



ORIGINAL ARTICLE

Non-steroidal anti-inflammatory drugs in chronic kidney disease: a systematic review of prescription practices and use in primary care

Claire Lefebvre^{1,2}, Jade Hindié¹, Michael Zappitelli^{3,4}, Robert W. Platt^{2,5,6,7} and Kristian B. Filion^{2,5,7}

¹Department of Pediatrics, University of Montreal, CHU Sainte-Justine, Montreal, Quebec, Canada, ²Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada, ³Department of Pediatrics, Division of Nephrology, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada, ⁴Peter Gilgan Centre for Research and Learning (PGCRL), Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada, ⁵Centre for Clinical Epidemiology, Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Quebec, Canada, ⁶Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada and ⁷Department of Pediatrics, McGill University, Montreal, Quebec, Canada

Correspondence and offprint requests to: Claire Lefebvre; E-mail: claire.lefebvre@mail.mcgill.ca

ABSTRACT

Background. Chronic kidney disease (CKD) management focuses on limiting further renal injury, including avoiding nephrotoxic medications such as non-steroidal anti-inflammatory drugs (NSAIDs). We performed a systematic review to evaluate the prevalence of primary care NSAID prescribing in this population.

Methods. We systematically searched MEDLINE and Embase from inception to October 2017 for observational studies examining NSAID prescribing practices or use in CKD patients in a primary care setting. The methodological quality of included studies was assessed independently by two authors using a modified version of the Agency for Healthcare Research and Quality's Methodological Evaluation of Observational Research checklist.

Results. Our search generated 8055 potentially relevant publications, 304 of which were retrieved for full-text review. A total of 14 studies from 13 publications met our inclusion criteria. There were eight cohort and three cross-sectional studies, two quality improvement intervention studies and one prospective survey, representing a total of 49 209 CKD patients. Cross-sectional point prevalence of NSAID use in CKD patients ranged from 8 to 21%. Annual period prevalence rates ranged from 3 to 33%. Meta-analysis was not performed due to important clinical heterogeneity across study populations.

Conclusions. Evidence suggests that NSAID prescriptions/use in primary care among patients with CKD is variable and relatively high. Future research should explore reasons for this to better focus knowledge translation interventions aimed at reducing NSAID use in this patient population.

Keywords: chronic kidney disease, nephrotoxicity, non-steroidal anti-inflammatory drugs, primary care, systematic review

Received: 14.11.2018. Editorial decision: 8.4.2019

© The Author(s) 2019. Published by Oxford University Press on behalf of ERA-EDTA.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

INTRODUCTION

Chronic kidney disease (CKD) is a global health burden to patients and health care systems, with an estimated population prevalence of ~10% [1, 2]. Treatment is supportive and aimed at preventing CKD progression. Key to achieving this goal is limiting further kidney injury [3, 4] by avoiding the use of nephrotoxic medications when alternative, safer therapies exist. Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most ubiquitously prescribed medications, and alternatives exist for many of their clinical applications [5, 6]. NSAIDs lead to decreased kidney perfusion via inhibition of prostaglandin synthesis [7]. Their use in the general population is known to be strongly associated with the development of acute kidney injury, which in turn is a risk factor for CKD [8, 9].

International practice guidelines recommend complete NSAID avoidance in patients with a glomerular filtration rate (GFR) $<30\text{ mL/min/1.73 m}^2$ and avoidance of prolonged use in patients with a GFR $<60\text{ mL/min/1.73 m}^2$ [4]. Despite these recommendations, there is evidence that many prescribers are unaware of the importance of NSAID avoidance in patients with impaired kidney function [10–12]. As the primary care setting is the most frequent point of health care provider contact for many patients with CKD, it is important to better understand prescribing practices to patients with CKD in this setting. We therefore performed a systematic review to evaluate prescribing practices and the use of NSAIDs in adults with CKD. Our objective was to quantify and describe primary care NSAID prescribing practices and use among patients with CKD to elucidate the need for knowledge translation interventions aimed at reducing NSAID exposure in this vulnerable population.

MATERIALS AND METHODS

The protocol for this systematic review has been published on PROSPERO (registration number CRD42018081292). The review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Search strategy

We systematically searched MEDLINE and Embase (via Ovid) from inception to 17 October 2017 to identify observational studies examining NSAID prescribing practices or usage in CKD patients in a primary care setting. The full search strategy is reported in the [online appendix \(Supplementary data, Items SA1–SA2 and Tables SA1–SA2\)](#). We applied keywords for the concepts of ‘kidney disease’, ‘non-steroidal anti-inflammatory’ and ‘prescription’ and relevant database-specific Medical Subject Heading (MEDLINE) and Emtree (Embase) terms. An exhaustive list of generic NSAID names was also included. Trade names were not included, as they were deemed unlikely to substantially increase the search sensitivity [13]. To limit our search to the primary care setting, we combined two validated primary care/family practice search filters with a Boolean ‘OR’ operator to maximize sensitivity [14, 15]. We restricted our search to non-animal studies and conducted it without language restrictions. We queried authors of relevant studies regarding knowledge of ongoing or unpublished research in the area. We also manually searched the reference lists of relevant reviews and articles to identify additional studies.

Study selection

Two reviewers (C.L. and J.H.) independently screened titles and abstracts of identified studies. Studies deemed potentially relevant by either reviewer were read in full. Decisions to include or exclude full-text articles were made independently and disagreements were resolved through consensus. We included studies reporting NSAID use and/or prescription prevalence in CKD patients in primary care. For studies within multiple health care settings, $>50\%$ of patients had to be included from the primary care setting and extraction of primary care data had to be feasible. We excluded studies describing only hospitalized patients. We restricted inclusion to studies whose objectives included describing or quantifying medication use and those in which CKD diagnosis was objectively determined using diagnostic codes or laboratory testing (defined as per international guidelines) [4]. We restricted inclusion to cohort, case-control and cross-sectional designs (excluding commentaries, editorials, letters to the editor, reviews, case reports and case series). Clinical trials were excluded with the rationale that prescribing practices and factors influencing them would significantly differ from routine primary care practices [16, 17]. In studies where multiple prevalences were reported from the same population, we included the first measure taken after CKD diagnosis. A single study could contribute more than one prevalence value if it described distinct CKD populations.

We excluded studies in which the timing of NSAID use/prescription in relation to CKD diagnosis could not be established and those in which NSAID use/prescription clearly preceded CKD diagnosis or was established at the same time as CKD diagnosis; prevalence measures from these studies do not likely reflect prescribing to patients with known CKD. Seven study authors were contacted to clarify the timing of NSAID use/prescription in relation to CKD diagnosis, five of whom confirmed that the timing did not meet our inclusion criteria [18–22] and two of whom provided information allowing us to include their study.

Data extraction

Data extraction was performed independently by two authors (C.L. and J.H.) using a standardized, pilot-tested form. Disagreements were resolved through consensus. Extracted data included study design, country, study period, number of CKD patients, method of CKD diagnosis, NSAID definition and prevalence of NSAID use and/or prescription.

Quality assessment

Study quality was assessed using a modified version of the Agency for Healthcare Research and Quality’s Methodological Evaluation of Observational Research (MORE) checklist [23]. This checklist is specifically designed for observational studies examining the incidence and prevalence of chronic diseases [24]. MORE provides a descriptive quality assessment of studies and assigns ‘no flaw’, ‘minor flaw’, ‘major flaw’ or ‘poor reporting’ descriptors to each criterion that we adapted to signify a low, moderate, high or unclear risk of bias (due to poor reporting). All studies were included in the systematic review, regardless of their quality.

The checklist was adapted to our specific research question. In assessing external validity, MORE assigns a major flaw when the sampling frame is health care based, as it may not capture

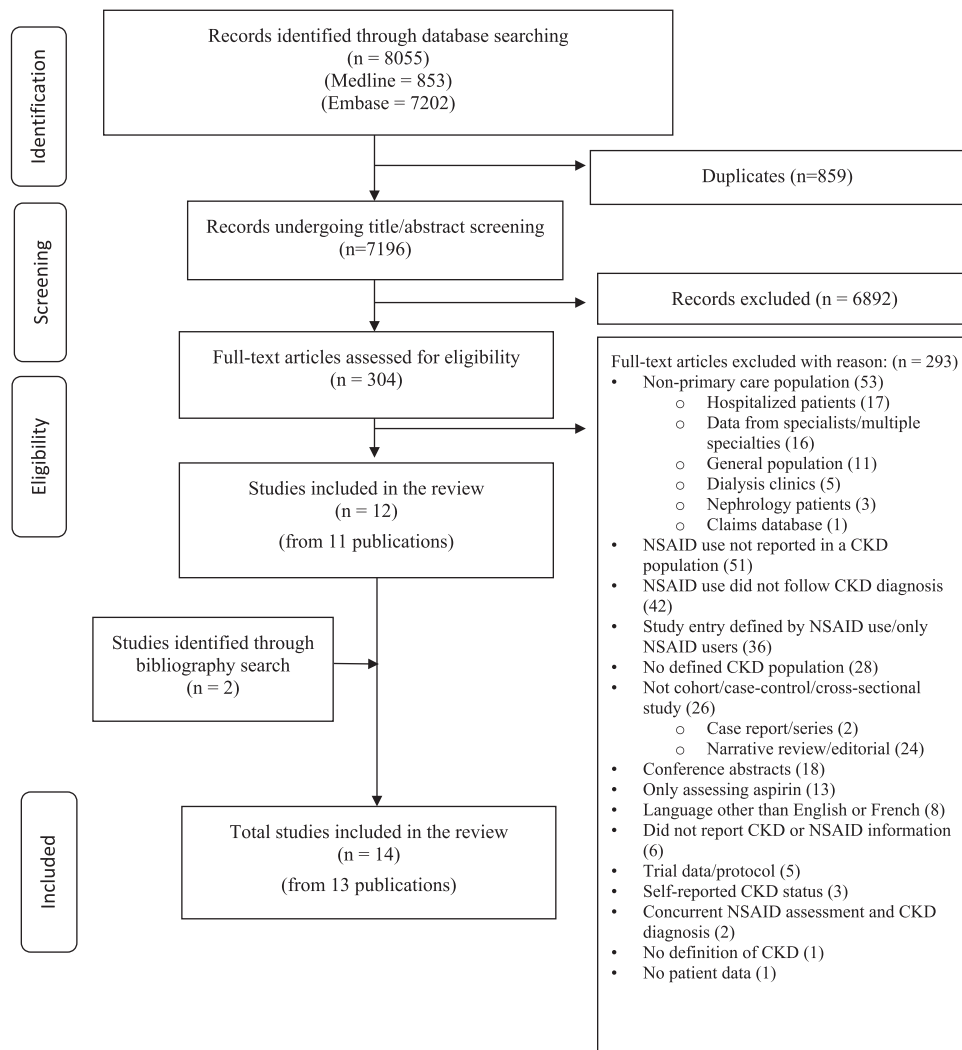


FIGURE 1: Flow diagram of included observational studies of NSAID prescription prevalence in primary care CKD patients.

prevalence rates in the general population [23]. As the purpose of our study was to evaluate prescriptions by health care practitioners, we did not assign a major flaw to studies using such sampling methods. However, we did assign a minor flaw to studies that used claims data that restricted to insured patients. MORE also assigns flaws to studies based on absolute cut-offs for participant response rates and exclusions from analysis, whereas we also considered whether studies assessed differences between responders and non-responders and between included and excluded patients. For the assessment of internal validity, we specifically evaluated whether NSAID prevalence was assessed objectively, whether it relied on patient recall for <6 months or patient recall for >6 months, assigning no flaw, a minor flaw or a major flaw, respectively.

Statistical analysis

Prevalences of use/prescription are presented along with 95% confidence intervals (CIs). Period prevalences over varying follow-up times were converted to a yearly prevalence to allow comparability of results, assuming that the NSAID prescription rate remained stable throughout each individual study's

follow-up period. Data from included studies were synthesized qualitatively via systematic review rather than quantitatively via meta-analysis due to important clinical heterogeneity across studies. As there were only two studies comparing NSAID use in CKD patients to that in non-CKD patients, we did not present relative effect measures [25, 26].

RESULTS

Our search generated 8055 potentially relevant publications (Figure 1). After removal of duplicates and title/abstract screening, 304 articles were retrieved for full-text review. Of these, 12 met our inclusion criteria, 2 of which were derived from a single publication [27]. Two additional studies were identified through reference screening of included articles. A total of 14 studies from 13 separate publications were thus included in our review.

Study and patient characteristics

The 14 studies included 49 209 CKD patients (Tables 1 and 2). Study size varied from 8 [28] to 27 668 CKD patients [29]. There were eight cohort studies [26, 27, 29–33], three cross-sectional

Table 1. Characteristics of studies assessing point prevalence of NSAID use among patients with CKD

Reference (location)	Source population	Patients with CKD, n (% female)	Age (years), mean (SD)	CKD definition (calculation equation)	NSAID definition	Study period	Prevalence of NSAIDs, % (95% CI)
Dorks et al. [25] (Germany)	21 nursing homes (>96% followed by primary care physician)	436 (75) ^a	83 (11) ^a	Single eCcr <60 (C-G) Stage 3: 76% Stages 4–5: 24%	NSAID prescription or OTC use in nursing home chart	2014–15	20 (17–25)
Fox et al. [35] (USA)	Patients from a private primary care practice and DM and/or HTN patients from an urban primary care practice	181 (NR)	NR (>18)	Single eGFR (NR) Stages 3–5: 100%	NSAID use in EMR or paper chart review	NR	13 (8–18)
Koffeman et al. [26] (The Netherlands)	Patients presenting a musculoskeletal complaint at primary care practices participating in the Integrated Primary Care Information database	285 (54) ^a	47 (17) ^a	Single eGFR (NR) Stages 4–5: 100%	NSAID prescription issued during musculoskeletal complaint episode from EMR	2000–10	19 (14–24)
Lioté et al. [37] (France)	Patients with gout or gout-related arthritis in a random sample of primary care and rheumatology practices (primary care data presented)	112 (13) ^a	63 (11) ^a	Single eCcr (C-G or measured using a 24-h urine sample) Stages 3–5: 100%	NSAID prescription recorded on a case report form during baseline visit	2008–09	10 (4–15)
McIntyre et al. [34] (UK)	Thirty-two primary care practices participating in the Renal Risk in Derby study	1741 (60)	73 (10)	Two eGFRs separated by at least 3 months (MDRD) Stage 3A: 77% Stage 3B: 23%	NSAID prescription or OTC use by questionnaire (validated with latest prescription)	2008–10	8 (7–10)
Weddle et al. ^b [27] (USA)	Resident-based primary care clinic	29 (NR)	72 (6)	CKD diagnosis present in patient's EMR	NSAID prescription in EMR	2014–15	21 (6–35)
Weddle et al. ^c [27] (USA)	Resident-based primary care clinic	32 (NR)	74 (7)	CKD diagnosis present in patient's EMR	NSAID prescription in EMR	2014	13 (10–24)

^aValues are given for whole study population.

^bProspective cohort.

^cRetrospective cohort.

SD, standard deviation; eCcr, estimated creatinine clearance; C-G, Cockcroft-Gault formula; OTC, over the counter; HTN, hypertension; NR, not reported; EMR, electronic medical record; MDRD, Modification of Diet in Renal Disease equation.

studies [25, 28, 34], two studies of quality improvement interventions [35, 36] and one prospective survey [37]. One publication described two separate CKD populations, which were considered independently in our analysis [27]. Two studies were performed within a single primary practice center [27]. The remaining studies were conducted across two or more practices, four of which grouped data from >100 practices using centralized electronic medical records databases [21, 26, 29, 30].

Study populations varied widely (Tables 1 and 2). The mean age ranged from 47 to 83 years, with all patients >18 years of age. Four studies selected their patient population based on

comorbidity other than CKD (e.g. diabetes, hypertension, musculoskeletal complaints and gout) [26, 35–37]. Two studies were not specifically based in a primary care practice. One was conducted using claims data from a major New York State insurer and was eligible for inclusion because the authors specifically provided prescription data for patients who had not been seen by a nephrologist and were therefore considered primary care patients [32]. The other study was conducted in a nursing home and was included because >96% of the patients were regularly followed by a primary care physician and a very small proportion were followed by medical specialists [25].

Table 2. Characteristics of studies assessing period prevalence of NSAID use among patients with CKD

Reference (location)	Source population	Patients with CKD, n (% female)	Age (years), mean (SD)	CKD definition (calculation equation)	NSAID definition	Study period	Prevalence of NSAIDs, % (95% CI)
Allen et al. [31] (USA)	Multispecialty group practice of 15 ambulatory health centers in Massachusetts (only 10% followed by a nephrologist)	11 774 (60)	73 (12)	Two eGFRs separated by at least 3 months (MDRD) Stage 3: 97% Stage 4: 3%	NSAID prescription in the EMR	2008–9	10 (9–10)
Arora et al. [32] (USA)	Claims data from major insurer (analysis restricted to patients not referred to a nephrologist)	15 177 (61)	72 (NR)	Two eGFRs separated by at least 3 months (MDRD) Stage 3: 97% Stage 4: 3% Stage 5: <1%	Insurance claim for NSAID prescription	2007–13	24 (23–25)
Guthrie et al. [29] (Scotland)	315 primary care practices contributing to the Scottish program for improving clinical effectiveness in primary care	27 668 (52) ^a	NR (≥65)	CKD diagnosis codes	NSAID prescription in the EMR	2007	8 (8–9)
Ingrasciotta et al. [30] (Italy)	123 primary care physicians meeting standard quality criteria within Ariana database	1989 (51)	72 (NR)	CKD diagnosis codes	NSAID prescription reimbursed by National Health System	2006–11	56 (54–58)
Keohane et al. [36] (Ireland)	At risk patients ^b from primary care ‘training practice’ (currently 18 practices)	158 (56) ^a	76 (10)	Single eGFR (MDRD) Stage 3: 92% Stage 4: 6% Stage 5: 1%	NSAID prescription in EMR	NR	3 (1–5)
Koffeman et al. [28] (Netherlands)	Four primary care practices in the Rotterdam region	8 (49) ^a	69 (10) ^a	Single eGFR (NR) Stages 4–5: 100%	Any OTC NSAID use reported via questionnaire	2012	25 (0–50)
Martinez-Ramirez et al. [33] (Mexico)	Patients without a nephrology referral from two primary care units	53 (38)	62.8 (9.9)	eGFR (MDRD) and/or micro-/macroalbuminuria Stage 1: 39% (plus albuminuria) ^c Stage 2: 34% (plus albuminuria) ^c Stage 3: 27%	NSAID use in medical chart	NR	32 (20–45)

^aValues are given for whole study population.

^bPatients with a known renal disorder or impairment, type 1 or 2 diabetes mellitus, hypertension, cardiovascular disease, peripheral vascular disease, hyperlipidemia and structural urological disorders.

^cAll patients within this eGFR stage also had ≥30 mg/day of albuminuria.

SD, standard deviation; MDRD, Modification of Diet in Renal Disease equation; EMR, electronic medical record; NR, not reported; OTC, over the counter.

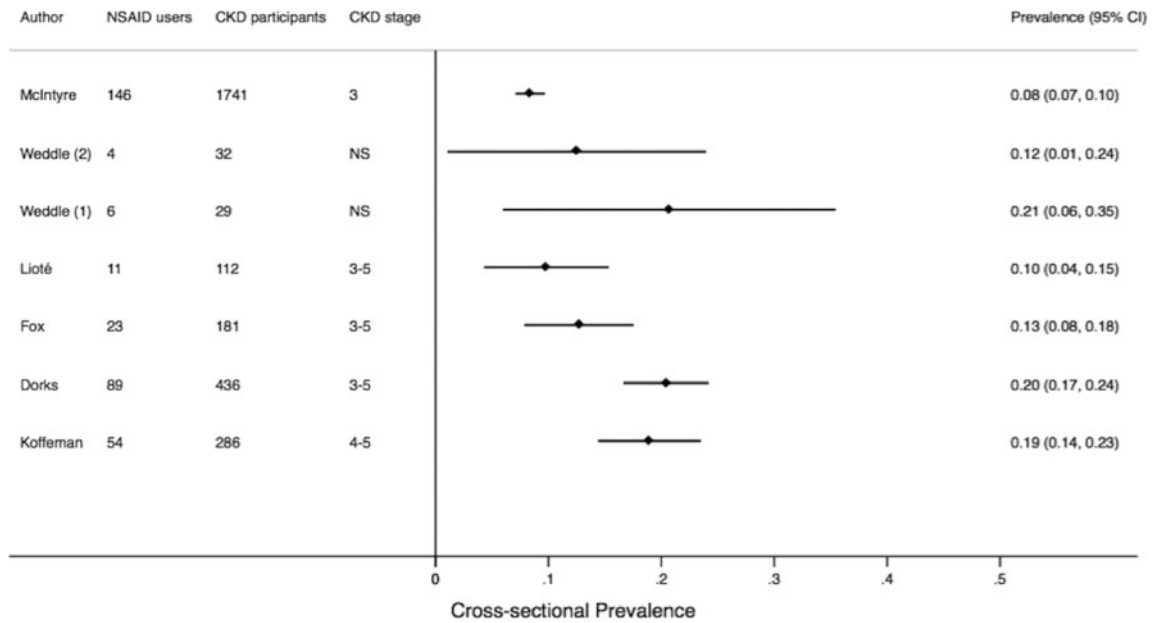


FIGURE 2: Forest plot of studies assessing point prevalence of NSAID prescription/use among CKD patients in primary care. Weddle (2), retrospective cohort; Weddle (1), prospective cohort; NS, not specified.

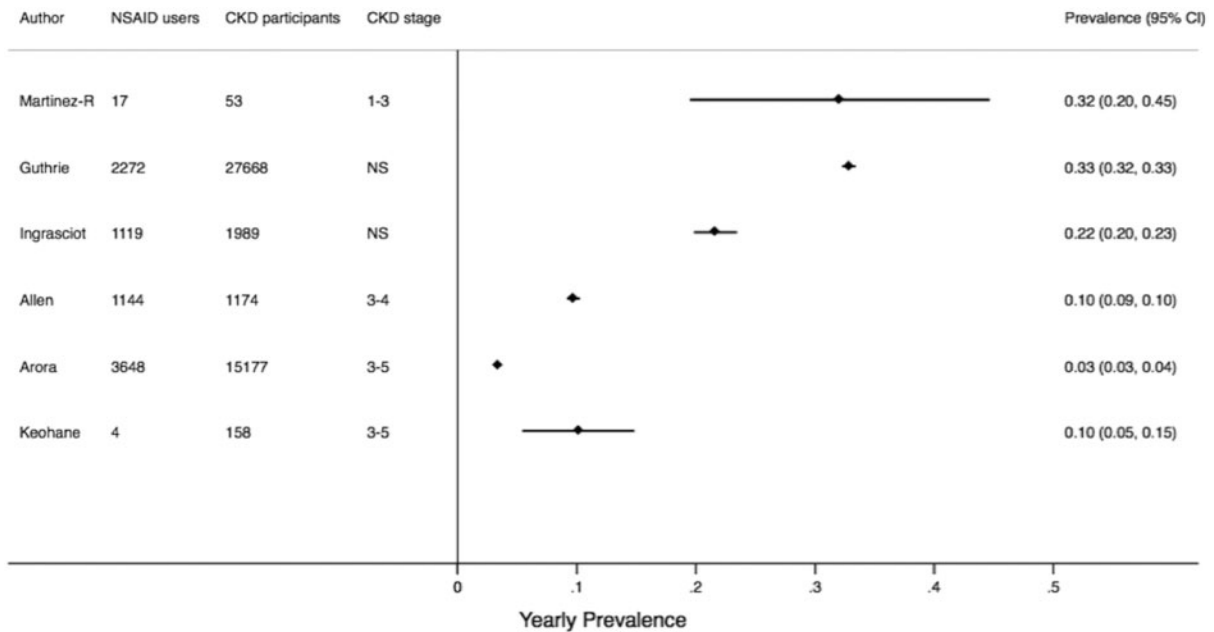


FIGURE 3: Forest plot of studies assessing period prevalence of NSAID prescription/use among CKD patients in primary care, expressed as yearly prevalence. NS, not specified.

CKD and NSAID definitions

The definition of CKD differed substantially across studies. Seven studies required a single low estimated GFR (eGFR) value [25, 26, 28, 33, 35–37]. Three studies required two separate eGFR values separated by at least 3 months [31, 32, 34]. Of the studies using eGFR, the severity of CKD among included patients varied widely (Tables 1 and 2) [26, 28, 33, 37]. Only one study considered microalbuminuria, allowing for the identification of CKD

Stages 1 and 2 [33]. Three studies relied on recorded CKD diagnostic and procedure codes without specific staging information [27, 29, 30].

Nine studies assessed NSAID prescriptions using patients' medical records [25–27, 29, 31, 33, 35, 36], of which five specifically excluded low-dose aspirin from reported estimates [27, 33, 35, 36]. Two studies reported on prescriptions reimbursed by either a national health provider [30] or by private insurance [32]. Two

studies used patient-administered questionnaires [28, 34] and one used physician-completed study forms [37] to assess NSAID use. Only one study provided a list of included NSAIDs [30].

Quality assessment

All the studies had at least a moderate risk of bias (Supplementary data, Tables SA3 and SA4). Eleven studies were considered to have a moderate risk of sampling bias and all but one failed to provide age-adjusted prevalences. Two studies were deemed to be at a high risk of bias [28, 37]. The first had a sample size of eight CKD patients and relied on questionnaire data to assess NSAID use, with a 26% response rate [28]. Furthermore, patients could be excluded based on their treating physicians' preference and relevant clinical characteristics differed significantly between included and excluded patients. The second study used a random sampling method to identify multiple primary care practitioners but had a <50% participation rate and provided no comparisons between patients from participating and non-participating practices [37].

Prevalence of NSAID use/prescriptions

Eleven studies reported exclusively on NSAID prescriptions by primary care physicians, one study evaluated over-the-counter NSAID use [28] and two others evaluated a combination of both [25, 34]. The seven studies reporting cross-sectional point prevalences of NSAID use in CKD patients found prevalences between 8% and 21% (Figure 2) [25–27, 34, 35, 37]. The remaining seven studies reported period prevalences over follow-up times ranging from 4 weeks [28] to 7 years [32]. Assuming stable prescription rates, the annual prevalence of NSAID use in CKD patients ranged from 3 to 33% (Figure 3) [29–31, 33]. One study was excluded from this analysis due to very small study size (eight CKD patients, two of which had been prescribed NSAIDs), making the prevalence too unstable for meaningful extrapolation to an annual prevalence value [28]. Due to the small number of studies, we were unable to perform a meta-regression analysis to examine the impact of follow-up duration on the overall NSAID prevalence.

DISCUSSION

To our knowledge, this is the first systematic review to evaluate physician prescribing or patient use of NSAIDs among CKD patients. We identified 14 studies (13 publications) addressing this question specifically in a primary care setting. Cross-sectional (point) prevalence of NSAID use/prescriptions ranged from 8 to 21% and annual period prevalence ranged from 3 to 33%. These results suggest that despite guidelines recommending against their use, a substantial proportion of CKD patients continue to receive NSAIDs.

Several factors may explain these findings, including lack of awareness of a CKD diagnosis by patients and physicians as well as lack of appreciation of the importance of NSAID avoidance in CKD. Two studies in our review assessing physicians' recognition of CKD status found it to be only 21–24% [31, 35]. While strategies such as automated GFR reporting may be helpful in increasing physicians' identification of CKD patients [38, 39], this may not be the only challenge. In our review, one study assessed the change in NSAID prevalence before and after a physician-documented CKD diagnosis and found only a very small decrease in NSAID prescribing (from 47% to 42%) [30]. A much more significant decrease in prescribing prevalence

was seen in the year following patient entry into dialysis (30%). Furthermore, another study [31] reported only a small decrease (from 24% to 20%) in inappropriate medication prescriptions between CKD patients whose physicians had recognized their diagnosis versus those whose physicians had not, although data for NSAIDs alone were not available.

Only one study evaluated the indication for NSAID prescription and found that the overwhelming majority were prescribed for osteoarticular disease [30]. Although alternative therapies exist, NSAIDs may offer superior pain relief in conditions such as arthritis, and our findings may reflect instances where alternatives to NSAIDs have been attempted but were unsuccessful [40]. Thus, despite recommendations to avoid NSAIDs in CKD patients, it may be difficult to do so, given the potential beneficial effects of NSAIDs on quality of life and pain relief in such patients. Indications of use and the presence of therapeutic alternatives remain important considerations to be assessed in future studies in this area.

Our study has several potential limitations. There was heterogeneity of the primary care settings of individual studies (e.g. variations in health care organization and practice characteristics). Heterogeneity was also present in the quality of NSAID reporting. Due to the absence of NSAID dose and duration data in most studies, we were unable to present data for chronic NSAID use as we had originally intended [41]. The only study to explicitly evaluate chronic NSAID use reported elevated rates, with 36% of CKD patients treated with NSAIDs for periods >90 days and 17% for >6 months [30]. Lastly, only one study reported NSAID use stratified by sex, showing similar use between men and women (Supplementary data, Figure SA1); thus we could not evaluate sex differences in NSAID prescribing in this population, a potential area for future research [30].

CONCLUSION

Overall, there are few studies specifically evaluating NSAID prescriptions to CKD patients in the primary care setting despite the widespread use of NSAIDs in the general population and the relatively high prevalence of CKD. More research designed to understand and reduce NSAID prescribing in CKD is warranted. Future studies should use standardized and accepted CKD definitions and should explore the reasons behind persistent NSAID use in patients with CKD to tailor knowledge translation interventions with a goal of reducing NSAID use in this patient population.

SUPPLEMENTARY DATA

Supplementary data are available at ckjonline.com.

ACKNOWLEDGEMENTS

We would like to thank Geneviève Gore for her help in building the search strategy. We also thank the authors of the included studies who provided important clarifications.

FUNDING

C.L. was supported by a Canadian Institute of Health Research Frederick Banting and Charles Best Canada Master's Scholarship funded through the McGill University Research Bursary Program as well as a master's bursary from the Fonds de Recherche du Québec—Santé [Quebec

Foundation for Health Research (FRQS)] in partnership with Fondation des Étoiles. R.W.P. holds the Albert Boehringer I Chair in Pharmacoepidemiology at McGill University. K.B.F. was supported by a Junior II salary support award from the FRQS.

CONFLICT OF INTEREST STATEMENT

None declared. Results presented in this article have not been published previously in whole or part, except in abstract format.

REFERENCES

- Hill NR, Fatoba ST, Oke JL et al. Global prevalence of chronic kidney disease—a systematic review and meta-analysis. *PLoS One* 2016; 11: e0158765
- Eckardt K-U, Coresh J, Devuyst O et al. Evolving importance of kidney disease: from subspecialty to global health burden. *Lancet* 2013; 382: 158–169
- Turner JM, Bauer C, Abramowitz MK et al. Treatment of chronic kidney disease. *Kidney Int* 2012; 81: 351–362
- 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* 2013; 3: 1–50
- Ong CK, Lirk P, Tan CH et al. An evidence-based update on nonsteroidal anti-inflammatory drugs. *Clin Med Res* 2007; 5: 19–34
- Conaghan PG. A turbulent decade for NSAIDs: update on current concepts of classification, epidemiology, comparative efficacy, and toxicity. *Rheumatol Int* 2012; 32: 1491–1502
- Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. *Am J Med* 1999; 106(5 Suppl 2): 13S–24S
- Ungprasert P, Cheungpasitporn W, Crowson CS et al. Individual non-steroidal anti-inflammatory drugs and risk of acute kidney injury: a systematic review and meta-analysis of observational studies. *Eur J Intern Med* 2015; 26: 285–291
- Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int* 2012; 81: 442–448
- Plantinga L, Grubbs V, Sarkar U et al. Nonsteroidal anti-inflammatory drug use among persons with chronic kidney disease in the United States. *Ann Fam Med* 2011; 9: 423–430
- Davis-Ajami ML, Fink JC, Wu J. Nephrotoxic medication exposure in U.S. adults with predialysis chronic kidney disease: health services utilization and cost outcomes. *J Manag Care Spec Pharm* 2016; 22: 959–968
- Samuelsen PJ, Slørdal L, Mathisen UD et al. Analgesic use in a Norwegian general population: change over time and high-risk use—the Tromsø Study. *BMC Pharmacol Toxicol* 2015; 16: 16
- Waffenschmidt S, Guddat C. Searches for randomized controlled trials of drugs in MEDLINE and EMBASE using only generic drug names compared with searches applied in current practice in systematic reviews. *Res Synth Methods* 2015; 6: 188–194
- Pols DH, Bramer WM, Bindels PJ et al. Development and validation of search filters to identify articles on family medicine in online medical databases. *Ann Fam Med* 2015; 13: 364–366
- Gill PJ, Roberts NW, Wang KY et al. Development of a search filter for identifying studies completed in primary care. *Fam Pract* 2014; 31: 739–745
- Messner DA, Moloney R, Warriner AH et al. Understanding practice-based research participation: the differing motivations of engaged vs. non-engaged clinicians in pragmatic clinical trials. *Contemp Clin Trials Commun* 2016; 4: 136–140
- Rengerink KO, Kalkman S, Collier S et al. Series: pragmatic trials and real world evidence: Paper 3. Patient selection challenges and consequences. *J Clin Epidemiol* 2016; 89: 173–180
- Litvin C, Nietert P, Wessell A et al. Recognition and management of chronic kidney disease in primary care. *Am J Kidney Dis* 2011; 57: 646–647
- Mold JW, Aspy CB, Smith PD et al. Leveraging practice-based research networks to accelerate implementation and diffusion of chronic kidney disease guidelines in primary care practices: a prospective cohort study. *Implement Sci* 2014; 9: 169
- Hsieh CF, Huang SL, Chen CL et al. Non-aristolochic acid prescribed Chinese herbal medicines and the risk of mortality in patients with chronic kidney disease: results from a population-based follow-up study. *BMJ Open* 2014; 4: e004033
- Tu K, Bevan L, Hunter K et al. Quality indicators for the detection and management of chronic kidney disease in primary care in Canada derived from a modified Delphi panel approach. *CMAJ Open* 2017; 5: E74–E81
- Modig S, Lanngren C, Ostgren CJ et al. The assessment of renal function in relation to the use of drugs in elderly in nursing homes: a cohort study. *BMC Geriatrics* 2011; 11: 1
- Shamliyan T, Ansari MT, Raman G et al. Development and implementation of the standards for evaluating and reporting epidemiologic studies on chronic disease incidence or prevalence. *Am J Public Health Res* 2013; 1: 183–190
- Shamliyan TA, Kane RL, Ansari MT et al. Development quality criteria to evaluate nontherapeutic studies of incidence, prevalence, or risk factors of chronic diseases: pilot study of new checklists. *J Clin Epidemiol* 2011; 64: 637–657
- Dorks M, Herget-Rosenthal S, Schmiemann G et al. Use of nonsteroidal anti-inflammatory drugs and renal failure in nursing home residents—results of the study “Inappropriate Medication in Patients with Renal Insufficiency in Nursing Homes.” *Wien Klin Wochenschr* 2016; 128: 287–290
- Koffeman AR, Valkhoff VE, Jong GW et al. Ischaemic cardiovascular risk and prescription of non-steroidal anti-inflammatory drugs for musculoskeletal complaints. *Scand J Prim Health Care* 2014; 32: 90–98
- Weddle SC, Shaun Rowe A, Jeter JW et al. Assessment of clinical pharmacy interventions to reduce outpatient use of high-risk medications in the elderly. *J Manag Care Spec Pharm* 2017; 23: 520–524
- Koffeman AR, Valkhoff VE, Çelik S et al. High-risk use of over-the-counter non-steroidal anti-inflammatory drugs: a population-based cross-sectional study. *Br J Gen Pract* 2014; 64: e191–e198
- Guthrie B, McCowan C, Davey P et al. High risk prescribing in primary care patients particularly vulnerable to adverse drug events: cross sectional population database analysis in Scottish general practice. *BMJ* 2011; 342: d3514
- Ingrasciotta Y, Sultana J, Giorgianni F et al. The burden of nephrotoxic drug prescriptions in patients with chronic kidney disease: a retrospective population-based study in southern Italy. *PLoS One* 2014; 9: e89072

31. Allen A, Forman J, Orav J et al. Quality of chronic kidney disease care in primary care. *J Gen Intern Med* 25: S373
32. Arora P, Elkin PL, Eberle J et al. An observational study of the quality of care for chronic kidney disease: a Buffalo and Albany, New York metropolitan area study. *BMC Nephrol* 2015; 16: 199
33. Martinez-Ramirez HR, Jalomo-Martinez B, Cortes-Sanabria L et al. Renal function preservation in type 2 diabetes mellitus patients with early nephropathy: a comparative prospective cohort study between primary health care doctors and a nephrologist. *Am J Kidney Dis* 47: 78–87
34. McIntyre NJ, Fluck R, McIntyre C et al. Treatment needs and diagnosis awareness in primary care patients with chronic kidney disease. *Br J Gen Pract* 2012; 62: e227–e232
35. Fox CH, Swanson A, Kahn LS et al. Improving chronic kidney disease care in primary care practices: an upstate New York practice-based research network (UNYNET) study. *J Am Board Fam Med* 2008; 21: 522–530
36. Keohane DM, Dennehy T, Keohane KP et al. Reducing inappropriate non-steroidal anti-inflammatory prescription in primary care patients with chronic kidney disease. *Int J Health Care Qual Assur* 2017; 30: 638–644
37. Lioté F, Lancrenon S, Lanz S et al. GOSPEL: prospective survey of gout in France. Part I: design and patient characteristics (n = 1003). *Joint Bone Spine* 2012; 79: 464–470
38. Akbari A, Swedko PJ, Clark HD et al. Detection of chronic kidney disease with laboratory reporting of estimated glomerular filtration rate and an educational program. *Arch Intern Med* 2004; 164: 1788–1792
39. Wyatt C, Konduri V, Eng J et al. Reporting of estimated GFR in the primary care clinic. *Am J Kidney Dis* 2007; 49: 634–641
40. Towheed TE, Maxwell L, Judd MG et al. Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev* 2006; 1: CD004257
41. Nderitu P, Doos L, Jones PW et al. Non-steroidal anti-inflammatory drugs and chronic kidney disease progression: a systematic review. *Fam Pract* 2013; 30: 247–255