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Population-Based Analysis of Nonsteroidal Anti-inflammatory Drug Prescription in Subjects With Chronic Kidney Disease

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Abstract

Background: Pain is a prevalent symptom experienced by patients with chronic kidney disease (CKD) and appropriate management of pain is an important element of comprehensive care. Nonsteroidal anti-inflammatory drugs (NSAID) are known to be nephrotoxic in persons with CKD.

Objective: This study examined the pattern of NSAID prescribing practices in a population based-cohort of patients with CKD.

Design: Retrospective cohort study using linked population-based health care data.

Setting: Entire province of Alberta, Canada.

Participants: All adults in Alberta with eGFR defined CKD G3 or greater between 2009 and 2017 were included.

Measurements: CKD was defined using at least 2 outpatient serum creatinine (SCr) greater than 90 days apart; the date of second SCr measurement was used as index date. We determined the incidence of hyperkalemia using the peak serum potassium. Prescription drug information was obtained from the Pharmaceutical Information Network (PIN) database.

Methods: All patients were followed from the index date until March 31, 2019, with a minimum follow-up of 2 years. Prescription drug information and the follow-up laboratory testing of serum creatinine and serum potassium were obtained. Patients with kidney failure defined as eGFR $<$ 15 mL/min per 1.73 m^2, receiving chronic dialysis, or prior kidney transplant at baseline were excluded.

Results: A total of 170 574 adults (mean age 76.3; 44% male) with CKD were identified and followed for a median of 7 years; 27% were dispensed at least 1 NSAID prescription. While there was a trend toward fewer prescriptions in patients with more advanced CKD ($P < .001$), 16% of those with CKD G4 were prescribed an NSAID. Primary care providers provided 79% of the prescriptions. Among NSAID users, 21% had a follow-up serum creatinine (SCr) within 30 days of the index prescription.

Limitations: Data collected were from clinical and administrative databases not created for research purposes. The study cohort is limited to subjects who sought medical care and had a serum creatinine measurement obtained. Measurement of NSAID use is limited to those who were dispensed a prescription, over-the-counter NSAIDs use is not captured.

Conclusions: Despite guidelines advocating cautious use of NSAIDs in patients with CKD, this study indicates that there is a discrepancy from best practice recommendations. Effective strategies to better support and educate prescribers, as well as patients, may help reduce inappropriate prescribing and adverse events.

Abrégé

Contexte: La douleur est un symptôme fréquent chez les patients atteints d'insuffisance rénale chronique (IRC); sa prise en charge appropriée est un élément important des soins complets. Les anti-inflammatoires non stéroïdiens (AINS) sont connus pour être néphrotoxiques dans cette population de patients.

Objectif: Cette étude a examiné les tendances de prescription d'AINS dans une cohorte de patients atteints d'IRC.

Conception: Étude de cohorte rétrospective menée à partir des données couplées de santé de la population étudiée.

Cadre: L'ensemble de la province de l'Alberta (Canada).

Sujets: Tous les adultes de l'Alberta dont la mesure du DFGe correspondait à une IRC de stade 3 ou plus entre 2009 et 2017.

Mesures: L'IRC a été définie par au moins deux mesures espacées de plus de 90 jours du taux de créatinine sérique (Cr_s) en consultation externe; la date de la deuxième mesure de Cr_s a servi de date indice. Le pic de potassium sérique a servi à

déterminer l'incidence de l'hyperkaliémie. Les renseignements sur les médicaments d'ordonnance sont tirés de la base de données du réseau d'information pharmaceutique.
Méthodologie: Tous les patients ont été suivis de leur date indice jusqu'au 31 mars 2019, soit pour un minimum de deux ans. Les renseignements sur les médicaments d'ordonnance et les résultats des tests de suivi pour la créatinine et le potassium sériques ont été obtenus. Les patients qui, au moment de l'inclusion, étaient atteints d'une insuffisance rénale définie par un DFGe inférieur à 15 mL/min/1.73 m^2, sous dialyze chronique ou qui avaient reçu une greffe rénale ont été exclus.
Résultats: En tout, 170 574 adultes atteints d'IRC (âge moyen: 76,3 ans; 44 % d'hommes) ont été répertoriés et suivis sur une période médiane de 7 ans; 27 % avaient reçu au moins une ordonnance d'AINS. Bien qu'on ait observé une tendance à réduire les prescriptions chez les patients atteints d'un stade plus avancé d'IRC ($p < 0,001$), 16 % des patients atteints d'IRC G4 avaient reçu une ordonnance d'AINS. Les prestataires de soins primaires étaient responsables de 79 % des ordonnances. Parmi les utilisateurs d'AINS, 21 % avaient une mesure de suivi pour la Cr_s dans les 30 jours suivant la prescription indice.
Limites: Les données proviennent de bases de données cliniques et administratives qui ne sont pas créées à des fins de recherche. La cohorte est limitée aux sujets ayant requis des soins médicaux et pour qui on avait une mesure de créatinine sérique. La mesure de l'utilization d'AINS est limitée aux personnes ayant reçu une ordonnance, l'utilization d'AINS en vente libre n'est pas saisie.
Conclusion: Bien que les lignes directrices prônent la prudence en ce qui concerne la prescription d'AINS chez les patients atteints d'IRC, cette étude indique que la pratique diverge des recommandations. Des stratégies efficaces pour soutenir et mieux éduquer les prescripteurs et les patients pourraient contribuer à réduire les prescriptions inappropriées et les effets indésirables.

Keywords
clinical epidemiology, CKD, pharmacology, administrative data

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Introduction

Pain is a prevalent symptom experienced by patients with chronic kidney disease (CKD), with reports of 50% to 70% of patients with CKD experiencing pain.[1-4] Pain is associated with increased symptom burden and lower quality of life[5] and identified as a key priority for patients.[6] Appropriate management of pain is an important element of comprehensive care for patients with CKD and remains a challenge.

Nonsteroidal anti-inflammatory drugs (NSAIDs), a class of commonly used analgesic medications, are known to be nephrotoxic in patients with CKD. NSAID use has been associated with acute kidney injury (AKI), progressive loss of glomerular filtration rate in CKD, electrolyte derangements, and hypervolemia with attendant heart failure and hypertension.[7-9] Guidelines from organizations including Kidney Disease: Improving Global Outcomes (KDIGO) caution against the use of NSAIDs in a majority of CKD patients.[10] At present, reports on NSAID use in CKD are heterogeneous, often relying on self-report data and from older studies.[11] Furthermore, previous studies have largely been limited to the elderly population and to those with kidney failure and/or on dialysis.[9,11,12]

This study sought to examine the pattern of NSAID prescribing practices in a population-based cohort of patients with CKD excluding kidney failure, as well as details on physician prescriber specialty and frequency of follow-up serum creatinine (SCr) testing. These data will help to guide future quality improvement initiatives and identify areas for targeted interventions.

Methods

Study Design

We conducted a retrospective cohort study using linked population-based health care data from Alberta, Canada. The study was reviewed and approved by the Research Ethics Boards at the Universities of Alberta and Calgary with a waiver of individual signed patient consent (Ethics ID: REB 16-1575). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[13]

Data Source and Study Population

We identified the study population through the Alberta Kidney Disease Network (AKDN) population-based

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database, which has been described in detail elsewhere.[14] Briefly, it incorporates administrative data from the provincial health ministry such as registry, ambulatory care utilization, hospital admissions and physician claims, and the clinical laboratories and pharmacy data in Alberta. The study cohort included all adult Albertans (aged ≥ 18 years) with CKD G3 or greater[10] identified between January 1, 2009, and March 31, 2017, who have not received an NSAID prescription in the 12 months preceding study inclusion. CKD was defined as at least 2 outpatient serum creatinine measurements (SCr) greater than 90 days apart with estimated glomerular filtration rate (eGFR) values of less than 60 mL/min/1.73m^2 rate (eGFR).[10,15] The date of the second SCr measurement was used as index date for each patient. Patients with CKD G5 (eGFR < 15 mL/min per 1.73 m^2, on chronic dialysis, or with prior kidney transplant) at baseline were excluded. All patients were followed from the index date until March 31, 2019, or until date of death with a minimum follow-up of 2 years.

Assessment of Demographic Characteristics and Co-morbid Conditions

We identified baseline characteristics at index date (date of cohort entry). Relevant demographic characteristics, including age, sex, and postal code of residence were obtained from the Alberta Health administrative data files. Postal codes were linked to the Canadian Census using the Postal Code Conversion File (www.statcan.ca) to determine rural versus urban location of residence. The material deprivation index (level 1 being least deprived and level 5 being most deprived) was derived from 2016 Alberta Pampalon Deprivation Index.[16,17] Preexisting comorbid conditions were defined using validated algorithms.[18-24] Hospitalizations and outpatient physician nephrologist visits were obtained from hospital discharge records, physician claims, and ambulatory care classification system file. Data were complete except for material deprivation index (2.8% missing) and residence location (0.003% missing).

Assessment of Baseline Kidney Function and Albuminuria

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to determine the eGFR.[15] Baseline eGFR was defined as the mean value of the 2 eGFR used to define CKD, and it was categorized as 45 to 60, 30 to 44, or 15 to 29 mL/min/1.73 m^2 based on the 2012 KDIGO stages of CKD.[10] Albuminuria was ascertained from outpatient urine measurements of albumin-creatinine ratio (ACR), protein-creatinine ratio (PCR), or urine dipstick (UDip) in the 1 year before the cohort entry date and was defined as ACR > 3 mg/mmol, PCR > 15mg/mmol, or UDip 1+ or higher. The median value was selected for the participants with multiple measurements.

Assessment of Medication Use

Prescription drug information was obtained from the Pharmaceutical Information Network (PIN) database which captures dispensing information, including prescription drugs, day supplies, physician prescriber specialty, and dosage in Alberta since January 1st, 2008. NSAIDs were identified using their drug identification numbers (DINs) (see Supplemental Material). Oral route and rectal formulations of all NSAIDs with the exception of acetylsalicylic acid were included. Acetylsalicylic acid was excluded as it was readily available over-the-counter and often prescribed at low doses for cardiovascular protection. Eye-drops and topical formulations of NSAIDs were specifically excluded due to the over-the-counter nature as well as lack of data on systemic absorption being related to adverse kidney outcomes. To document new NSAID starts in CKD patients, participants who had any documented NSAID prescription filled in the PIN database in the 12 months prior to cohort entry were excluded.

The date of the index prescription of any NSAID for each participant was used as day zero. The exposure to NSAID was based on the dose and duration of the prescription registered in the PIN database. The average daily dose of each NSAID was calculated by adding the total dose of the prescription and dividing by the sum of the drug quantity day supply. Exposure duration for each patient was calculated in 2 approaches. One is the cumulative days supply of all the prescription – the days supply for each prescription is the number of days that each dispensing event covers. Another is the cumulative defined daily dose (DDDs),[25] which was defined as: DDDs exposure = Drug Strength × Drug Quantity Dispensed / DDD.

Participants who had prescriptions of more than 1 NSAID were analyzed based on their index prescription but subsequent NSAIDs within the 12 months following the index prescription and over the entire follow up period were included in the cumulative exposure calculations.

Concurrent opioid, proton-pump inhibitors (PPIs), and angiotensin converting enzyme inhibitors (ACEi), angiotensin-receptor blockers (ARB), or diuretic use was defined as at least 2 prescriptions of the drug category between 6 months before the index NSAID date and 6 months after. These medications were identified using DINs (see Supplementary Material for full list).

Assessment of Laboratory Outcomes

We determined the proportion of patients with at least 1 outpatient serum creatinine (SCr) or serum potassium measurement within 30 days of index NSAID prescription. The median change in SCr was defined using the difference

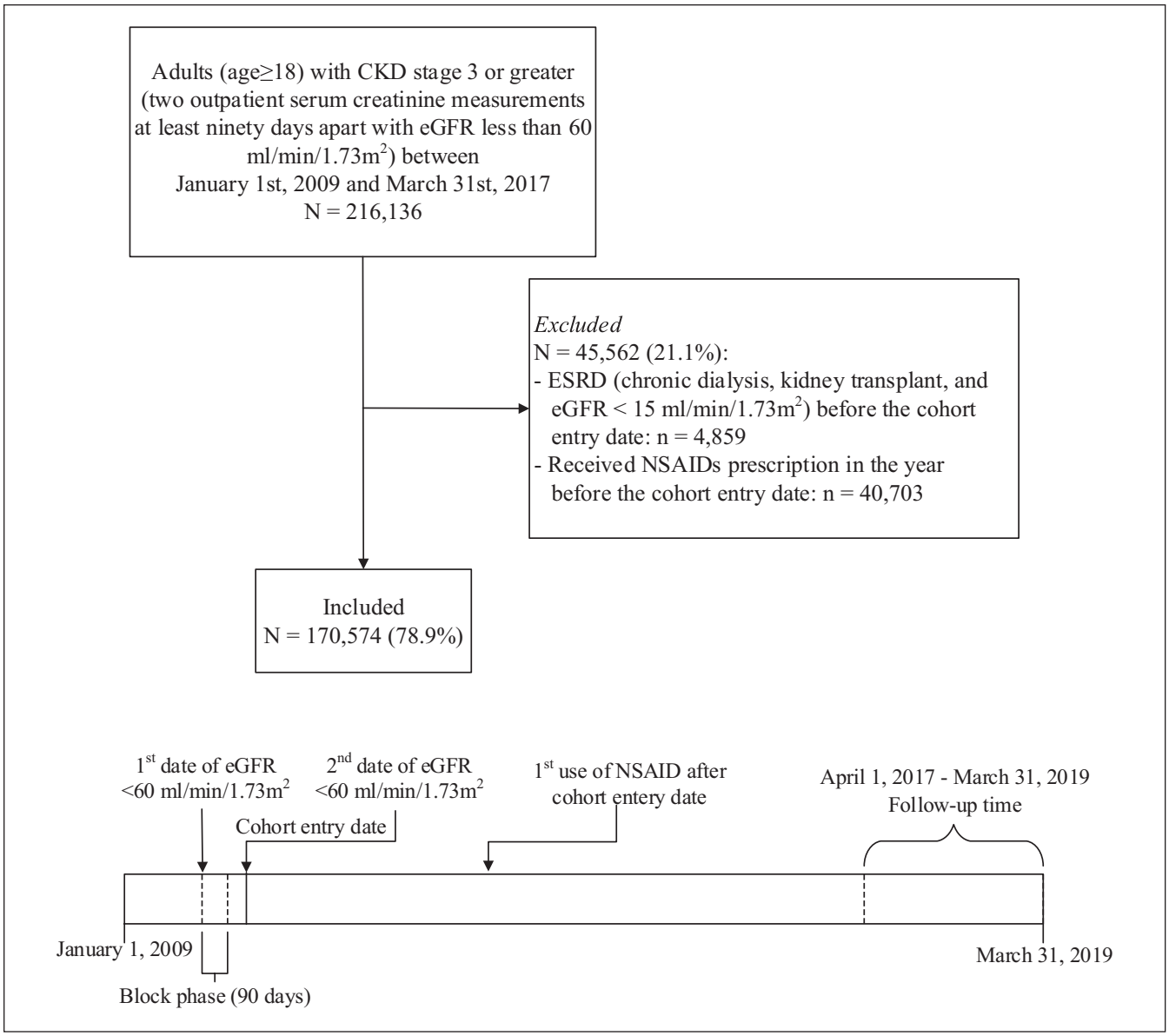

Figure 1. Selection of CKD study population.
Note. CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; NSAIDs = nonsteroidal anti-inflammatory drugs.

between the peak SCr within 30 days of index NSAID prescription and the baseline SCr values. We also determined the incidence of hyperkalemia using the peak serum potassium defined as ≥5.5 mmol/L.

Statistical Analysis

Baseline descriptive data were expressed as count with percentage for categorical variables and median with interquartile range for continuous variables. Differences between groups were compared using chi-square test for categorical variables and Kruskal-Wallis tests for all continuous variables. We tested for trend across the CKD categories using chi-square test for proportions, and Jonckheere-Terpstra[26] test for continuous variables. Follow up time was from cohort entry date to date of death, out-migration, or the end of study period. A 2-tailed P-value $< .05$ was considered statistically significant. Statistical analyses were performed using Statistical Stata/MP 17.0 software (www.stata.com).

Results

Patient Characteristics

We identified 170 574 patients in Alberta with CKD G3 or greater between January 1, 2009, and March 31, 2017 (Figure 1). Among these patients, 46 414 (27.2%) were identified to have received at least 1 prescription for an

Table 1. Baseline Characteristics of CKD Cohort.

Characteristic	All subjects n (%)	NSAID prescription n (%)	No-NSAID prescription n (%)
Number of subjects, N	170 574	46 414 (27.2)	124 160 (72.8)
Age in years, median [IQR]	76.3 [67.8-83.3]	73.2 [65.3-80.2]	77.5 [69.0-84.4]
Male	75 131 (44.0)	20 587 (44.4)	54 544 (43.9)[a]
Material deprivation index			
1 (least deprived)	30 218 (17.7)	7445 (16.0)	22 773 (18.3)
2	29 314 (17.2)	7640 (16.5)	21 674 (17.5)
3	33 043 (19.4)	9099 (19.6)	23 944 (19.3)[a]
4	37 653 (22.1)	10 667 (23.0)	26 986 (21.7)
5 (most deprived)	35 539 (20.8)	10 370 (22.3)	25 169 (20.3)
Missing	4807 (2.8)	1193 (2.6)	3614 (2.9)
Urban location	151 339 (88.7)	40 077 (86.3)	111 262 (89.6)
Missing	5 (0.003)	0	5 (0.004)
Baseline eGFR, in mL/min/1.73 m^2	51.7 [44.9-55.6]	52.7 [47.1-56.0]	51.3 [44.0-55.4]
CKD GFR Stage			
G3A 45-60	127 593 (74.8)	37 372 (80.5)	90 221 (72.7)
G3B 30-44	34 487 (20.2)	7728 (16.7)	26 759 (21.6)
G4 15-29	8494 (5.0)	1314 (2.8)	7180 (5.8)
Potassium, in mmol/L[b]	4.4 [4.1-4.7]	4.4 [4.1-4.7]	4.4 [4.1-4.7]
Albuminuria	32 426 (19.0)	7445 (16.0)	24 981 (20.1)
No PCR, ACR, or UDip measurements	69 309 (40.6)	19 265 (41.5)	50 044 (40.3)
Nephrology Visit within prior 18 months	11 207 (6.6)	2681 (5.8)	8526 (6.9)
Hypertension	139 287 (81.7)	37 218 (80.2)	102 069 (82.2)
Diabetes	54 797 (32.1)	14 151 (30.5)	40 646 (32.7)
Cardiovascular Disease	73 250 (42.9)	15 854 (34.2)	57 396 (46.2)
Heart Failure	34 779 (20.4)	6442 (13.9)	28 337 (22.8)
Atrial Fibrillation	29 508 (17.3)	5079 (10.9)	24 429 (19.7)
Peripheral Vascular Disease	7991 (4.7)	1676 (3.6)	6315 (5.1)
Myocardial Infarction	13 682 (8.0)	3033 (6.5)	10 649 (8.6)
Stroke/TIA	32 750 (19.2)	7310 (15.7)	25 440 (20.5)
Gout	25 290 (14.8)	8513 (18.3)	16 777 (13.5)
Rheumatoid Arthritis	8345 (4.9)	2313 (5.0)	6032 (4.9)[a]
Osteoarthritis	66 127 (38.8)	19 173 (41.3)	46 954 (37.8)
Chronic Pain	29 264 (17.2)	10 519 (22.7)	18 745 (15.1)
Cancer metastatic	3815 (2.2)	0764 (1.6)	3051 (2.5)
Cancer non-metastatic	13 666 (8.0)	3331 (7.2)	10 335 (8.3)
CCI	1.0 [0.0-3.0]	1.0 [0.0-2.0]	2.0 [0.0-3.0]
Concurrent prescription medications			
Opioid	13 475 (7.9)	13 475 (29.0)	—
PPI	17 436 (10.2)	17 436 (37.6)	—
ACEi/ARB	14 885 (8.7)	14 885 (32.1)	—
Diuretic	21 758 (12.8)	21 758 (46.9)	—
Spironolactone	1880 (1.1)	1880 (4.1)	—
Potassium resin	43 (0.02)	43 (0.1)	—

Note. Data are presented as n (%) or median [IQR]. NSAID = nonsteroidal anti-inflammatory drug; CKD = chronic kidney disease; IQR = interquartile range; eGFR = estimated glomerular filtration rate; PCR = urine protein-to-creatinine ratio; ACR = urine albumin-to-creatinine ratio; UDip = urine dipstick; TIA = transient ischemic attack; CCI = Charlson Comorbidity Index; PPI = proton-pump inhibitor; ACEi = angiotensin-converting-enzyme inhibitor; ARB = angiotensin-receptor blockers; SCr = serum creatinine.

[a]Comparison has a *P*-value $> .05$.

[b]Potassium was measured from 29 953 NSAID users and 83 202 non-NSAID users who had at least 1 outpatient potassium measurement 1 year before the cohort entry date.

NSAID medication during follow-up (Table 1). The median follow-up time was 7.4 years (IQR: 4.8-9.0). The population prescribed NSAIDs (compared with those who were not) was younger (median age 73.2 vs. 77.5), had less advanced

Table 2. Details of NSAID Prescriptions.

	Total Rx number (n)	Total unique patient (n)	COX-2 Rx n (%)[a]	Median duration of treatment over 1 year from index Rx[b] (days [IQR])	Prescriptions < 3 months in duration n (%)[c]	Patients who received > 1 NSAIDs over 2 years[b] n (%)[c]	Median cumulative dose for year[b] 1 DDDs [IQR]	Median cumulative dose for entire follow-up period[b] DDDs [IQR]
NSAID Rx	162,733	46,414	25,146 (15.5)	15 [10-40]	40,128 (86.5)	7,798 (16.8)	22 [10-50]	30 [13-75]
CKD GFR category								
45-60	131,352	37,372	20,410 (15.5)	15 [10-40]	32,335 (86.5)	6,500 (17.4)	23 [11-50]	30 [13-79]
30-44	27,638	7,728	4,116 (14.9)	15 [8-40]	6,620 (85.7)	1,136 (14.7)	20 [10-48]	26 [12-69]
15-29	3,743	1,314	620 (16.6)	15 [7-30]	1,173 (89.3)	162 (12.3)	17 [10-37]	21 [10-50]

Note. Data are presented as n (%) or median [IQR]. NSAID = nonsteroidal anti-inflammatory drug; COX2 = cyclooxygenase-2; Rx = prescription; DDDs = defined daily doses; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; IQR = interquartile range.
[a]The proportions are calculated as the number divided by the total Rx number.
[b]Trend test across CKD category has a *P*-value < .05.
[c]The proportions are calculated as the number divided by the total unique patient.

Table 3. Prescriber Details of NSAID Prescriptions by CKD Category.

	Overall		CKD G3a		CKD G3b		CKD G4	
	Number of patients	Total number of Rx	Number of patients	Total number of Rx	Number of patients	Total number of Rx	Number of patients	Total number of Rx
Total, N	46414	106831	37372 (80.5)	85561 (80.1)	7728 (16.7)	18649 (17.5)	1314 (2.8)	2621 (2.5)
Index Prescriber								
FP/GP	32195 (69.4)	84491 (79.1)	25836 (69.1)	67544 (78.9)	5518 (71.4)	15065 (80.8)	841 (64.0)	1882 (71.8)
Nephrologist	157 (0.3)	372 (0.3)	37 (0.1)	88 (0.1)	42 (0.5)	106 (0.6)	78 (5.9)	178 (6.8)
Other Internists	541 (1.2)	1512 (1.4)	447 (1.2)	1309 (1.5)	79 (1.0)	175 (0.9)	15 (1.1)	28 (1.1)
Surgeon	943 (2.0)	1265 (1.2)	781 (2.1)	1052 (1.2)	139 (1.8)	187 (1.0)	23 (1.8)	26 (1.0)
Other specialist	2299 (5.0)	2945 (2.8)	1866 (5.0)	2357 (2.8)	371 (4.8)	526 (2.8)	62 (4.7)	62 (2.4)
Unknown	10279 (22.1)	16246 (15.2)	8405 (22.5)	13211 (15.4)	1579 (20.4)	2590 (13.9)	295 (22.5)	445 (17.0)

Note. Data are presented as n (%). Number of patients is number of unique patients who received a Rx. NSAID = nonsteroidal anti-inflammatory drug; CKD = chronic kidney disease; Rx = prescription; FP = family practitioner; GP = general practitioner.

CKD (80.5% category CKD 3A vs. 72.7%) and less cardiovascular disease (34.2% vs. 46.2%) (Table 1). The NSAID group was more likely to have gout, osteoarthritis, and chronic pain. Among the identified cohort, 6.6% of patients had a nephrologist visit within the past 18 months and 41% did not have any measure of urinary protein within the follow-up period. NSAID prescription was lower with increasing CKD stage; the proportion of patients who received at least 1 NSAID prescription was 29.3% in CKD G3a, 22.4% in CKD G3b and 15.5% in CKD G4. Concomitant use of other medications was common, as seen with opioids (29.0%), PPIs (37.6%), ACEi/ARB (32.1%), and diuretics (46.9%). The proportion of individuals who died over the follow-up period was 24% in the group who had received an NSAID prescription and 42% in those who had not received a prescription; the rate of kidney failure was 1.8% versus 2.2%, respectively.

Prescription Details

Details regarding NSAID prescriptions are provided in Table 2. The median duration of treatment in the first year after index prescription for all NSAID users was 15 days (IQR: 10-40), with 86.5% of prescriptions being less than 3 months in duration and 16.8% of patients receiving more than 1 NSAID prescription over 2 years. Median cumulative DDDs were 22 for year 1 and 30 over the entire follow-up period.

Table 3 outlines the index prescriber details by CKD category. The specialty of the prescriber was documented in 84.8% of the NSAID prescriptions. The majority (79.1%) of prescriptions for these CKD patients were written by primary care physicians regardless of CKD category. Celecoxib was the only prescribed COX-2 inhibitor and was dispensed in 15.5% of NSAID prescriptions (Table S1). The majority of prescriptions were non-COX2 selective with diclofenac and naproxen being the most commonly prescribed at 23.5% and 26.2%, respectively.

Follow-up Laboratory Measurements

Among the 46414 identified NSAID users, 20.6% and 17.6% had a follow-up outpatient SCr and potassium within 30 days of the index prescription (see Table 4). The median change from baseline to the peak outpatient SCr within 30 days was

Table 4. Laboratory Outcomes Within 30 Days of Index NSAID Prescription.

Outpatient laboratory	Overall	CKD G3a	CKD G3b	CKD G4
Serum creatinine measured, n (%)[a]	9,560 (20.6)	7,028 (18.8)	1,979 (25.6)	553 (42.1)
Serum potassium measured, n (%)[a]	8,189 (17.6)	5,869 (15.7)	1,783 (23.1)	537 (40.9)
Peak serum creatinine in μmol/L, median [IQR][a]	114.3 [95.5-141.9]	107.2 [91.7-126.1]	139.5 [114.8-173.5]	226.0 [171.8-402.8]
Peak serum potassium in mmol/L, median [IQR][a]	4.5 [4.2-4.8]	4.4 [4.1-4.8]	4.6 [4.2-4.9]	4.7 [4.3-5.1]
Change of serum creatinine from baseline measurement, μmol/L, median [IQR][a]	2.3 [−9.1, 19.3]	1.2 [−8.6, 14.8]	5.8 [−12.3, 30.9]	25.9 [−13.7, 160.1]
Hyperkalemia, n (%)[a]	424 (5.2)	222 (3.8)	132 (7.4)	70 (13.0)

Note. Data are presented as n (%) or median [IQR]. Hyperkalemia was defined as a potassium ≥5.5 mmol/L. NSAID = nonsteroidal anti-inflammatory drug; CKD = chronic kidney disease; IQR = interquartile range.
[a]Trend test across CKD categories has a *P*-value < .05.

2.3 μmol/L (interquartile range: –9.1, 19.3), however, when stratified by CKD category there was a larger increase in the change in SCr in the post prescription period as CKD category advanced, 25.9 μmol/L increase (IQR: –13.7, 160.1) in CKD G4. Among all NSAID users, 5.2% of the patients with outpatient potassium measurements developed hyperkalemia.

Sub-analysis of Patient With CKD G4

We examined the characteristics of patients with CKD G4 (Table 5). In the 8494 identified patients, we found that 15.5% of patients with CKD G had been prescribed an NSAID. Patients who were prescribed an NSAIDS had more gout, osteoarthritis, and chronic pain –but tended to have less heart failure, atrial fibrillation, peripheral vascular disease, and stroke. Use of concurrent medication such as opioids (35.3%), PPIs (47.3%), ACEi/ARB (35.2%), and diuretics (64.7%) was also common in these patients with CKD G4.

Discussion

In this cohort of 170 574 adults with CKD without kidney failure, we found that 27% were prescribed at least 1 NSAID over a median follow-up of 7 years. Among these patients, only 21% had an outpatient SCr measured with 30 days of the prescription, despite the known nephrotoxicity in patients with CKD. In patients who had SCr assessed post NSAID usage, there was a decrement in kidney function as GFR stage increased, particularly in those with CKD G4. The KDIGO clinical guidelines[10] currently recommend avoidance of prolonged NSAID use in CKD with eGFR above 30 mL/min/1.73 m^2 and complete avoidance with eGFR < 30 mL/min/1.73 m^2; however, our study findings suggest that there is still an ongoing discrepancy from best practice recommendations. In our study cohort, the median duration of NSAID prescription was 15 days, with a median cumulative DDD of 22 for year 1. Although there was a trend toward fewer prescriptions in patients with more advanced CKD, 16% of those with CKD G4 received at least 1 prescription for an NSAID.

Perhaps not surprisingly, within the earlier categories of kidney disease, the majority of kidney-related care lies within the purview of primary care with only 7% of patients in this cohort having been seen by a nephrologist within the last 18 months. In turn, the majority (79%) of prescriptions were written by family physicians/general practitioners. These findings may help to direct the development of possible quality improvement initiatives. Strategies such as targeted physician/practitioner educational outreach,[27] audit and feedback reporting,[28,29] clinical decision support systems,[30] and improved guideline dissemination[31] may help toward changing practice.

The incidence of NSAID use in our study was higher compared with a cohort of 649 339 Medicare patients with CKD which found that NSAID use has increased from 11% to 17% from 2006 to 2015.[12] However, the cohort in that study was restricted to those over the age of 65, did not exclude patients with CKD G5 kidney disease, and was 5 years earlier. Our findings, while not directly comparable, are population-based and may reflect differences in health systems and access to care. A recent systematic review and meta-analysis[11] of patients with GFR category CKD G3-5 CKD reported a point prevalence of 17% for NSAID use. This review also reported an increase in NSAID use in more recent studies and speculated that this may reflect the desire of care providers to avoid opioids for pain management.

Previous studies have illustrated that the increased risk for rapid CKD progression and AKI associated with NSAID use is dose-dependent.[9] In our cohort, the majority of prescriptions were less than 3 months in duration. However, even short-term exposure to NSAIDs can carry significant risk to the CKD population, especially risk for AKI.[32,33] Moreover, CKD patients are already at an increased risk for AKI and, as shown in our study, are often on other medications such as diuretics and RAAS blocking agents, which may exacerbate the nephrotoxic effects of NSAIDs.[34,35] Previous cohort studies in CKD have shown that as frequency and severity of chronic pain increases, improper medication usage is more prevalent.[36]

Table 5. Characteristics for Patients With CKD G4.

Characteristic	All CKD G4 n (%)	NSAID users n (%)	Non-NSAID users n (%)
Number of subjects, N	8494	1314 (15.5)	7180 (84.5)
Age, years, median [IQR]	79.5 [68.2-86.5]	76.8 [65.2-84.2]	80.1 [68.9-86.9]
Male	3883 (45.7)	557 (42.4)	3326 (46.3)
Material deprivation index			
1 (least deprived)	1341 (15.8)	169 (12.9)	1172 (16.3)
2	1397 (16.4)	178 (13.5)	1219 (17.0)
3	1566 (18.4)	253 (19.3)	1313 (18.3)[a]
4	1894 (22.3)	297 (22.6)	1597 (22.2)[a]
5 (most deprived)	2010 (23.7)	370 (28.2)	1640 (22.8)
Missing	286 (3.4)	47 (3.6)	239 (3.3)[a]
Urban location	7500 (88.3)	1,096 (83.4)	6404 (89.2)
Baseline eGFR, in mL/min/1.73 m^2	25.2 [21.4-27.9]	25.7 [22.0-28.2]	25.1 [21.3-27.8]
Potassium, in mmol/L[b]	4.6 [4.3-5.0]	4.6 [4.3-5.0]	4.7 [4.3-5.0][a]
Albuminuria	4077 (48.0)	594 (45.2)	3483 (48.5)
No PCR, ACR, or UDip measurements	2033 (23.9)	320 (24.4)	1713 (23.9)[a]
Nephrology visit within prior 18 months	3407 (40.1)	563 (42.8)	2844 (39.6)
Hypertension	7686 (90.5)	1,209 (92.0)	6477 (90.2)
Diabetes	3759 (44.3)	615 (46.8)	3144 (43.8)
Cardiovascular disease	4928 (58.0)	681 (51.8)	4,247 (59.2)
Heart failure	3168 (37.3)	403 (30.7)	2765 (38.5)
Atrial fibrillation	1938 (22.8)	213 (16.2)	1725 (24.0)
Peripheral vascular disease	631 (7.4)	61 (4.6)	570 (7.9)
Myocardial infarction	1000 (11.8)	128 (9.7)	872 (12.1)
Stroke/TIA	2183 (25.7)	313 (23.8)	1870 (26.0)[a]
Gout	2255 (26.5)	392 (29.8)	1863 (25.9)
Rheumatoid arthritis	486 (5.7)	62 (4.7)	424 (5.9)[a]
Osteoarthritis	3446 (40.6)	575 (43.8)	2871 (40.0)
Chronic pain	1440 (17.0)	343 (26.1)	1097 (15.3)
Cancer metastatic	200 (2.4)	17 (1.3)	183 (2.5)
Cancer nonmetastatic	722 (8.5)	90 (6.8)	632 (8.8)
CCI	3.0 [2.0-5.0]	3.0 [2.0-5.0]	3.0 [2.0-5.0]
Concurrent prescription medications			
Opioid	464 (5.5)	464 (35.3)	—
PPI	621 (7.3)	621 (47.3)	—
ACEi/ARB	463 (5.5)	463 (35.2)	—
Diuretic	850 (10.0)	850 (64.7)	—
Spironolactone	85 (1.0)	85 (6.5)	—
Potassium resin	4 (0.04)	4 (0.3)	—

Note. Data are presented as n (%) or median [IQR]. NSAID = nonsteroidal anti-inflammatory drug; CKD = chronic kidney disease; IQR = interquartile range; eGFR = estimated glomerular filtration rate; PCR = urine protein-to-creatinine ratio; ACR = urine albumin-to-creatinine ratio; UDip = urine dipstick; TIA = transient ischemic attack; CCI = Charlson Comorbidity Index; PPI = proton-pump inhibitor; ACEi = angiotensin-converting-enzyme inhibitor; ARB = angiotensin-receptor blockers; SCr = serum creatinine.

[a]Comparison has a *P*-value $> .05$.

[b]Potassium was measured from 1121 NSAID users and 6091 non-NSAID users who had at least 1 outpatient potassium measurement 1 year before the cohort entry date.

The management of pain in patients with CKD remains a challenge, especially given the multiple comorbidities found in the CKD population. Guidelines and recommendations suggest the cautious use of NSAIDs in the management of CKD,[7,10,37] with a suggested duration of treatment no more than 5 days,[7] with close monitoring for nephrotoxicity and development of risk factors for nephrotoxicity such as AKI, hyperkalemia, hyponatremia, and hypervolemia. For patients with CKD G4, it is suggested to consider short-term, low-dose NSAID use on a case-by-case basis with close monitoring, while in patients with hyperkalemia, NSAID use should be considered contraindicated. Our study finds suggest follow-up SCr and serum potassium measurements are frequently

overlooked as we found that only 21% of patient had these laboratory measures done within 30 days of an NSAID prescription.

There are limitations to this study as result of study design. Data collected were from clinical and administrative databases not created for research purposes. The use of laboratory data to define the study cohort limited the study to subjects who sought medical care and had a serum creatinine measurement obtained. We were not able to capture indication for the NSAID prescription, but we did ascertain relevant comorbidities. We did exclude 19% of patients because they received an NSAID prescription within the year before cohort entry which supports our finding that NSAID prescription is frequent in this population and that our results likely underestimate usage. Although the prescription drug database eliminates recall bias, exposure bias may still exist as it is not certain that the dispensed NSAID was consumed as prescribed. Conversely, the NSAID use reported in our study is undoubtedly a significant underestimate of actual use due to the frequent use of over-the-counter and topical NSAIDs. Our findings highlight the need and importance of patient education by primary care providers and pharmacists alike.

Conclusions

This study demonstrates that prescription NSAID use is common in the CKD population despite current recommendations. Future research into how to best support and educate primary care providers on the safety of NSAIDs in CKD, as well as how to optimize pain management in CKD, should be a priority. Strategies to address provider and patient education through innovative technologies may help to improve outcomes and reduce adverse events in this population.

Ethics Approval and Consent to Participate

Ethics approval for the study was obtained from the research ethics review board at the Universities of Calgary and Alberta. As this study uses secondary data, individual patient consent was not required.

Consent for Publication

All authors reviewed the final manuscript and provided consent for publication.

Availability of Data and Materials

The authors conducted this research after ethics approval, and in the context of a contract with Alberta Health enabling this research. Given the constraints of this contract, the health administrative data used to conduct this research can not be shared.

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Declaration of Conflicting Interests

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Supplemental Material

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