5)	11 912 (53.3)	16 964 (45.5)
Calcium channel blockers	135 197 (21.4)	131 628 (20.8)	138 906 (21.3)	311 416 (22.9)	10 108 (49.3)	10 098 (49.2)	10 814 (48.4)	18 572 (49.8)
Antibiotics	220 881 (34.9)	218 761 (34.6)	227 209 (34.9)	511 004 (37.7)	10 508 (51.2)	10 366 (50.5)	11 390 (51.0)	19 317 (51.8)

Data are no (%) of patients. NSAID=non-steroidal anti-inflammatory drug; ACE=angiotensin-converting-enzyme.

(continued)

	Patients without chronic kidney disease				Patients with chronic kidney disease			
	Subset with matched propensity score*		Full cohort		Subset with matched propensity score*		Full cohort	
	High potency statins (n=633 054)	Low potency statins (n=633 054)	High potency statins (n=651 069)	Low potency statins (n=1 356 934)	High potency statins (n=20 511)	Low potency statins (n=20 511)	High potency statins (n=22 341)	Low potency statins (n=37 295)

*One to one matching was used. Within the same sex and age within one year, each patient using high potency statins was matched to a patient using low potency statin with the nearest propensity score. If multiple controls had the same propensity score, one was chosen at random.

Figures

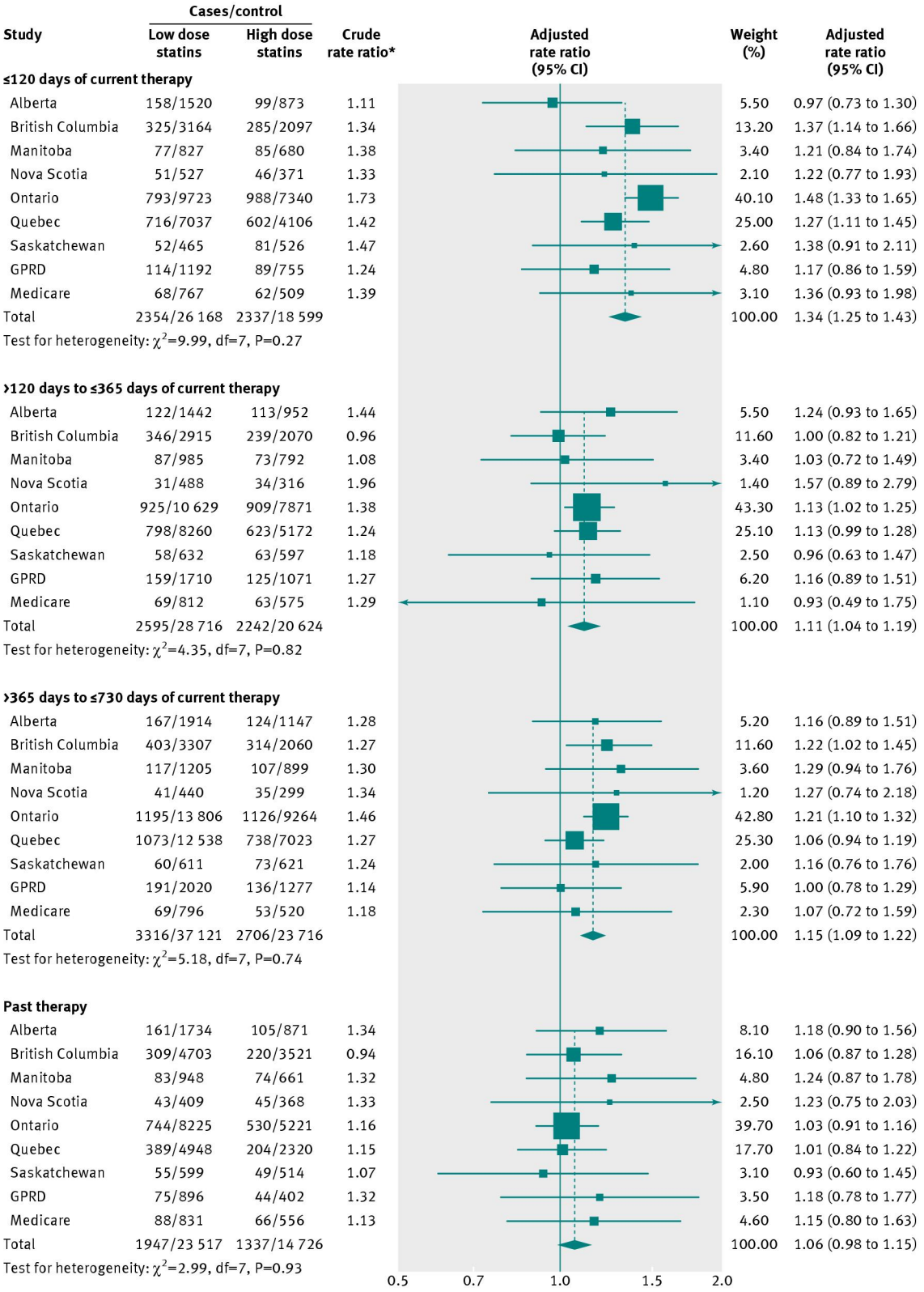

Fig 1 As treated analysis of hospitalization for acute kidney injury up to two years after cohort entry in patients without chronic kidney disease. *Crude rate ratios were obtained from conditional logistic regression, conditioned on the matching variables age, sex, and cohort entry date

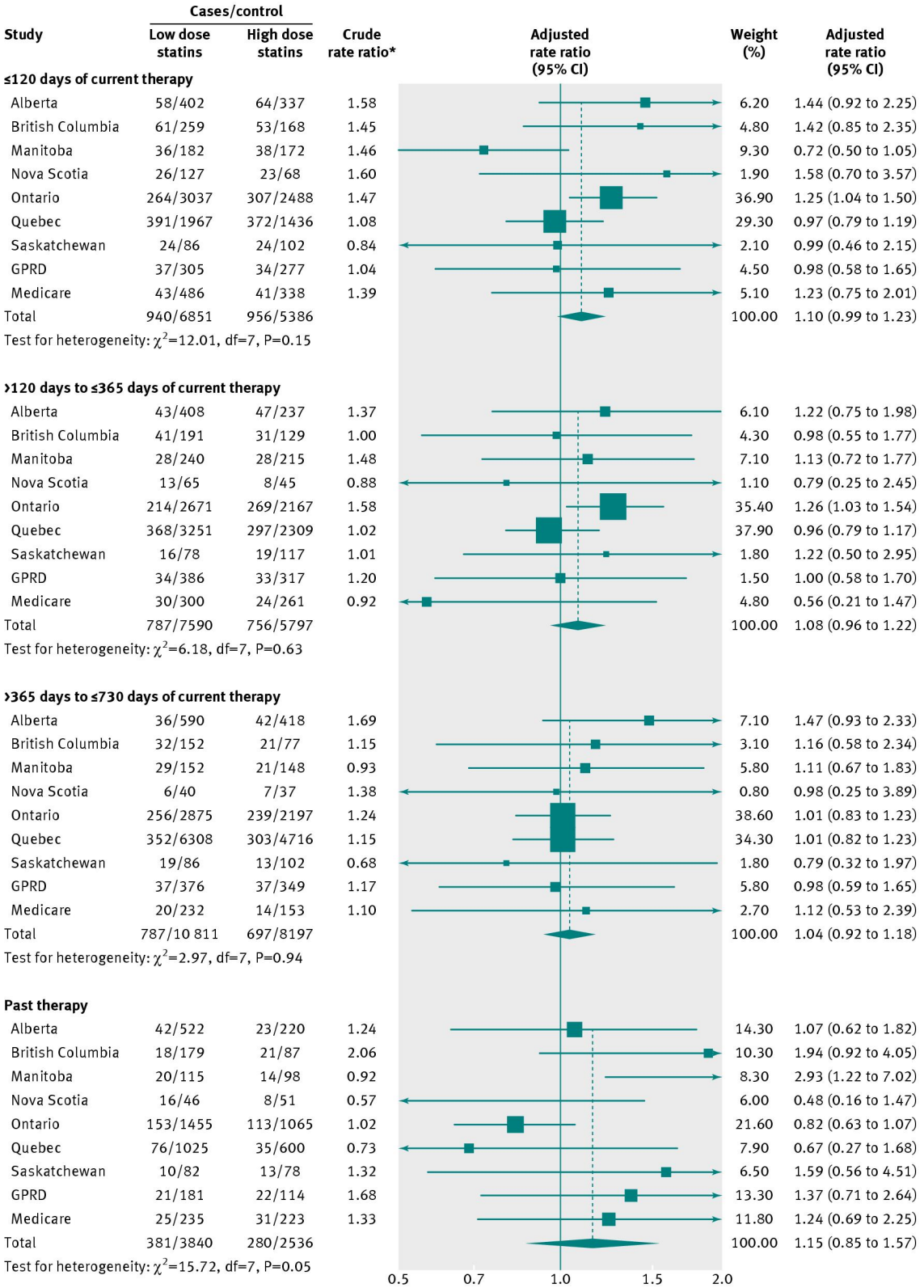

Fig 2 As treated analysis of hospitalization for acute kidney injury up to two years after cohort entry in patients with chronic kidney disease. *Crude rate ratios were obtained from conditional logistic regression, conditioned on the matching variables age, sex, and cohort entry date