Patterns of NSAIDs Use and Their Association with Other Analgesic Use in CKD

Min Zhan, Wendy L. St. Peter, Rebecca M. Doerfler, Corinne M. Woods, Jacob B. Blumenthal, Clarissa J. Diamantidis, Chi-yuan Hsu, James P. Lash, Eva Lustigova, Erin B. Mahone, Akinlolu O. Ojo, Anne Slaven, Louise Strauss, Jonathan J. Taliercio, Wolfgang C. Winkelmayer, Dawei Xie, Jeffery C. Fink, and the Chronic Renal Insufficiency Cohort (CRIC) Study Investigators

Due to the number of contributing authors, the affiliations are provided in the Supplemental Material.

Correspondence: Dr. Jeffrey C. Fink, Department of Medicine, University of Maryland School of Medicine, Room N3e03, 22 South Greene Street, Baltimore, MD 21201. Email: jfink@som.umaryland.edu

Abstract

Background and objectives Avoiding nonsteroidal anti-inflammatory drugs is important for safe CKD care. This study examined nonsteroidal anti-inflammatory drug use patterns and their association with other analgesic use in CKD.

Design, setting, participants, & measurements The Chronic Renal Insufficiency Cohort Study is an observational cohort study that enrolled 3939 adults ages 21–74 years old with CKD between 2003 and 2008 using age-based eGFR inclusion criteria. Annual visits between June of 2003 and December of 2011 were organized into 15,917 visit-pairs (with an antecedent and subsequent visit) for 3872 participants with medication information. Demographics, kidney function, and clinical factors were ascertained along with report of nonsteroidal anti-inflammatory drug or other analgesic use in the prior 30 days.

Results In our study, 24% of participants reported nonsteroidal anti-inflammatory drug use at baseline or at least one follow-up study visit. Having a 10 ml/min per 1.73 m^2 higher eGFR level at an antecedent visit was associated with higher odds of starting nonsteroidal anti-inflammatory drugs at a subsequent visit (odds ratio, 1.44; 95% confidence interval, 1.34 to 1.56). Seeing a nephrologist at the antecedent visit was associated with lower odds of starting or staying on nonsteroidal anti-inflammatory drugs at a subsequent visit (odds ratio, 0.70; 95% confidence interval, 0.56 to 0.87 and odds ratio, 0.61; 95% confidence interval, 0.46 to 0.81, respectively). Starting and stopping nonsteroidal anti-inflammatory drugs were both associated with higher odds of increasing the number of other analgesics (odds ratio, 1.52; 95% confidence interval, 1.25 to 1.85 and odds ratio, 1.78; 95% confidence interval, 1.39 to 2.28, respectively) and higher odds of increasing the number of opioid analgesics specifically (odds ratio, 1.92; 95% confidence interval, 1.48 to 2.48 and odds ratio, 1.46; 95% confidence interval, 1.04 to 2.03, respectively).

Conclusions Nonsteroidal anti-inflammatory drug use is common among patients with CKD but less so among those with worse kidney function or those who see a nephrologist. Initiation or discontinuation of nonsteroidal anti-inflammatory drugs is often associated with supplementation with or replacement by, respectively, other analgesics, including opioids, which introduces possible drug-related problems when taking these alternative analgesics.

Clin J Am Soc Nephrol 12: 1778–1786, 2017. doi: https://doi.org/10.2215/CJN.12311216

Introduction

Maintaining patient safety is important for quality CKD care. To ensure patient safety, CKD practice guidelines recommend avoidance of nephrotoxic medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), given their recognized renal toxicity (1–3). Nonetheless, studies reveal a surprisingly high rate of NSAID use in CKD (4,5). Automated reporting of eGFR is associated with a decline in NSAID prescribing in CKD (6), but it has had limited effect on dosing errors of other drugs (7), and serum creatinine may be a stronger determinant of NSAID avoidance than eGFR (8).

The Chronic Renal Insufficiency Cohort (CRIC) Study is an observational study of persons with predialysis CKD who undergo annual visits and ascertainment of prescription and over-the-counter medication usage. Longitudinal follow-up of the CRIC Study participants permits determination of trends in NSAID usage and factors associated with changes in use. This study attempts to identify the frequency and patterns of NSAID usage, determine how kidney function influences NSAID usage, and examine how NSAIDs affect other analgesic use.

Materials and Methods

The CRIC Study enrolled 3939 individuals 21–74 years old with age-specific eGFR eligibility criteria of 20–70 ml/min per 1.73 m^2 between June of 2003 and

December of 2008 from seven United States centers with 13 clinical sites and Institutional Review Board approval at each site. Study design details were previously published (9,10) (ClinicalTrials.gov Identifier: NCT00304148). Briefly, the CRIC Study participants provided written consent for data collected at annual in-center visits, including demographics, medical history, vital signs, blood and urine samples, and other survey-based information. Kidney function was estimated using the abbreviated Modification of Diet in Renal Disease equation for eGFR, the prevailing clinical measure of kidney function at study commencement. The analysis included a question asking how much pain interfered with work in the prior 4 weeks and the broader SF12 Physical Health Composite Score (SF12-PCS), both derived from the Kidney Disease Quality of Life (KDQOL) assessment; the pain question was included in the composite score.

Medication Ascertainment

Study coordinators recorded the CRIC Study participants' prescription and over-the-counter medications, herbal and dietary supplements, and vitamins for the 30 days preceding the study visit. To reduce recall bias, participants were asked to maintain a medication list or bring medications to visits. The drug name, frequency, total daily dosage, dosage units, and administration route were documented. Individual medications were identified using the First Databank (11) dictionary for common medications and supplements available on the market.

Classification of NSAIDs and Other Analgesics

The CRIC Study data file was closed on December 8, 2011 for this analysis. The NSAID classification included all NSAIDs and cyclooxygenase-2 inhibitors. Additional drug categories were created for opioids, including tramadol, and nonopioid analgesics. Aspirin was classified as a nonopioid analgesic if total daily dosage was >325 mg, frequency was more than once a day, or the drug was part of a combination analgesic. Combination medications were separated into individual constituents, with each individually classified.

Visit-Pairings

For trends in NSAID use, visits were assembled into rolling consecutive pairs to determine changes in use patterns and examine whether factors identified at the antecedent visit were associated with NSAID use at the subsequent visit of each pair and how a change or continuation of NSAIDs affected other analgesic use. The visit-pairs were categorized into four groups: (*1*) no NSAIDs (stay off), (*2*) switching from no NSAIDs to NSAID use (start), (*3*) switching from NSAID use to nonuse (stop), and (*4*) persistent NSAID use (stay on).

Definition of a Drug-Related Problem

We considered analgesic use as either appropriate or a drug-related problem (DRP) defined as follows (12). All NSAID use was classified as a DRP. The use of other nonopioid and opioid analgesics was classified as a DRP if excessively dosed or inappropriately given for the participant's eGFR. We used dosing guidance from multiple medication guideline references, including Lexi-Comp online; the Directory of Drug Dosage in Kidney Disease; Micromedex; the article "Drug prescribing in renal failure: Dosing guidelines for adults"; and the American Hospital Formulary Service (13–18). The most commonly used recommendation was selected as the dosing guidance. DRP flags were generated for the subsequent visit using the eGFR from the antecedent visit, because this eGFR was available at the time of a provider's prescription at a subsequent visit.

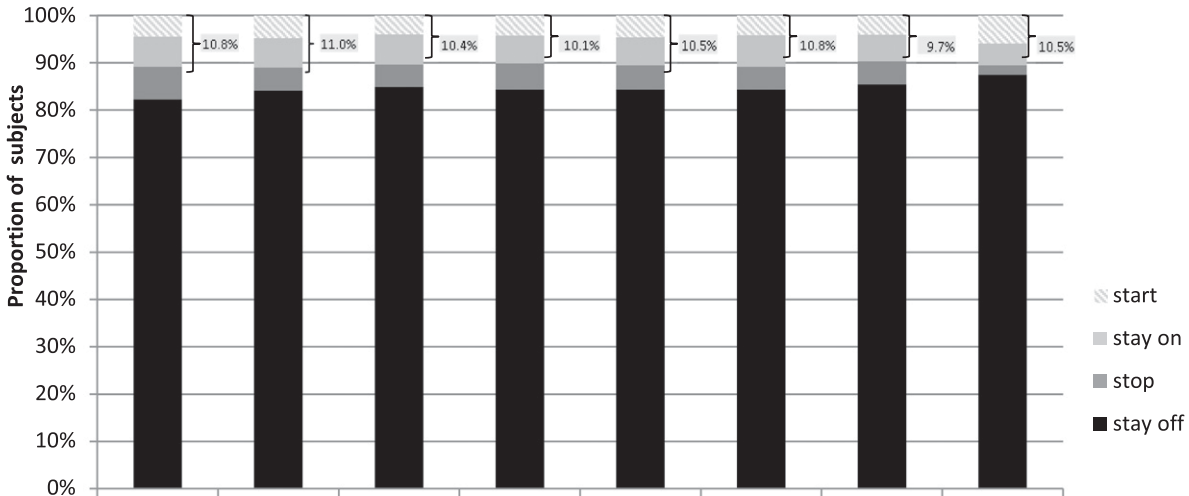
Statistical Methods

For descriptive analyses, chi-squared tests and *t* tests compared discrete characteristics and continuous variables, respectively, across groups. Generalized estimating equations (GEEs) compared the odds of starting or stopping NSAIDs across visit-pairs. A logistic transition model was used to assess if factors at the antecedent visit were associated with change in NSAID use at the subsequent visit, conditional on NSAID use at the antecedent visit (19). The factors included eGFR, urine protein, seeing a nephrologist, and pain interfering with work. The logistic transition models were of first-order binary Markov chain type, with two transition probabilities, π_{01} and π_{10}, of starting NSAIDs and stopping NSAIDs at the subsequent visit, respectively. The models included interaction terms between covariates and NSAID use at the antecedent visit to distinguish their associations with the two different transition probabilities. Demographic (age, sex, and race) and case mix factors, including body mass index, diabetes, cardiovascular disease, hypertension, arthritis, and years from baseline visit to current visit, were included as confounders in multivariate models. All except sex and race were updated at each antecedent visit for analysis. A robust variance estimator accounted for potential correlations in NSAID use by individuals at different visits.

To determine whether change in NSAID use across a visit-pair was associated other analgesic use, we used a binary outcome (whether there was an increase in the total number of non-NSAID analgesics) in a GEE regression with binomial distribution and a logit link function. In addition to NSAID use at both antecedent and subsequent visits, only those covariates significantly associated with the outcome were included in the final model. The same approach was used for examining the association of the switch in NSAID use with the change in the number of opioid analgesics and pain as measured with the KDQOL at subsequent visits. GEE regressions with a normal distribution and an identity link were used for change in eGFR and the broader KDQOL SF12-PCS at subsequent visits. Adjusted odds ratios (ORs) and their 95% confidence intervals (95% CIs) were computed. Analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC).

Results

Of 3939 CRIC Study participants with a baseline visit, 67 were excluded due to lack of baseline medication information. The remaining 3872 subjects underwent 19,789 predialysis visits with 15,917 visit-pairs. The majority of the visit-pairs (97%) were consecutive annual visits, but 2% and 0.7% of the pairs had one or two or more missing visits



visit	1	2	3	4	5	6	7	8
start	149	142	108	101	95	61	33	9
stay on	214	186	174	139	122	97	46	7
stop	233	145	129	131	106	70	40	3
stay off	2760	2508	2307	2002	1739	1230	698	133
Patient N	3356	2981	2718	2373	2062	1458	817	152

Figure 1. | The distribution of nonsteroidal anti-inflammatory drug switch patterns at each follow-up annual visit indicates the proportion of participants starting or staying on NSAID was relatively stable.

between paired visits, respectively. Nine hundred forty (24%) participants reported NSAID use at one or more visits and 2170 (11%) visits overall, with 487 (13%) reporting NSAID use at the baseline visit and 453 initiating NSAID use at a later visit.

Table 1 shows the baseline characteristics of the CRIC Study participants on the basis of whether they ever reported NSAID use. Being older than 65 years old or having advanced CKD stages, urine protein >0.5 g/d, diabetes, cardiovascular disease, hypertension, or report of seeing a nephrologist were associated with a lower chance of ever reporting NSAID use. Being a woman, having arthritis, and having pain interfering with work moderately or greater were associated with ever reporting NSAID use.

Pattern of Change in NSAID Use

Among the 487 participants reporting baseline NSAID use, 25 had a baseline visit only, 233 did not report NSAID use at the first follow-up visit, and an additional 162 stopped reporting NSAID use at a later visit.

Figure 1 shows the distribution of subsequent visits from a pair on the basis of NSAID use pattern over 8 study years. The proportion of participants starting NSAIDs was between 4% and 6%, whereas the proportion of participants staying on an NSAID from the prior visit was between 5% and 7%. The proportion of participants who either started or stayed on an NSAID was relatively stable. The proportion of participants stopping NSAIDs was the highest at the first annual visit (7%) and between 5% and 6% at the second to seventh visits before dropping to 2% at the eighth visit ($P<0.001$ for comparing the proportions of stopping NSAIDs among visits).

Association of Antecedent Visit Characteristics with Switch in NSAID Use at Subsequent Visit

Table 2 displays the associations of the antecedent visit factors (eGFR, urine protein excretion, nephrologist contact, and pain) with change (starting or stopping) in NSAID use at the subsequent visit in a pair. Higher eGFR level at the antecedent visit was associated with higher odds of starting NSAIDs, but eGFR at an antecedent visit was not associated with stopping NSAIDs. Report of nephrologist contact at the antecedent visit was associated with lower odds of starting NSAIDs and higher odds of stopping NSAIDs. Proteinuria was not a significant factor associated with reported NSAIDs. Pain interfering moderately or greater with work was associated with higher odds of starting an NSAID.

Association of Switch in NSAID Use with Other Analgesic Use

Table 3 shows how change in reported usage of NSAID was associated with changes in use of other analgesics. Compared with visit-pairs with no NSAID use, starting NSAIDs was associated with higher odds of increasing the number of all non-NSAIDs and opioid analgesic use specifically (adjusted OR, 1.52; 95% CI, 1.25 to 1.85 and OR, 1.92; 95% CI, 1.48 to 2.48, respectively; both $P<0.001$). Similarly, compared with visit-pairs where participants stayed on NSAIDs, stopping NSAIDs was associated with a higher odds of increasing the number of both all non-NSAID analgesics used and opioid analgesics used specifically (adjusted OR, 1.78; 95% CI, 1.39 to 2.28 and OR, 1.46; 95% CI, 1.04 to 2.03; $P=0.001$ and $P=0.03$, respectively).

Table 1. Baseline characteristics of the Chronic Renal Insufficiency Cohort Study participants on the basis of whether they ever reported nonsteroidal anti-inflammatory drug use at a study visit (n=3872)

Baseline Characteristics	Total	NSAID Use		*P* Value
		Ever (Column %)	Never (Column %)	
All	3872	940	2932	
Age, yr				0.004
<45	513	123 (13)	390 (13)	
45–<65	2227	581 (62)	1646 (56)	
≥65	1132	236 (25)	896 (31)	
Race				0.11
Nonblack	2241	565 (60)	1676 (57)	
Black	1631	375 (40)	1256 (42.8)	
Sex				<0.001
Men	2125	430 (46)	1695 (58)	
Women	1747	510 (54)	1237 (42)	
CKD stage at baseline				<0.001
1/2	389	186 (20)	203 (7)	
3A	1242	386 (41)	856 (29)	
3B	1486	301 (32)	1185 (40)	
4/5	755	67 (7)	688 (24)	
Urine protein, g/24 h				<0.001
<0.1	1350	476 (53)	874 (31)	
0.1 to <0.5	1076	246 (27)	830 (30)	
≥0.5	1253	183 (20)	1070 (39)	
BMI				0.01
<25.0	614	121 (13)	493 (17)	
25.0 to <30.0	1099	264 (28)	835 (28)	
≥30.0	2149	552 (59)	1597 (55)	
Diabetes				<0.001
No	1979	568 (60)	1411 (48)	
Yes	1893	372 (40)	1521 (52)	
CVD				<0.001
No	2567	680 (72)	1887 (64)	
Yes	1305	260 (28)	1045 (36)	
Hypertension				<0.001
No	511	165 (186)	346 (12)	
Yes	3361	775 (82)	2586 (88)	
Arthritis				0.04
No	3190	759 (85)	2431 (87)	
Yes	489	137 (15)	352 (13)	
Nephrologist visit				<0.001
No	1310	483 (51)	827 (28)	
Yes	2562	457 (49)	2105 (72)	
Pain interfering moderately or greater with work				<0.001
No	2490	543 (58)	1947 (67)	
Yes	1362	394 (42)	968 (33)	
SF12-PCS (mean±SD)	41.2±11.5	41.2±11.6	41.2±11.5	0.86

All variables were measured at baseline, except for never/ever NSAID use, which is a cumulative variable including any NSAID use at baseline or follow-up visits. NSAID, nonsteroidal anti-inflammatory drug; BMI, body mass index; CVD, cardiovascular disease; SF12-PCS, SF12 Physical Health Composite Score.

Table 4 displays the most common NSAIDs, opioid and nonopioid analgesics by participant-visit, and proportion of visits where each analgesic was reported with DRPs. Ibuprofen was the most frequently reported NSAID, and hydrocodone was the most frequently reported opioid medication, with only a minority of visits with hydrocodone dosed high enough to classify the drug as a DRP. Several opioids were reported less commonly but with a higher proportion of visits where doses were high enough to classify as DRPs. These included methadone, propoxyphene, and fentanyl, with at least one quarter of visits where the opioid use was classified as a DRP. Acetaminophen was the most frequently used nonopioid analgesic (27% of visits), but the proportion of acetaminophen entries with a DRP was very low (0.3%). Aspirin, the second most common nonopioid, was only used in 3% of the visits at a dose high enough to classify as an analgesic, but 15% of the entries were classified as a DRP. The remaining nonopioid

Table 2. Adjusted odds ratio of nonsteroidal anti-inflammatory drug start (or stay on) with eGFR, proteinuria, and nephrology visit (visit-pair *n*=15,917)

Covariate[a]	Stay off *n* (Row %)	Start *n* (Row %)	Adjusted OR (95% CI) of Starting NSAID	Stop *n* (Row %)	Stay on *n* (Row %)	Adjusted OR (95% CI) of Staying on NSAID
N visit-pairs (row %)	*n*=14,075 (88.3)			*n*=1842 (11.7)		
Within-stratum *n* visit-pairs (row %)	13,377 (95.0)	698 (5.0)		857 (46.5)	985 (53.5)	
eGFR at antecedent visit, ml/min per 1.73 m^2	Mean 41.6±13.9	Mean 49.6±13.8	1.44 (1.34 to 1.56)[b]	Mean 48.0±14.1	51.0±12.6	1.06 (0.95 to 1.18)[b]
Urine protein at antecedent visit, g/24 h						
<0.1	3526 (93)	254 (7)[c]	Reference	317 (43	423 (57)	Reference
0.1 to <0.5	3181 (95)	168 (5)	0.91 (0.73 to 1.13)	204 (47)	227 (53)	1.00 (0.89 to 1.49)
≥0.5	3112 (97)	112 (3)	0.82 (0.62 to 1.08)	138 (62)	86 (38)	0.77 (0.53 to 1.11)
Seeing a nephrologist at antecedent visit						
No	2660 (92)	247 (8)	Reference	320 (38)	523 (62)	Reference
Yes	10,717 (96)	451 (4)	0.70 (0.56 to 0.87)	537 (54)	462 (46)	0.61 (0.46 to 0.81)
Pain at antecedent visit interfering moderately or greater with normal work						
No	9171 (96)	424 (4)	Reference	495 (47)	559 (53)	Reference
Yes	4038 (94)	266 (6)	1.48 (1.19 to 1.85)	352 (46)	410 (54)	1.15 (0.89 to 1.49)

OR, odds ratio; 95% CI, 95% confidence interval; NSAID, nonsteroidal anti-inflammatory drug.

[a]The transition model included the following variables: NSAID use at antecedent visit, black race, sex, age group, eGFR, urine protein group, body mass index group, diabetes, cardiovascular disease, hypertension, arthritis, seeing a nephrologist, pain interfering with normal work moderately or greater (all at antecedent visit except for black race and sex, which were evaluated at baseline), years from baseline visit to the subsequent visit, and the interactions of these variables with NSAID use at antecedent visit.

[b]OR comparing participants with a 10 ml/min per 1.73 m^2 higher eGFR level at antecedent visit with those with a specific eGFR level.

[c]The row percentage of NSAID switch at each urine protein stratum or nephrologist visit stratum is conditioned on NSAID use or not at the antecedent visit: for example, the row percentage of No to Yes = (number of No to Yes pairs)/[(number of No to No pairs) + (number of No to Yes pairs)].

Table 3. Associations of nonsteroidal anti-inflammatory drug switch with change in other analgesic and opioid use (*n*=15,917)

NSAID at Antecedent Visit	NSAID at Subsequent (Current) Visit	Total in Group	Increase in No. of Any Other (Non-NSAID) Analgesics		Increase in No. of Opioid Analgesics Only	
			n (%) Increase	Adjusted OR (95% CI)[a]	*n* (%) Increase	Adjusted OR (95% CI)[a]
No	No (row %)	13,377	1863 (14)	Reference 1	818 (6)	Reference 1
No	Yes (row %)	698	139 (20)	1.52 (1.25 to 1.85)	78 (11)	1.92 (1.48 to 2.48)
Yes	Yes (row %)	985	153 (16)	Reference 2	78 (8)	Reference 2
Yes	No (row %)	857	211 (25)	1.78 (1.39 to 2.28)	93 (11)	1.46 (1.04 to 2.03)

NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; 95% CI, 95% confidence interval.
[a]Model includes NSAID status at antecedent and subsequent visits and their interactions, age category, sex, body mass index category, cardiovascular disease, arthritis (all at antecedent visit), and number of years since baseline visit.

analgesics all had variable proportions of entries with a DRP but with low total use.

Intervisit Changes on the Basis of NSAID Use Patterns

Kidney function did not change significantly between paired visits in any of the usage groups (Supplemental Table 1), even with adjustment for kidney function at antecedent visit and other factors. Compared with visit-pairs with no NSAID use, starting NSAIDs was associated with higher odds of pain interfering moderately or greater with work and a lower SF12-PCS at the subsequent visit (Supplemental Table 2, A and B, respectively). Participants who stayed on NSAIDs also had a higher odds of such pain and a lower SF12-PCS at the subsequent visit relative to those who stopped an NSAID.

Discussion

In this analysis, we showed that a substantial portion of patients with CKD reported NSAID use over time. Although most CRIC Study participants reporting baseline NSAID use stopped them during follow-up, additional participants initiated NSAIDs at a follow-up visit, resulting in a relatively constant proportion of the cohort reporting NSAID use annually. Better kidney function at an antecedent visit was associated with a greater likelihood of starting NSAIDs at the subsequent visit but not stopping them. Hence, kidney function was more likely to be a factor associated with starting NSAIDs versus whether they were continued. Seeing a nephrologist at the antecedent visit was associated with either ceasing or avoiding an NSAID, which indicates that nephrologists tend to acknowledge the risks of NSAID in CKD. Pain interfering with work was associated with higher odds of starting an NSAID, confirming that NSAID use is an underpinning to pain management. Participants either starting or stopping NSAID use were more likely to increase non-NSAID analgesic use, including opioids, versus those remaining NSAID free or with sustained NSAID use, highlighting non-NSAID analgesics' role as supplements or alternatives for CKD pain management. Participants reported a notable portion of these additional analgesics, especially opioids, at excessive doses for their kidney function.

Other reports recognized the increasing use of analgesics, particularly opioids, in the general and ESRD populations (20–22). Our data extend these findings by showing a linkage between NSAID and opioid use in nondialysis-dependent CKD, with a significant proportion of analgesics inappropriately dosed for kidney function at the time of drug use (23). The comingling of NSAIDs and other analgesics, particularly opioid use, in CKD puts focus on a previously under-recognized safety concern in this disease population.

The estimated prevalence of NSAID use in the CRIC Study participants was consistent with several prior reports of 9%–36% of patients with CKD using NSAIDs (5,6,8,24–26). One study from the National Health and Nutrition Examination Survey suggested that the frequency of NSAID use was slightly higher in United States adults with moderate to severe versus mild CKD (27), a reverse trend to that reported here. Differences in sampling methods to identify patients with CKD and determine NSAID use may account for the differences. Previous studies also provide some evidence on the association of NSAIDs and other analgesics with decline of kidney function (4,28,29), supporting the likelihood of harm with use of these agents. However, higher cumulative doses of NSAIDs may be required to increase the risk of accelerated CKD progression (30).

Few studies have looked at longitudinal changes in NSAID use in CKD. Wei *et al.* (6) showed that patients with CKD in Scotland who stopped NSAIDs had significant improvement in kidney function up to 180 days after cessation, but long-term kidney function effects were not reported. In another study, approximately 20% of patients on dialysis have been reported to use NSAIDs consistently for an average of 40 days over each of 3 years before initiating kidney replacement therapy (31).

This study is unique in reporting on the frequency and trends in NSAID use over time, examining factors associated with change in NSAID use, and describing the relationship between changes in NSAID use and non-NSAID analgesic use in CKD. The observed association between either cessation or initiation of NSAIDs and greater opioid use is significant given the problem of growing dependency on the latter class of agents among some patients (32).

Table 4. Top nonsteroidal anti-inflammatory drugs, opioid analgesic medications, and nonopioid analgesic medications by frequency of visits with a report of medication and proportion of those visits with a drug-related problem

Medication[a]	*N* (%) of Visits	*N* (%) of Visits Where Drug Is Recorded as a DRP
NSAIDs		
Ibuprofen	983 (5)	
Naproxen	561 (3)	
Celecoxib	183 (0.9)	
Indomethacin	146 (0.7)	
Diclofenac	118 (0.6)	
Nabumetone	68 (0.3)	
Meloxicam	65 (0.3)	
Etodolac	63 (0.3)	
Sulindac	53 (0.3)	
Valdecoxib	31 (0.2)	
Rofecoxib	25 (0.1)	
Opioid analgesics		
Hydrocodone	1108 (6)	20 (2)
Tramadol	697 (4)	42 (6)
Codeine	545 (3)	4 (0.7)
Oxycodone	505 (3)	10 (2)
Propoxyphene	320 (2)	98 (31)
Morphine	97 (0.5)	5 (5)
Fentanyl	59 (0.3)	17 (29)
Hydromorphone	40 (0.2)	0 (0.0)
Methadone	24 (0.1)	14 (58)
Nonopioid analgesics		
Acetaminophen	5262 (27)	14 (0.3)
Aspirin	490 (3)	73 (15)
Salsalate	54 (0.3)	11 (20)
Acetaminophen/caffeine/butalbital	26 (0.1)	0 (0.0)
Magnesium salicylate	10 (0.1)	5 (50)
Acetaminophen	5262 (27)	14 (0.3)

Individual analgesics at each visit were defined as a DRP if they were recommended for avoidance in CKD or if dose exceeded recommended dosing for a specific GFR. DRP, drug-related problem; NSAID, nonsteroidal anti-inflammatory drug.
[a]NSAIDs are all considered DRPs.

One possible explanation for frequent use of NSAIDs and other analgesics among patients with CKD is the preponderance of chronic pain in this population (25). About 61% of patients with CKD in a recent study reported chronic pain (33). Approximately 13% of the CRIC Study participants had arthritis at baseline, and more than one third had pain interfering moderately or greater with work; hence, they may have required multiple analgesics to manage their pain. Ill-advised use of NSAIDs may be exacerbated by low recognition of CKD (34), although the awareness of CKD might be higher in the CRIC Study than in patients with CKD who are not study participants. The observed higher use of non-NSAID analgesics both with persistent NSAID use and as a substitute for NSAIDs may reflect countervailing provider tactics, with intensification of analgesics in patients having difficulty managing pain and efforts to identify alternatives to NSAID use in patients for whom these agents are identified as ill advised.

As with all retrospective studies, this analysis has limitations to consider when interpreting the findings. Recording of NSAID and other analgesic use was on the basis of self-report and hence, subject to recall bias. However, only medication use in the 30 days before visits was recorded, and participants were asked to maintain a list of medications or bring them to visits as a means of optimizing recall. Although we did not validate the approach of collecting self-reported medication use, in a study comparing self-reported analgesic use with detection of urinary ibuprofen and acetaminophen metabolites, the overall rate of concordance was 81%–84% (35). Although herbal medications and other supplements were recorded as part of the CRIC Study medication assessment, reliable determination of the quantity of constituents, which might be categorized as NSAIDs like (*e.g.*, cyclooxygenase-2 inhibitory activity), was not feasible. The 30-day reporting period also limited the assessment of cumulative exposure between visits; however, our use of transition models to examine visit-pairs takes advantage of this study structure to assess factors associated with changes in analgesic use. As an observational study, confounding by either measured or unmeasured factors is possible. In addition, some participants missed several annual visits before returning for follow-up, and the NSAID use status at missed visits was assumed unchanged from the last annual visit. As reported, only a small proportion of visit-pairs was spaced more than a year apart. Finally, the CRIC Study annual visits did not include pain assessment beyond that included in the SF12-PCS or motivations for NSAID switch,

which could illuminate the identified trends or patterns in NSAID and other analgesic usage. However, we used pain affecting work, which was ascertained from the KDQOL, as a proxy for general pain and identified a positive association of this report of pain with NSAID switch patterns. In addition, the identification of persistent analgesic users, including those individuals with intensification of other analgesic usage, can offer some valuable insight into the proportion of patients with CKD and chronic pain and their needs. In conclusion, our study showed that higher levels of kidney function were associated with a greater likelihood of starting NSAIDs, whereas contact with a nephrologist lowered the likelihood of either starting NSAIDs or staying on NSAIDs. Both initiating and stopping an NSAID were linked to increased use of other analgesics, most notably opioids. Starting and staying on NSAIDs were also associated with worse pain and physical health. The safety consequences of interchanging or supplementing NSAIDs with non-NSAID analgesics, especially opioid toxicity and dependency, need to be explored further in CKD. Future studies will need to examine the association of NSAID use with long-term CKD progression in conjunction with the unintended consequences or tradeoffs related to concomitant or alternative use of non-NSAID analgesics.

Acknowledgments

M.Z., R.M.D., and J.C.F. were supported by National Institutes of Health (NIH)/National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grant R01 DK090008. J.B.B. was supported by the Geriatric Research, Education and Clinical Center at the Baltimore Veterans Affairs Medical Center. Funding for the Chronic Renal Insufficiency Cohort (CRIC) Study was obtained under a cooperative agreement from the NIDDK (grants U01DK060990, U01DK060984, U01DK061022, U01DK061021, U01DK061028, U01DK060980, U01DK060963, and U01DK060902). In addition, this work was supported, in part, by Perelman School of Medicine at the University of Pennsylvania Clinical and Translational Science Award NIH/National Center for Advancing Translational Sciences (NCATS) grant UL1TR000003, Johns Hopkins University grant UL1 TR-000424, University of Maryland General Clinical Research Center grant M01 RR-16500, the Clinical and Translational Science Collaborative of Cleveland, grant UL1TR000439 from the NCATS component of the NIH and the NIH Roadmap for Medical Research, Michigan Institute for Clinical and Health Research grant V 2014.07.28 UL1TR000433, University of Illinois at Chicago Center for Clinical and Translational Science grant UL1RR029879, Tulane University Translational Research in Hypertension and Renal Biology grant P30GM103337, and Kaiser Permanente NIH/National Center for Research Resources University of California, San Francisco–Clinical and Translational Science Institute grant UL1 RR-024131.

The CRIC Study Investigators are Lawrence J. Appel (The Johns Hopkins University), Harold I. Feldman (University of Pennsylvania), Alan S. Go (Kaiser Permanente of Northern California), Jiang He (Tulane University), John W. Kusek (National Institute of Diabetes, and Digestive, and Kidney Diseases), Mahboob Rahman (Case Western Reserve University School of Medicine), Panduranga Rao (University of Michigan), and Raymond R. Townsend (University of Pennsylvania).

Disclosures

None.

References

1. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification and stratification. *Am J Kidney Dis* 39[Suppl 1]: 1–266, 2002
2. Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 3: 1–150, 2013
3. Winkelmayer WC, Waikar SS, Mogun H, Solomon DH: Nonselective and cyclooxygenase-2-selective NSAIDs and acute kidney injury. *Am J Med* 121: 1092–1098, 2008
4. Gooch K, Culleton BF, Manns BJ, Zhang J, Alfonso H, Tonelli M, Frank C, Klarenbach S, Hemmelgarn BR: NSAID use and progression of chronic kidney disease. *Am J Med* 120: 280.e1–280.e7, 2007
5. Hull S, Mathur R, Dreyer G, Yaqoob MM: Evaluating ethnic differences in the prescription of NSAIDs for chronic kidney disease: A cross-sectional survey of patients in general practice. *Br J Gen Pract* 64: e448–e455, 2014
6. Wei L, MacDonald TM, Jennings C, Sheng X, Flynn RW, Murphy MJ: Estimated GFR reporting is associated with decreased nonsteroidal anti-inflammatory drug prescribing and increased renal function. *Kidney Int* 84: 174–178, 2013
7. Farag A, Garg AX, Li L, Jain AK: Dosing errors in prescribed antibiotics for older persons with CKD: A retrospective time series analysis. *Am J Kidney Dis* 63: 422–428, 2014
8. Patel K, Diamantidis C, Zhan M, Hsu VD, Walker LD, Gardner J, Weir MR, Fink JC: Influence of creatinine versus glomerular filtration rate on non-steroidal anti-inflammatory drug prescriptions in chronic kidney disease. *Am J Nephrol* 36: 19–26, 2012
9. Feldman HI, Appel LJ, Chertow GM, Cifelli D, Cizman B, Daugirdas J, Fink JC, Franklin-Becker ED, Go AS, Hamm LL, He J, Hostetter T, Hsu CY, Jamerson K, Joffe M, Kusek JW, Landis JR, Lash JP, Miller ER, Mohler ER 3rd, Muntner P, Ojo AO, Rahman M, Townsend RR, Wright JT; Chronic Renal Insufficiency Cohort (CRIC) Study Investigators: The chronic renal insufficiency cohort (CRIC) study: Design and methods. *J Am Soc Nephrol* 14[Suppl 2]: S148–S153, 2003
10. Lash JP, Go AS, Appel LJ, He J, Ojo A, Rahman M, Townsend RR, Xie D, Cifelli D, Cohan J, Fink JC, Fischer MJ, Gadegbeku C, Hamm LL, Kusek JW, Landis JR, Narva A, Robinson N, Teal V, Feldman HI; Chronic Renal Insufficiency Cohort (CRIC) Study Group: Chronic Renal Insufficiency Cohort (CRIC) study: Baseline characteristics and associations with kidney function. *Clin J Am Soc Nephrol* 4: 1302–1311, 2009
11. First Databank: FDB MEDKNOWLEDGE. Available at: http://www.fdbhealth.com/fdb-medknowledge/. Accessed January 6, 2015
12. Strand LM, Cipolle RJ, Morley PC: Documenting the clinical pharmacist's activities: Back to basics. *Drug Intell Clin Pharm* 22: 63–67, 1988
13. Lexi-Comp I: Lexi-COMP ONLINE TM. Available at: http://online.lexi.com/lco/action/home/switch. Accessed October 8, 2013
14. Seyffart G: *Drug Dosage in Renal Insufficiency*, Boston, Kluwer Academic Publishers, 1991
15. Truven Health Analytics Inc.: Micromedex Healthcare Series. Available at: http://www.micromedexsolutions.com/home/dispatch. Accessed December 16, 2014
16. Wolters Kluwer Health Inc.: Drug Facts and Comparisons. Available at: http://www.factsandcomparisons.com/. Accessed December 16, 2014
17. Bennett WM, Aronoff GR, Morrison G, Golper TA, Pulliam J, Wolfson M, Singer I: Drug prescribing in renal failure: Dosing guidelines for adults. *Am J Kidney Dis* 3: 155–193, 1983
18. American Society of Health System Pharmacists publication: AHFS Drug Information. Available at: http://www.ahfsdruginformation.com/. Accessed December 16, 2014
19. Molenberghs G, Verbeke G: *Models for Discrete Longitudinal Data*, New York, Springer, 2005
20. Daubresse M, Chang HY, Yu Y, Viswanathan S, Shah ND, Stafford RS, Kruszewski SP, Alexander GC: Ambulatory diagnosis and treatment of nonmalignant pain in the United States, 2000-2010. *Med Care* 51: 870–878, 2013
21. Olivo RE, Hensley RL, Lewis JB, Saha S: Opioid use in hemodialysis patients. *Am J Kidney Dis* 66: 1103–1105, 2015
22. Butler AM, Kshirsagar AV, Brookhart MA: Opioid use in the US hemodialysis population. *Am J Kidney Dis* 63: 171–173, 2014

23. Smith HS: Opioid metabolism. *Mayo Clin Proc* 84: 613–624, 2009
24. Kuo HW, Tsai SS, Tiao MM, Liu YC, Lee IM, Yang CY: Analgesic use and the risk for progression of chronic kidney disease. *Pharmacoepidemiol Drug Saf* 19: 745–751, 2010
25. Pham PC, Dewar K, Hashmi S, Toscano E, Pham PM, Pham PA, Pham PT: Pain prevalence in patients with chronic kidney disease. *Clin Nephrol* 73: 294–299, 2010
26. Adams RJ, Appleton SL, Gill TK, Taylor AW, Wilson DH, Hill CL: Cause for concern in the use of non-steroidal anti-inflammatory medications in the community–a population-based study. *BMC Fam Pract* 12: 70, 2011
27. Plantinga L, Grubbs V, Sarkar U, Hsu CY, Hedgeman E, Robinson B, Saran R, Geiss L, Burrows NR, Eberhardt M, Powe N; CDC CKD Surveillance Team: Nonsteroidal anti-inflammatory drug use among persons with chronic kidney disease in the United States. *Ann Fam Med* 9: 423–430, 2011
28. Curhan GC, Knight EL, Rosner B, Hankinson SE, Stampfer MJ: Lifetime nonnarcotic analgesic use and decline in renal function in women. *Arch Intern Med* 164: 1519–1524, 2004
29. Möller B, Pruijm M, Adler S, Scherer A, Villiger PM, Finckh A; Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) Foundation, CH-8048 Zurich, Switzerland: Chronic NSAID use and long-term decline of renal function in a prospective rheumatoid arthritis cohort study. *Ann Rheum Dis* 74: 718–723, 2015
30. Nderitu P, Doos L, Jones PW, Davies SJ, Kadam UT: Non-steroidal anti-inflammatory drugs and chronic kidney disease progression: A systematic review. *Fam Pract* 30: 247–255, 2013
31. Kristensen SL, Fosbøl EL, Kamper AL, Køber L, Hommel K, Lamberts M, Abildstrøm SZ, Blicher TM, Torp-Pedersen C, Gislason GH: Use of nonsteroidal anti-inflammatory drugs prior to chronic renal replacement therapy initiation: A nationwide study. *Pharmacoepidemiol Drug Saf* 21: 428–434, 2012
32. Express Scripts: A Nation in Pain: An Express Scripts Report Focuses on U.S. Opioid Trends for Treatment of Short-Term and Longer-Term Pain, December 9, 2014. Available at: http://lab.express-scripts.com/lab/publications/a-nation-in-pain. Accessed July 27, 2017
33. Wu J, Ginsberg JS, Zhan M, Diamantidis CJ, Chen J, Woods C, Fink JC: Chronic pain and analgesic use in CKD: Implications for patient safety. *Clin J Am Soc Nephrol* 10: 435–442, 2015
34. Stevens LA, Fares G, Fleming J, Martin D, Murthy K, Qiu J, Stark PC, Uhlig K, Van Lente F, Levey AS: Low rates of testing and diagnostic codes usage in a commercial clinical laboratory: Evidence for lack of physician awareness of chronic kidney disease. *J Am Soc Nephrol* 16: 2439–2448, 2005
35. Loo RL, Chan Q, Brown IJ, Robertson CE, Stamler J, Nicholson JK, Holmes E, Elliott P; INTERMAP Research Group: A comparison of self-reported analgesic use and detection of urinary ibuprofen and acetaminophen metabolites by means of metabonomics: The INTERMAP study. *Am J Epidemiol* 175: 348–358, 2012

Received: December 1, 2016 **Accepted:** July 7, 2017

Published online ahead of print. Publication date available at www.cjasn.org.

Present addresses: Dr. Clarissa J. Diamantidis, Department of Medicine, Duke University School of Medicine, Durham, North Carolina. Dr. Akinlolu O. Ojo, Department of Medicine, University of Arizona, Tucson, Arizona.

This article contains supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.12311216/-/DCSupplemental.

Supplemental Table 1. Mean eGFR Change at subsequent visits by NSAID switch pattern (n=15971 subsequent visits)

	Stay-off	Start	P value (start vs stay-off)	Stop	Stay-on	P value (stop vs stay-on)
Crude mean change in eGFR at subsequent visit	-1.2 (-1.3,-1.1)	-1.0 (-1.6,-0.5)	0.52	-0.1 (-0.7,0.5)	-0.4 (-0.7,0.0)	0.45
Adjusted mean change in eGFR at subsequent visit*	-1.2 (-1.4,-1.0)	-0.8 (-1.4,-0.2)	0.25	-0.3 (-1.0,0.3)	-0.6 (-1.1,-0.1)	0.49

*Adjusted mean estimated glomerular filtration rate (eGFR) changes in non-steroidal anti-inflammatory drugs (NSAID) switch groups were computed by setting all other predictors/covariates to their mean values using a GEE model with an identity link. The GEE model included the following predictors/covariates: NSAID use at antecedent visit and at subsequent visit and the interaction of the two, African American (AA), sex, age group, eGFR, urine protein group, body mass index (BMI) group, diabetes, cardiovascular disease (CVD), hypertension, arthritis, seeing nephrologist (all at antecedent visit except for AA and sex which were evaluated at baseline), years from baseline visit to the subsequent visit.

Supplemental Table 2a. Odds ratios of KDQOL Question 8 response: pain interfering with normal work moderately or greater at subsequent visits comparing NSAID switch groups (n=15971 subsequent visits)

	Stay-off	Start	Adjusted OR (start vs stay-off)	Stop	Stay-on	Adjusted OR (stop vs stay-on)
Total N in each group	12999	680		834	950	
N and column % of pain interfering with normal work moderately or greater at subsequent visit*	3957 (30)	283 (42)	1.45 (1.19,1.78)	322 (39)	399 (42)	0.79 (0.62,1.01)

Adjusted ORs of starting or staying-on non-steroidal anti-inflammatory drugs (NSAID) were computed based on GEE models with binomial distribution and logit link. The GEE model included the following predictors/covariates: NSAID use at antecedent visit and at subsequent visit and the interaction of the two, African American (AA), sex, age group, estimated glomerular filtration rate (eGFR), urine protein group, body mass index (BMI) group, diabetes, cardiovascular disease (CVD), hypertension, arthritis, seeing nephrologist (all at antecedent visit except for AA and sex which were evaluated at baseline), years from baseline visit to the subsequent visit.

Supplemental Table 2b. Adjusted mean SF 12 physical health composite score at subsequent visits by NSAID switch pattern (n=15971 subsequent visits)

	Stay-off	Start	P value (start vs stay-off)	Stop	Stay-on	P value (stop vs stay-on)
Adjusted mean SF 12 physical health composite at subsequent visit*	42.3 (42.0,42.6)	41.3 (40.6,42.0)	0.006	42.6 (42.0,43.3)	41.7 (41.1,42.3)	0.04

Adjusted mean SF 12 physical health composite score in non-steroidal anti-inflammatory drugs (NSAID) switch groups were computed by setting all other predictors/covariates to their mean values using a GEE model with an identity link. The GEE model included the following predictors/covariates: NSAID use at antecedent visit and at subsequent visit and the interaction of the two, African American (AA), sex, age group, estimated glomerular filtration rate (eGFR), urine protein group, body mass index (BMI) group, diabetes, cardiovascular disease (CVD), hypertension, arthritis, seeing nephrologist (all at antecedent visit except for AA and sex which were evaluated at baseline), years from baseline visit to the subsequent visit

Supplemental Information

Author Affiliations for CJASN_12311216

Min Zhan: Department of Epidemiology and Public Health, School of Medicine, University of Maryland, Baltimore, MD

Wendy L. St. Peter: College of Pharmacy, University of Minnesota and Chronic Disease Research Group, Minneapolis, MN

Rebecca M Doerfler, Jacob B. Blumenthal, and Jeffery C. Fink**:** Department of Medicine, School of Medicine, University of Maryland, Baltimore, MD

Corinne M. Woods: Previously at Department of Pharmaceutical Health Services Research, school of Pharmacy, University of Maryland, Baltimore, MD

Clarissa J. Diamantidis: Formerly, Department of Medicine, School of Medicine, University of Maryland, Baltimore, MD; Currently, Department of Medicine, Duke University School of Medicine, Durham, NC

Chi-yuan Hsu: Division of Nephrology, University of California-San Francisco, San Francisco, CA

James P. Lash: Department of Medicine, University of Illinois at Chicago, Chicago, IL

Eva Lustigova and Erin B. Mahone: School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA

Akinlolu O. Ojo: Formerly, Department of Internal Medicine-Nephrology, University of Michigan, Ann Arbor, MI; Currently, Department of Medicine, University of Arizona, Tucson, AZ.

Anne Slaven: Previously at MetroHealth Medical Center, Cleveland, OH

Louise Strauss: *University Hospitals of Cleveland Case Medical Center,* Cleveland, OH

Jonathan J. Taliercio: Cleveland Clinic Lerner College of Medicine, and, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, Ohio

Wolfgang C. Winkelmayer: Section of Nephrology, Baylor College of Medicine, Houston, TX

Dawei Xie: Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, PA