Nonsteroidal anti-inflammatory drug use and risk of acute kidney injury and hyperkalemia in older adults: a population-based study

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ABSTRACT

Background. Clinical guidelines caution against nonsteroidal anti-inflammatory drug (NSAID) use in older adults. The study objective was to quantify the 30-day risk of acute kidney injury (AKI) and hyperkalemia in older adults after NSAID initiation and to develop a model to predict these outcomes.

Methods. We conducted a population-based retrospective cohort study in Ontario, Canada from 2007 to 2015 of patients ≥ 66 years. We matched 46 107 new NSAID users with 46 107 nonusers with similar baseline health. The primary outcome was 30-day risk of AKI and secondary outcomes were hyperkalemia and all-cause mortality.

Results. NSAID use versus nonuse was associated with a higher 30-day risk of AKI [380 [0.82%] versus 272 [0.59%]; odds ratio (OR) 1.41 [95% confidence interval (CI) 1.20–1.65] and hyperkalemia [184 (0.40%) versus 123 (0.27%); OR 1.50 (95% CI 1.20–1.89); risk difference 0.23% (95% CI 0.13–0.34)]. There was no association between NSAID use and all-cause mortality. A prediction model incorporated six predictors of AKI or hyperkalemia: older age, male gender, lower baseline estimated glomerular filtration rate, higher baseline serum potassium, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use or diuretic use. This model had moderate discrimination [C-statistic 0.72 (95% CI 0.70–0.74)] and good calibration.

Conclusions. In older adults, new NSAID use compared with nonuse was associated with a higher 30-day risk of AKI and hyperkalemia but not all-cause mortality. Prescription NSAID use among many older adults may be safe, but providers should use caution and assess individual risk.

Keywords: acute kidney injury, hyperkalemia, nonsteroidal anti-inflammatory drugs, prediction model

ADDITIONAL CONTENT

An author video to accompany this article is available at: https://academic.oup.com/ndt/pages/author_videos.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat pain and inflammation. Health Canada along with many clinical guidelines caution against NSAID use in older adults or patients with chronic kidney disease (CKD) due to the risk of adverse events, including acute kidney injury (AKI) ([Supplementary data, Table S1](#)) [1–11]. Over the last decade, 43% of older adults received at least one NSAID prescription in Ontario, Canada ([Supplementary data, Methods 1](#)). Furthermore, from 2006 to 2011, 16% of patients with CKD in Ontario received at least one NSAID prescription for >14 days [12]. While there is evidence from a meta-analysis of case-control studies that NSAID use is associated with a higher risk of AKI [13], studies that have assessed the risk of hyperkalemia have yielded conflicting results ([Supplementary data, Table S2](#)) [14–16]. Therefore we designed this large population-based cohort study to quantify the 30-day risk of AKI and hyperkalemia among older adults in Ontario, Canada who were dispensed a >14 -day supply for NSAIDs compared with older adults without prescription NSAID use. Because of the utility of risk prediction tools for NSAID-induced gastrointestinal complications [17–20], we also sought to develop and internally validate a prediction model to quantify a patient's 30-day risk of developing AKI or hyperkalemia after NSAID initiation based on patient characteristics at the time of prescribing.

MATERIALS AND METHODS

Study design and research setting

Ontario has >13 million residents, 17% of whom are ≥ 65 years of age [21]. Health care services in Ontario are publicly funded, with the exception of outpatient medications, which are only funded for individuals ≥ 65 years of age, and other special populations [22]. These health care encounters are recorded in administrative databases held at the Institute for Clinical Evaluative Sciences (ICES). All databases are linked using unique, encoded identifiers.

We conducted a population-based, retrospective cohort study using healthcare data at ICES. The use of ICES data in this project was authorized under Section 45 of Ontario's Personal Health Information Protection Act, which does not require research ethics board review. We followed reporting guidelines for observational and prediction studies (Supplementary data, Tables S3 and S4) [23, 24].

Data sources

We used the Ontario Drug Benefit database to identify prescriptions for individuals ≥ 65 years of age. This database contains accurate records of all dispensed outpatient prescriptions [25]. We used the Ontario Laboratories Information System database to identify laboratory values and estimated glomerular filtration rates (eGFRs) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [26]. We had no information on race and assumed all patients to be nonblack for the CKD-EPI equation (<5% of the Ontario population is of black race) [27]. We used seven additional linked databases held at ICES to ascertain information on hospitalizations and emergency department visits (Canadian Institute for Health Information's Discharge Abstract Database and National Ambulatory Care Reporting System), physician billings (Ontario Health Insurance Plan database), prescribing physicians (ICES Physician database, Client Agency Program Enrolment), treatment for end-stage kidney disease (the Ontario portion of the Canadian Organ Replacement Register) and demographics (Registered Persons Database).

We used the 10th edition of the Canadian Modified International Classification of Disease system to define comorbidities and the Canadian Classification for Health Interventions to define health care procedures. We also used the Johns Hopkins Aggregated Diagnosis Groups and the Expanded Diagnosis Clusters to assess baseline comorbidity (Johns Hopkins ACG System version 10.0) [28].

Our data sources were complete for all study variables except for NSAID prescriber data (15% missing), rural status (<0.005% missing) and income quintile (<0.5% missing). Emigration from Ontario is very low (0.1%/year) and was the only reason for lost study follow-up [29].

Cohort assembly and exposure categorization

We identified geographical areas across time where residents would likely visit a hospital with linked laboratory data (referred to as the laboratory catchment area). We included Ontarians who resided within this catchment area between 1 April 2007 and 30 September 2015. In the exposed group, we

identified patients with an NSAID prescription filled between 1 April 2007 and 31 August 2015 with a >14-day supply. For patients with multiple eligible NSAID prescriptions after exclusions, we restricted use to the first one. See [Supplementary data, Table S5](#) for a list of eligible drug names. The date of NSAID dispensing was referred to as the index date, also called the cohort entry date. For patients in our comparison group without an NSAID prescription, we randomly assigned an index date based on the distribution of index dates in the NSAID user group.

We excluded the following patients: (i) those in their first year of provincial drug coverage (between 65 and 66 years of age) to avoid incomplete medication history; (ii) those with an NSAID prescription in the prior 6 months to ensure new users only; (iii) those discharged from a hospital in the 2 days prior to the index date, to ensure new outpatient prescriptions since patients who initiate treatment in the hospital fill ongoing prescriptions on the hospital discharge date or the day after; (iv) those without at least one outpatient value for both serum creatinine and serum potassium in the prior year, to assess baseline kidney function and potassium levels; (v) those with baseline serum potassium values >5.5 mEq/L (5.5 mmol/L) or potassium binder prescriptions in the past 6 months; (vi) those with a baseline eGFR >150 mL/min/1.73 m², which was likely a data error; (vii) those not in the laboratory catchment area on their index date, to reliably assess laboratory results in follow-up; and (viii) patients with end-stage kidney disease as an outcome of AKI. For patients in the nonuser group, we excluded anyone without at least one health care encounter in our physician claims or drug benefit databases in the past 30 days, to ensure that patients were accessing the Ontario health care system.

Outcomes

Our primary outcome was AKI, defined by the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) thresholds: compared with baseline, a serum creatinine increase $\geq 50\%$ or an absolute increase of at least 0.3 mg/dL (26.5 μ mol/L) [30]. We selected an outpatient serum creatinine value within the past year that was closest to the index date. We compared this baseline value to the highest serum creatinine value in the following 30 days, whether the measurement was done in the community, emergency department or during a hospitalization. In additional analyses, we assessed more severe AKI, defined according to KDIGO staging thresholds (Supplementary data, Table S6) [30]. We assessed all outcomes in the 30 days following the index date since AKI onset generally occurs within 2 weeks of NSAID initiation [31].

Our secondary outcomes were hyperkalemia, all-cause mortality and a composite of AKI or hyperkalemia. We defined hyperkalemia as a serum potassium value in an outpatient, emergency department or inpatient setting that was ≥ 5.5 mEq/L. In additional analyses, we assessed outcomes of more severe hyperkalemia, defined as values of 6.0 and ≥ 6.5 mEq/L.

Statistical analyses

We conducted all analyses using SAS version 9.4 (SAS Institute, Cary, NC, USA). We compared baseline

characteristics between NSAID users and nonusers using standardized mean differences, where a difference $\geq 10\%$ was considered significant [32]. We calculated a propensity score for the probability of receiving an NSAID prescription using a multivariable logistic regression model that incorporated >150 baseline characteristics (including indications for NSAID use and risk factors for AKI and hyperkalemia; [Supplementary data, Table S7](#)). We matched NSAID users to nonusers 1:1 using greedy matching without replacement [33]. Matching criteria included eGFR (± 5 mL/min/1.73 m²), serum potassium (± 0.5 mEq/L), angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) use, diuretic use [categorized as (i) potassium sparing or (ii) loop or thiazide] and the logit of the propensity score (± 0.2 standard deviation).

We performed conditional logistic regression analyses to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Given the low incidences observed, we approximated all ORs as relative risks. We estimated the risk difference between the groups and the number needed to harm [34]. This latter measure indicates how many patients need to receive an NSAID prescription for one patient to have an adverse event who would not have experienced this event in the absence of an NSAID prescription. For AKI, we performed subgroup analyses on baseline eGFR, ACEi/ARB use, diuretic use and NSAID dose measured as the percentage of the maximum daily dose (for this subgroup, nonusers followed their matched users). For hyperkalemia, we performed the same subgroup analyses with the addition of baseline serum potassium. We performed an additional analysis for the primary AKI outcome where we restricted the analysis to patients who received at least one serum creatinine test within the 30-day follow-up. We did not account for matching in this additional analysis since the matched pairs were separated. We interpreted two-tailed P-values <0.05 as statistically significant in all analyses.

We developed a prediction model of 30-day AKI or hyperkalemia risk among all NSAID users and followed relevant reporting guidelines ([Supplementary data, Table S4](#)) [24]. For the potential predictors, we identified the following variables *a priori* that are easily ascertained in practice and were associated with a higher risk of AKI or hyperkalemia in the literature: older age [35–37], female sex [36, 38], lower baseline eGFR [35, 36, 38], higher baseline serum potassium concentration [39], higher NSAID dose [40, 41], ACEi/ARB use [35, 42] and use of loop, potassium-sparing or thiazide-type diuretics [35, 37, 42]. We kept continuous variables continuous and assumed that their relationship with the outcome was linear.

We performed stepwise multivariable logistic regression using a $P < 0.05$ threshold to retain variables. We assessed model discrimination using the C-statistic, which describes the ability of our model to assign higher predicted risks to those with the outcome versus those without [43]. We assessed model calibration by plotting the predicted probabilities versus the observed risk of the outcome using locally weighted scatterplot smoothing [44]. We validated the model internally using 200 bootstrap samples selected with replacement from the NSAID users [45]. We repeated stepwise logistic regression for each of these 200 samples and used Harrell's optimism for the C-statistic to estimate how the model might perform in new data [45]. Finally, we created an online calculator for ease of use.

RESULTS

See [Figure 1](#) for cohort assembly. We identified 9 131 660 individuals in the laboratory catchment area, where 428 825 received at least one NSAID prescription for >14 days. After exclusions, we had 61 219 NSAID users and 156 589 nonusers. We matched 46 107 NSAID users to 46 107 nonusers and matched pairs were similar across >150 baseline characteristics (see [Table 1](#) for select baseline characteristics and [Supplementary data, Table S7](#) for full baseline table). The mean age was 74 years and 58% were women.

Primary outcome: AKI

NSAID use was associated with a higher 30-day risk of AKI: 380 (0.82%) versus 272 (0.59%) events, respectively; OR 1.41 (95% CI 1.20–1.65); risk difference 0.23% (95% CI 0.13–0.34%). This association was consistent across AKI stages ([Table 2](#)). Baseline eGFR, ACEi or ARB use, diuretic use and NSAID dose did not significantly modify the association between NSAID use and AKI ([Figure 2](#)).

Secondary outcomes: hyperkalemia and all-cause mortality

NSAID use was associated with a higher 30-day risk of hyperkalemia: 184 (0.40%) versus 123 (0.27%) events, respectively [OR 1.50 (95% CI 1.20–1.89)]. We did not observe a statistically significant association between NSAID use and higher thresholds of hyperkalemia (serum potassium ≥ 6.0 or ≥ 6.5 mEq/L); there were few events and estimates were imprecise ([Table 2](#)). Baseline serum potassium, eGFR, ACEi or ARB use, diuretic use and NSAID dose did not significantly modify the association between NSAID use and hyperkalemia ([Supplementary data, Figure S1](#)).

NSAID use was associated with a higher 30-day risk of AKI or hyperkalemia: 510 (1.11%) versus 370 (0.80%) events, respectively [OR 1.39 (95% CI 1.21–1.59)]. NSAID use versus nonuse was not significantly associated with all-cause mortality: 66 (0.14%) versus 79 (0.17%) events, respectively [OR 0.83 (95% CI 0.60–1.16)].

Additional analysis

Over a 30-day follow-up, 16% (15 030) and 14% (12 519) of patients had at least one serum creatinine and serum potassium test completed, respectively. Among those with a follow-up serum creatinine test, 17% (7804) were NSAID users and 16% (7226) were nonusers. We found similar risk estimates when we looked at the association between NSAID use and AKI only among the 15 030 people with follow-up serum creatinine tests ([Table 2](#)).

Prediction model

Among 61 219 NSAID users, 701 (1.15%) developed AKI or hyperkalemia in the 30 days following prescription. Our model included six predictors of AKI or hyperkalemia: older age, male gender, lower baseline eGFR, higher baseline serum potassium, ACEi or ARB prescription and diuretic prescription ([Supplementary data, Table S8](#)).

FIGURE 1: Cohort assembly for patients in the NSAID user group and the matched nonuser group. Exclusions 11 and 12 were only applied to the nonuser group. N/A, not applicable.

Predicted risk ranged from 0.05 to 22.6% (see [Supplementary data, Table S9](#) for distribution). The optimism-adjusted C-statistic was 0.72 (95% CI 0.70–0.74), indicating moderate discrimination ([Supplementary data, Figure S2](#)) and the model had good calibration ([Figure 3](#)). [Supplementary data, Table S10](#) demonstrates the clinical utility of the model to identify high-risk patients based on predicted risk thresholds >1 , >5 and $>10\%$. The sensitivity ranged from 2.6 to 67.8% and the specificity from 64.1 to 99.8%. This model is available as an online calculator: <https://qxmd.com/calculate-by-qxmd>.

DISCUSSION

In this large population-based cohort study of older adults, we found that receiving a new NSAID prescription (with a supply

>14 days) was associated with a higher 30-day risk of AKI and hyperkalemia compared with no prescription NSAID use. However, absolute 30-day risks of AKI and hyperkalemia after NSAID initiation were low ($<1\%$). Since only 15% of people received serum creatinine and potassium tests within a 30-day follow-up, the true incidence of AKI and hyperkalemia in this population is likely higher. We also found that NSAID users did not have a higher risk of 30-day mortality. This was likely because the majority of the adverse outcomes were mild: 79% of AKI events were stage 1 and 63% of people with hyperkalemia had serum potassium values from 5.5 to 6 mEq/L. Therefore, prescription NSAID use may be safe for many older adults, but given the higher relative risk, providers should still use caution and assess individual risk when considering NSAID prescriptions for older adults.

Table 1. Select baseline characteristics of the cohort before and after matching

Variable	Baselines before matching			Baselines after matching		
	NSAID users (<i>n</i> = 61 219)	Nonusers (<i>n</i> = 156 589)	Standard difference (%)	NSAID users (<i>n</i> = 46 107)	Nonusers (<i>n</i> = 46 107)	Standard difference (%)
Demographics						
Age (years), mean (SD)	74.1 (6.4)	76.0 (8.1)	27	74.2 (6.5)	74.2 (7.1)	1
Female sex, <i>n</i> (%)	36 016 (58.8)	84 355 (53.9)	10	26 654 (57.8)	26 552 (57.6)	0
Rural status, <i>n</i> (%) ^a	3489 (5.7)	8431 (5.4)	1	2298 (5.0)	2334 (5.1)	0
Income quintile, <i>n</i> (%) ^b						
1 (lowest)	11 523 (18.8)	26 116 (16.7)	5	8337 (18.1)	8234 (17.9)	1
2	12 365 (20.2)	29 469 (18.8)	4	9215 (20.0)	9055 (19.6)	1
3	12 823 (20.9)	31 049 (19.8)	3	9510 (20.6)	9457 (20.5)	0
4	12 653 (20.7)	33 721 (21.5)	2	9622 (20.9)	9680 (21.0)	0
5 (highest)	11 855 (19.4)	36 234 (23.1)	9	9423 (20.4)	9681 (21.0)	1
Index prescription information						
Index NSAID is a COX2 inhibitor, <i>n</i> (%)	30 741 (50.2)			23 208 (50.3)		
Percentage of maximum daily dosage, mean (SD)	61.9 (28.3)			61.5 (28.2)		
Prescribing physician characteristics						
Age (years), mean (SD)	55.6 (11.3)			55.8 (11.3)		
Missing, <i>n</i> (%)	3256 (5.3)			2395 (5.2)		
Female sex, <i>n</i> (%)	15 972 (26.1)			12 019 (26.1)		
Missing, <i>n</i> (%)	2620 (4.3)			1862 (4.0)		
Rural status, <i>n</i> (%)	2719 (4.4)			1778 (3.9)		
Missing, <i>n</i> (%)	2574 (4.2)			1827 (4.0)		
Medical specialty, <i>n</i> (%)						
Primary care	52 772 (86.2)			40 040 (86.8)		
Nephrologist	54 (0.1)			38 (0.1)		
Cardiologist	127 (0.2)			107 (0.2)		
Other	5694 (9.3)			4097 (8.9)		
Missing	2572 (4.2)			1825 (4.0)		
Health care visits in prior year, <i>n</i>						
Hospitalizations, mean (SD)	0.2 (0.5)	0.2 (0.6)	11	0.1 (0.5)	0.1 (0.5)	0
Emergency department, mean (SD)	0.5 (1.2)	0.5 (1.1)	3	0.5 (1.2)	0.5 (1.1)	1
Family physician, mean (SD)	9.2 (7.4)	8.9 (9.4)	4	8.8 (7.2)	8.7 (8.0)	2
Nephrologist, mean (SD)	0.1 (0.6)	0.2 (1.0)	15	0.1 (0.6)	0.1 (0.5)	0
Comorbidity in past 5 years, <i>n</i> (%)						
Charlson comorbidity score						
0 or no hospitalization	46 909 (76.6)	104 469 (66.7)	22	35 055 (76.0)	34 918 (75.7)	1
1	6668 (10.9)	19 989 (12.8)	6	5017 (10.9)	5089 (11.0)	0
2	4426 (7.2)	15 417 (9.8)	9	3442 (7.5)	3493 (7.6)	0
≥3	3216 (5.3)	16 714 (10.7)	20	2593 (5.6)	2607 (5.7)	0
John Hopkins ADG score, mean (SD)	12.4 (4.0)	11.6 (4.2)	18	12.1 (4.0)	12.1 (4.0)	1
Ischemic heart disease	15 950 (26.1)	49 501 (31.6)	12	12 150 (26.4)	12 265 (26.6)	0
Congestive heart failure	4105 (6.7)	21 268 (13.6)	23	3178 (6.9)	3269 (7.1)	1
Ventricular arrhythmia	91 (0.1)	791 (0.5)	7	71 (0.2)	76 (0.2)	0
Myocardial infarction	2119 (3.5)	8828 (5.6)	10	1634 (3.5)	1686 (3.7)	1
Peripheral vascular disease	2320 (3.8)	7572 (4.8)	5	1752 (3.8)	1736 (3.8)	0
Atrial fibrillation	1548 (2.5)	12 489 (8.0)	25	1277 (2.8)	1407 (3.1)	2
Coronary artery bypass graft	570 (0.9)	2 301 (1.5)	6	450 (1.0)	479 (1.0)	0
Percutaneous coronary intervention	1360 (2.2)	4957 (3.2)	6	1091 (2.4)	1093 (2.4)	0
Diabetes	22 177 (36.2)	57 397 (36.7)	1	16 653 (36.1)	16 610 (36.0)	0
Hypertension	46 410 (75.8)	116 542 (74.4)	3	34 526 (74.9)	34 391 (74.6)	1
Chronic liver disease	642 (1.0)	2455 (1.6)	5	509 (1.1)	519 (1.1)	0
Chronic lung disease	14 709 (24.0)	34 723 (22.2)	4	10 473 (22.7)	10 403 (22.6)	0
Malignancy	7407 (12.1)	21 501 (13.7)	5	5669 (12.3)	5657 (12.3)	0
Osteoporosis	10 193 (16.7)	23 428 (15.0)	5	7570 (16.4)	7519 (16.3)	0
Joint disease	34 669 (56.6)	44 363 (28.3)	60	23 064 (50.0)	22 681 (49.2)	2
Joint disorder	7378 (12.1)	9779 (6.2)	21	4706 (10.2)	4572 (9.9)	1
Bursitis	18 345 (30.0)	23 268 (14.9)	37	11 902 (25.8)	11 626 (25.2)	1
Fibromyalgia	4417 (7.2)	5305 (3.4)	17	2686 (5.8)	2514 (5.5)	1
Fracture	7630 (12.5)	20 413 (13.0)	1	5634 (12.2)	5558 (12.1)	0
Hip fracture	531 (0.9)	3297 (2.1)	10	436 (0.9)	454 (1.0)	1

Continued

Table 1. Continued

Variable	Baselines before matching			Baselines after matching		
	NSAID users (n = 61 219)	Nonusers (n = 156 589)	Standard difference (%)	NSAID users (n = 46 107)	Nonusers (n = 46 107)	Standard difference (%)
Back pain	30 486 (49.8)	41 164 (26.3)	50	20 383 (44.2)	20 051 (43.5)	1
Back surgery	790 (1.3)	836 (0.5)	8	454 (1.0)	428 (0.9)	1
Knee surgery	3829 (6.3)	3755 (2.4)	19	2221 (4.8)	2130 (4.6)	1
Hip surgery	1612 (2.6)	2604 (1.7)	6	1091 (2.4)	1091 (2.4)	0
Cerebrovascular disease	4783 (7.8)	20 211 (12.9)	17	3765 (8.2)	3778 (8.2)	0
Dementia	3729 (6.1)	24 123 (15.4)	30	3142 (6.8)	3106 (6.7)	0
Migraine	2649 (4.3)	4491 (2.9)	8	1801 (3.9)	1804 (3.9)	0
Gout	4985 (8.1)	4581 (2.9)	23	2804 (6.1)	2426 (5.3)	3
Rheumatoid arthritis	3994 (6.5)	4517 (2.9)	17	2436 (5.3)	2320 (5.0)	1
Osteoarthritis	7031 (11.5)	7861 (5.0)	24	4 245 (9.2)	4163 (9.0)	1
Sciatica	21 449 (35.0)	26 131 (16.7)	43	13 872 (30.1)	13 479 (29.2)	2
Pain	32 285 (52.7)	54 717 (34.9)	36	22 548 (48.9)	22 434 (48.7)	0
Schizophrenia	704 (1.1)	3766 (2.4)	10	576 (1.2)	580 (1.3)	1
Depression	5161 (8.4)	13 267 (8.5)	0	3729 (8.1)	3766 (8.2)	0
Health care procedures in prior year, n (%)						
Carotid ultrasound	2812 (4.6)	8492 (5.4)	4	2179 (4.7)	2230 (4.8)	0
Coronary angiogram	1005 (1.6)	3557 (2.3)	5	785 (1.7)	797 (1.7)	0
Coronary revascularization	415 (0.7)	1731 (1.1)	4	344 (0.7)	359 (0.8)	1
Echocardiogram	12 466 (20.4)	37 234 (23.8)	8	9526 (20.7)	9649 (20.9)	0
Holter test	4684 (7.7)	14 820 (9.5)	6	3616 (7.8)	3675 (8.0)	1
Stress test	8472 (13.8)	19 822 (12.7)	3	6223 (13.5)	6213 (13.5)	0
Cardiac catheterization	1032 (1.7)	3 699 (2.4)	5	807 (1.8)	819 (1.8)	0
Back X-ray	29 048 (47.4)	44 677 (28.5)	40	19 685 (42.7)	19 347 (42.0)	1
At least one albumin:creatinine ratio test	35 803 (58.5)	79 468 (50.7)	16	26 481 (57.4)	26 330 (57.1)	1
Laboratory tests in prior year						
Time from baseline serum creatinine to index date (days), median (IQR)	94 (33–192)	88 (34–179)		94 (32–193)	95 (37–187)	
Baseline serum creatinine value (mg/dL), mean (SD)	0.9 (0.3)	1.0 (0.4)	27	0.9 (0.3)	0.9 (0.3)	0
Baseline eGFR value (mL/min/1.73 m ²), mean (SD)	73.0 (16.0)	69.1 (18.6)	23	73.0 (16.0)	73.0 (16.0)	0
Baseline potassium value (mEq/L), mean (SD)	4.4 (0.4)	4.4 (0.4)	2	4.4 (0.4)	4.4 (0.4)	0
Prescriptions in prior 120 days, n (%)						
Aspirin	1549 (2.5)	2532 (1.6)	6	1018 (2.2)	959 (2.1)	1
Tylenol	2939 (4.8)	2879 (1.8)	17	1664 (3.6)	1473 (3.2)	2
Opiates	12 499 (20.4)	15 521 (9.9)	30	7697 (16.7)	7166 (15.5)	3
ACEi	15 898 (26.0)	48 917 (31.2)	12	12 190 (26.4)	12 190 (26.4)	0
ARB	16 618 (27.1)	37 556 (24.0)	7	12 139 (26.3)	12 139 (26.3)	0
Statin	32 296 (52.8)	84 994 (54.3)	3	24 343 (52.8)	24 269 (52.6)	0
Diabetes drug	13 159 (21.5)	37 247 (23.8)	5	10 097 (21.9)	10 087 (21.9)	0
Calcium channel blocker	16 386 (26.8)	45 357 (29.0)	5	12 400 (26.9)	12 244 (26.6)	1
β-blocker	14 136 (23.1)	48 987 (31.3)	19	10 921 (23.7)	11 045 (24.0)	1
Proton pump inhibitor	24 196 (39.5)	40 148 (25.6)	30	16 246 (35.2)	15 737 (34.1)	2
Thiazide diuretic	8871 (14.5)	22 768 (14.5)	0	6461 (14.0)	6466 (14.0)	0
Loop diuretic	3137 (5.1)	16 247 (10.4)	20	2270 (4.9)	2213 (4.8)	0
Potassium-sparing diuretic	1877 (3.1)	6000 (3.8)	4	1251 (2.7)	1230 (2.7)	0

SI conversion factors: to convert serum creatinine from mg/dL to μmol/L, multiply by 88.4; to convert serum potassium from mEq/L to mmol/L, multiply by 1.0.

^aMissing rural status was categorized as not rural.

^bMissing income quintile was imputed into the third quintile.

ADG, aggregated diagnostic group; IQR, interquartile range.

A systematic review and meta-analysis by Zhang *et al.* [13], examining 1.6 million people from 10 case-control studies, showed that NSAID use versus nonuse was associated with 70% greater odds of developing AKI [13]. Similarly, we found a 40% greater relative risk of AKI with NSAID use compared with nonuse. A recent population-based retrospective cohort study from Ontario, Canada of older patients with CKD, congestive

heart failure or hypertension found a new NSAID prescription compared with no such prescription was not associated with a higher risk of hospitalization with AKI, hospitalization with hyperkalemia or death within 30 days of prescription date [46]. However, these authors used diagnosis codes to define hospitalization with AKI and hyperkalemia, which are known to have low sensitivity compared with laboratory data [47, 48].

Table 2. 30-day primary and secondary outcomes of prescription NSAID users compared with nonusers

Outcome	NSAID users, number of events (%) (n = 46 107)	Nonusers, number of events (%) (n = 46 107)	OR (95% CI)	Risk difference (95% CI)	Number needed to harm (95% CI)
AKI ^{a,b}	380 (0.82)	272 (0.59)	1.41 (1.20–1.65)	0.23 (0.13–0.34)	427 (292–787)
AKI Stage 2 or more ^c	60 (0.13)	40 (0.09)	1.50 (1.01–2.24)	0.04 (0.00–0.09)	2305 (1164–114 916)
AKI Stage 3 ^d	25 (0.05)	12 (0.03)	2.08 (1.05–4.15)	0.03 (0.002–0.05)	3547 (1848–43 478)
Hyperkalemia ^e (≥5.5 mEq/L)	184 (0.40)	123 (0.27)	1.50 (1.20–1.89)	0.13 (0.06–0.2)	756 (485–1715)
Hyperkalemia (≥6.0 mEq/L)	38 (0.08)	30 (0.07)	1.27 (0.79–2.04)	0.02 (–0.02–0.05)	N/A
Hyperkalemia (≥6.5 mEq/L)	16 (0.03)	30 (0.02)	2.29 (0.94–5.56)	0.02 (0.00–0.04)	N/A
Composite of AKI ^a or hyperkalemia (≥5.5 mEq/L)	510 (1.11)	370 (0.80)	1.39 (1.21–1.59)	0.30 (0.18–0.43)	329 (234–558)
All-cause mortality	66 (0.14)	79 (0.17)	0.83 (0.60–1.16)	–0.03 (–0.08–0.02)	N/A
AKI additional analysis ^{a,f}	380 (4.87)	272 (3.76)	1.31 (1.12–1.53)	1.11 (0.46–1.75)	90 (57–217)

SI conversion factor: to convert serum potassium from mEq/L to mmol/L, multiply by 1.0.

^aThe primary definition of AKI was a serum creatinine increase ≥50% or an absolute increase of at least 0.3 mg/dL (26.5 μmol/L) compared with baseline.

^bAmong all patients with an AKI event, 37% were in the hospital at the time of the serum creatinine test (241/652 patients); 87% of these patients in the hospital had the laboratory test done within the first 3 days of hospital admission (209/241 patients).

^cA serum creatinine increase of 100% but <200% from baseline.

^dA serum creatinine increase of at least 200% from baseline, an absolute value of 4.0 mg/dL (353.6 μmol/L) or receipt of acute dialysis.

^eAmong all patients with a hyperkalemia event, 23% were in the hospital at the time of the potassium test (71/307 patients); 76% of these patients in the hospital had the laboratory test done on the day of or after the admission date (54/71 patients).

^fAnalysis performed among 15 030 people with 30-day follow-up serum creatinine tests (7804 NSAID users and 7226 nonusers).

N/A, not applicable.

FIGURE 2: Subgroup analyses for the outcome of AKI from prescription NSAID use. N/A, not applicable. ^aWe defined the percentage of maximum NSAID daily dose by the NSAID group, with the nonuser group following their matched NSAID user.

The association between NSAID use and hyperkalemia is less consistent in the literature. Two large case-control studies comparing NSAID use versus no use found opposing results [14, 16]. Our large population-based cohort study helps remove some of the uncertainty of hyperkalemia risk, as we found that NSAID use was associated with a 50% increased risk of developing hyperkalemia.

Clinical guidelines recommend that patients with CKD avoid NSAIDs [2–6]. In our study, baseline eGFR did not

significantly modify the relative association between NSAID use and AKI risk. Consistent with our findings, Zhang *et al.* [13] also found that patients with CKD had a similar relative risk of AKI with NSAID use compared with the general population. However, patients with lower baseline eGFR have the highest absolute increase in AKI risk with NSAID use.

We developed a prediction model that may be useful to discriminate between people at low versus high risk of AKI or

FIGURE 3: Calibration plot of predicted probabilities versus observed events of AKI or hyperkalemia among patients in the NSAID user group.

hyperkalemia if they initiated NSAID treatment. Our model predicted patients' risk of experiencing AKI or hyperkalemia within 30 days of NSAID initiation with acceptable accuracy. Using a predicted risk threshold of $>5\%$, we showed that our model had high specificity, which means we can be confident that people with a predicted risk $>5\%$ are truly at high risk. Using our model, clinicians can identify high-risk patients who should either receive serum creatinine and potassium monitoring after initiating NSAIDs or should avoid taking NSAIDs altogether. Our calibration plot shows that it may slightly underestimate risk for individuals at higher levels of risk. This model should be externally validated in other datasets and populations before it is used in practice.

Study strengths and limitations

We completed a large population-based study to assess the association of an uncommon, yet important complication of NSAID use among older adults. This is the first study to use a cohort design with laboratory data to quantify the absolute risk of AKI and hyperkalemia with NSAID use. This is also the first study to develop a prediction model to estimate patients' risk of developing these outcomes after NSAID prescription. Given the observational study design, we cannot infer causality. Comparing NSAID users to nonusers (rather than people prescribed other drugs) may have introduced some confounding by indication bias. Although we cannot completely eliminate residual confounding, we attempted to reduce it by using propensity scores to balance patients on >150 baseline characteristics.

We used laboratory data to ascertain AKI and hyperkalemia events because these events are underrepresented in administrative databases [47, 48]. This also allowed us to examine associations among subgroups with varying baseline risk of our outcomes, as everyone required a baseline serum creatinine and potassium value. However, we only captured patients who received laboratory tests as part of routine care ($\sim 15\%$ of cohort). There may have been a tendency for NSAID users to receive

testing compared with nonusers (17% versus 16%); however, we do not expect this small difference to bias our results since there was a similar association between NSAID use and AKI in the additional analysis restricted to patients with follow-up serum creatinine testing.

Another limitation is that we only had data on NSAID prescriptions and are unaware of over-the-counter NSAID use. However, researchers have shown that not accounting for over-the-counter medications likely contributes only a small amount of bias [49]. Another limitation is that we could only identify prescriptions dispensed by a pharmacy, but we do not know if patients were taking their medications. Similarly, patients may take NSAIDs on an as-needed basis rather than daily. Both these limitations—the possibility of the nonuser group taking over-the-counter NSAIDs and the NSAID users not taking their medication as prescribed—would likely attenuate the estimated effect of NSAID use on AKI and hyperkalemia.

We only included patients >66 years of age, but our findings were consistent with other studies that included adults of all ages [14, 16].

CONCLUSIONS

In summary, we found that older adults prescribed NSAIDs for >14 days are at greater risk for AKI and hyperkalemia in the following 30 days compared with similar patients not prescribed NSAIDs; however, this did not translate into an increased short-term mortality risk. Therefore, prescription NSAID use among many older adults may be safe, but providers should still use caution and assess individual patient risk.

SUPPLEMENTARY DATA

Supplementary data are available at [ndt online](#).

FUNDING

This study was supported by the ICES Western site. ICES is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). Core funding for ICES Western is provided by the Academic Medical Organization of Southwestern Ontario (AMOSO), the Schulich School of Medicine and Dentistry (SSMD), Western University and the Lawson Health Research Institute (LHRI). This research was conducted by members of the ICES Kidney, Dialysis and Transplantation team at the ICES Western facility, who are supported by a grant from the Canadian Institutes of Health Research (CIHR). Parts of this material are based on data and/or information compiled and provided by the Canadian Institute for Health Information (CIHI). The opinions, results and conclusions are those of the authors and are independent from the funding and data sources. No endorsement by the ICES, AMOSO, SSMD, LHRI, CIHR, CIHI or MOHLTC is intended or should be inferred. D.M.N.'s training is supported by a CIHR Doctoral Scholarship. A.X.G. was supported by the Dr Adam Linton Chair in Kidney Health Analytics and a Clinician Investigator Award from the CIHR. This research was undertaken, in part, thanks to funding from the Canada Research Chairs program for M.M.-R.

AUTHORS' CONTRIBUTIONS

D.M.N. and A.X.G. developed the initial study and analysis plan. K.S.B., M.M.-R., E.M., J.C.F., P.S.R. and M.A.W. provided input and approved the study and analysis plan. D.M.N. completed all data programming and statistical analyses. All authors helped with interpretation of the results. P.S.R. created the online calculator. D.M.N. drafted the initial manuscript with oversight by A.X.G. and all other authors critically reviewed and revised the manuscript. All authors reviewed and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Novick and Grams. Safely treating pain in older adults. *Nephrol Dial Transplant* 2019; 34: 1075–1077)

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Received: 5.11.2018; Editorial decision: 7.3.2019

Nephrol Dial Transplant (2019) 34: 1154–1162

doi: 10.1093/ndt/gfy119

Advance Access publication 22 May 2018

Proteinuria-associated renal magnesium wasting leads to hypomagnesemia: a common electrolyte abnormality in chronic kidney disease

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ABSTRACT

Background. Hypomagnesemia (Hypo-Mg) predicts mortality and chronic kidney disease (CKD) progression. However, in CKD, its prevalence, kidney-intrinsic risk factors, and the

effectiveness of oral magnesium (Mg) therapy on serum Mg levels is uncertain.

Methods. In a cross-sectional study enrolling pre-dialysis outpatients with CKD, the prevalence of electrolyte abnormalities (Mg,