Family Practice 2013; **30**:247–255
doi:10.1093/fampra/cms086
Advance Access publication 8 January 2013

Non-steroidal anti-inflammatory drugs and chronic kidney disease progression: a systematic review

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Received 20 August 2012; Revised 16 December 2012; Accepted 20 December 2012.

Background. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely regarded as one risk factor, which influences chronic kidney disease (CKD) progression. However, previous literature reviews have not quantified the risk in moderate to severe CKD patients.

Objective. To estimate the strength of association between chronic NSAID use and CKD progression.

Methods. We conducted a systematic review and meta-analysis of observational general practice or population studies featuring patients aged 45 years and over. The electronic databases searched were MEDLINE, EMBASE, Cochrane, AMED, BNI and CINAHL until September 2011 without date or language restrictions. Searches included the reference lists of relevant identified studies, WEB of KNOWLEDGE, openSIGLE, specific journals, the British Library and expert networks. For relevant studies, random effects meta-analysis was used to estimate the association between NSAID use and accelerated CKD progression (estimated glomerular filtration rate decline ≥ 15 ml/min/1.73 m2).

Results. From a possible 768 articles, after screening and selection, seven studies were identified (5 cohort, 1 case–control and 1 cross-sectional) and three were included in the meta-analysis. Regular-dose NSAID use did not significantly affect the risk of accelerated CKD progression; pooled odds ratio (OR) = 0.96 (95%CI: 0.86–1.07), but high-dose NSAID use significantly increased the risk of accelerated CKD progression; pooled OR = 1.26 (95%CI: 1.06–1.50).

Conclusions. The avoidance of NSAIDs in the medium term is unnecessary in patients with moderate to severe CKD, if not otherwise contraindicated. As the definition of high-dose of NSAID use remains unclear, the lowest effective dose of NSAIDs should be prescribed where indicated.

Keywords. Disease progression, general practice, glomerular filtration rate, kidney disease, non-steroidal anti-inflammatory agents, systematic review.

Introduction

Chronic kidney disease (CKD) is a major cause of morbidity and mortality worldwide[1] with an estimated prevalence for moderate to severe CKD of 8.5% in the adult UK population.[2] CKD progression can lead to the development of end-stage renal disease (ESRD) requiring renal replacement therapy,[3] which consumes 2% of the National Health Service budget.[4] This makes the identification of factors associated with CKD progression a matter of clinical and economic importance.[3]

CKD is significantly associated with increasing age, co-morbidity (commonly diabetes, cardiovascular disease and hypertension) and numerous drugs (e.g. cyclosporine).[3–6] National Institute for Health and Clinical Excellence (NICE) guidelines (2008)[3] consider NSAIDs to be nephrotoxic and recommend their use be avoided or that the renal function is checked annually in CKD patients. On the other hand, the guidelines are based on limited evidence, including 1 small randomized control trial[7] and three case–control studies.[8–10] However, NSAIDs are commonly used in the control of pain in patients with chronic inflammatory musculoskeletal conditions,[11] especially in general practice and general populations.[12,13] Over 50% of elderly patients with CKD are prescribed NSAIDs with low-dose aspirin accounting for the majority of prescriptions.[13] Given the recent emphasis on primary and secondary prevention of CKD progression,[3,5,14–16] it is important to quantify the risk to CKD patients.

Previous studies investigating the relationship between NSAIDs and CKD status have been conflicting, due in part to methodological limitations.[17,18] Such studies focused on the late stages of CKD and did not

investigate the development and onset of CKD.[17,18] Two previous systematic reviews by McLaughlin *et al*. (1998) and Delzell *et al*. (1998) were therefore unable to outline clear conclusions from this evidence.[17,18] However, these reviews were completed over 10 years ago; therefore, we intend to review and synthesize the latest evidence on the relationship between NSAIDs and CKD, which is now categorized into five stages[1] as shown in Table 1.

Methods

Study design

Using systematic review methods, the aims were to answer two major questions: (i) whether chronic NSAID use increases the risk of CKD progression and (ii) whether chronic NSAID use increases the risk of developing moderate to severe CKD.

Search strategy

Three interfaces (NHS, EBSCO and Cochrane) were searched using the following free text and exploded MeSH terms:

Drug measures: (NSAID*); (non-steroidal anti-inflammatory drugs); (nonsteroidal antiinflammatory drugs); (Analgesics); (Analgesic Agent); (Anti-Inflammatory Agents); (Anti-Inflammatory Agents, Non-Steroidal).
CKD status: (Chronic Kidney Disease); (Kidney Failure, Chronic); (Renal Insufficiency, Chronic).
Renal function measure: (eGFR); (GFR); (Glomerular Filtration); (Glomerular Filtration Rate).

The full database search strategy is available as Supplementary data, Web Supplement 1.

Searches were for relevant studies conducted up to the 30 September 2011 without language or date of publication restrictions. Searches were limited to human studies and participants aged 45 and over, as this is the age group in whom renal function is likely to be regularly assessed. Searched databases were MEDLINE, EMBASE, Cochrane, CINAHL and AMED. Other sources included the reference lists of all relevant articles, WEB of KNOWLEDGE, OpenSIGLE (*unpublished literature database*), hand searching of the Lancet journal (*for CKD seminar papers*), the British Library (*main catalogue*), NICE (*CKD guidelines*) and access to renal networks (SJD).

Table 1 *National Kidney Foundation—Kidney Disease Outcomes and Quality Initiatives stages of Chronic Kidney Disease*[1]

Stage	Description	GFR (ml/min/1.73 m^2)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mild reduction in GFR	60–89
3A*	Moderate reduction in GFR	45–59
3B*	Moderate reduction in GFR	30–44
4	Severe reduction in GFR	15–29
5	End-stage renal disease	<15 (or dialysis)

*As categorized by NICE[3]
Shaded = moderate to severe CKD.

Study inclusion criteria

In our review, we included population-based epidemiological studies with durations of ≥6 months and sample sizes of ≥50 participants. The duration of ≥6 months ensured that the participants were likely to have CKD[1] and NSAID use was long enough to result in a clinically significant decline in renal function. A sample size of ≥50 participants ensured that only studies with a reasonable sample size were included and that smaller studies looking at the effects of NSAIDs on acute GFR decline were excluded.[7] Studies with both males and females where at least some of the study participants were aged ≥45 years with moderate to severe CKD (equivalent to NKF-KDOQI stage 3 to 5 CKD, see Table 1) were eligible. Only orally administered selective or non-selective NSAIDs including Aspirin were evaluated. Without a standard definition of regular NSAID use, studies were included where they had predefined regular and non-regular NSAID user groups. Renal function, as indicated by the glomerular filtration rate (GFR), could be measured or estimated (eGFR) using the 4-variable Modification of Diet in Renal Disease (MDRD) or body surface area (BSA) standardized Cockcroft-Gault (CG) equations. Studies reporting on the risk of a study defined GFR/eGFR decline or the risk for developing moderate to severe CKD were included.

Study exclusion criteria

Studies with only males or females and those with participants with stages 1–2 CKD only were excluded. Studies in which all the participants were aged <45 years were excluded. Studies on phenacetin or using ESRD requiring renal replacement as the primary outcome were also excluded.

Study selection and data extraction

Citations were pooled into the REFWORKS referencing software (version 2.0). The stages of selection included duplicate removal, titles screening, abstract screening and selection, full-text review, quality assessment and meta-analysis. Database searching and title screening were conducted by PN, abstracts and full-text articles were reviewed by PN and LD. Disagreement about studies for inclusion was solved by discussion between the two reviewers in order to ensure that the study methodology and outcomes

fulfilled the inclusion criteria and were appropriate for the systematic review objectives.

Included articles underwent a methodological quality and risk of bias assessment (performed by PN) of the selection process, NSAID measure, outcome and analysis using the Critical Appraisal Skill Program (CASP)[19] checklists for observational studies.

Data was extracted by PN on the study type, location, inclusion criteria, exclusion criteria, sample size, NSAID data type, NSAID use definitions and study outcome.

Primary and secondary outcome measures

In keeping with the two main study objectives, the outcome measures were chosen to both quantify the risk of CKD progression and the risk of developing moderate to severe CKD with NSAID use.

The primary outcome of CKD progression was accelerated CKD progression (eGFR decline ≥15 ml/min/1.73 m2 over a 2-year time period), which was the primary outcome of three of the selected studies (Gooch,[20] Yarger[21] and Hemmelgarn[22]). The study by Evans *et al*.[23] reported their findings using a continuous measure of CKD progression (difference in eGFR decline rates).

The secondary outcome was the risk of developing moderate to severe CKD as reported by the Fored,[10] Agodoa[24] and Hippisley-Cox and Coupland studies.[25]

Meta-analysis

Studies were included in the random effects meta-analysis if they had used a dichotomous outcome measure of CKD progression. RevMan software (version 5.1) was used for the statistical analysis using the odds ratio (OR) for accelerated CKD progression (*primary outcome*) with regular- and high-dose NSAID use as the primary outcome. The I^2 statistic was used to assess the degree of heterogeneity, an indicator of consistency between studies. I^2 statistics of 25–50%, 50–75% and >75% were considered evidence of mild, moderate and marked heterogeneity, respectively.[26]

Results

The initial literature search resulted in 768 articles (between 1966 and 2011) of which 31 full-text studies were identified (see Supplementary data, Web Supplement 2 for summaries of the included and excluded studies). Of these, seven studies meet the inclusion and quality criteria and hence were included. Figure 1 provides details of the selection process and data from the seven included studies are presented in Table 2.

Characteristics of included studies

All included studies were in English, were performed between 2001 and 2011 and with the exception of one[21] were available in a full-text format.[10,20,22–25] Although only available as a published abstract, the Yarger study[21] contained sufficient detail both to fulfil the inclusion criteria and to allow an assessment of the study outcome. Moreover, the methods used in the Yarger study[21] were extremely similar to those presented in the Gooch study,[20] which was available in full text. Three studies were European (two Swedish, one UK)[10,23,25] and four were American.[20–22,24] There were five cohort (Gooch *et al*., Evans *et al*., Yarger *et al*., Hemmelgarn *et al*. and Hippisley-Cox and Coupland),[20–23,25] one cross-sectional (Agodoa *et al*.)[24] and one case–control (Fored *et al*.)[10] studies.

The sample size varied from 801 to 1 574 749 adult participants with a minimum inclusion age of 18.[10,20–25] Although the minimum inclusion age in some of the included studies was <45, all had some inclusion of patients aged 45 or older, which satisfied the inclusion criteria. In reality, most of the included studies within this review had participants aged 45 or older.[10,20–25] The mean age of the participants in the included studies ranged between 45[24] and 76[20,22]. Given the fact that the prevalence of moderate to severe CKD increases markedly with age, especially in those aged 45 and over,[2] the participants included within selected studies are likely to be representative of the general CKD population.

There were variations in the gathering of drug information across the included studies. Three studies used self-reported lifetime consumption questionnaires (Agodoa, Evans and Fored),[10,23,24] whereas the remaining four studies used prescription databases (Gooch, Hippisley-Cox, Yarger and Hemmelgarn).[20–22,25]

Six studies estimated the GFR using the four-variable MDRD equation,[20,22–25] whereas Fored *et al*. used the BSA-standardized CG equation.[10] It was unclear which method was used by Yarger *et al*.[21]

NSAIDs and CKD progression

Three studies (Gooch,[20] Hemmelgarn[22] and Yarger[21]) recorded the change in the mean eGFR over a 2-year period. Accelerated CKD progression (eGFR decline ≥ 15 ml/min/1.73 m^2) occurred in 10.9–13.3% of the study participants.[20,21] Regular NSAID use was not associated with an increased risk of accelerated CKD progression in stage 3 CKD patients.[20–22] High-cumulative NSAID exposure was significantly associated with an increased risk of accelerated CKD progression in the Gooch[20] study but not in the Yarger[21] study.

Evans *et al*. recorded the rate of eGFR decline per year over a mean follow-up period of 2.1 years.[23] They found that regular aspirin users with stage 4–5 CKD had a slower rate of disease progression per year compared with non-users.[23]

The meta-analysis was applied to the Gooch, Yarger and Hemmelgarn cohort studies with a combined sample size of 54,663 patients as they reported on the risk of accelerated CKD progression.[20–22] Evans *et al*. reported

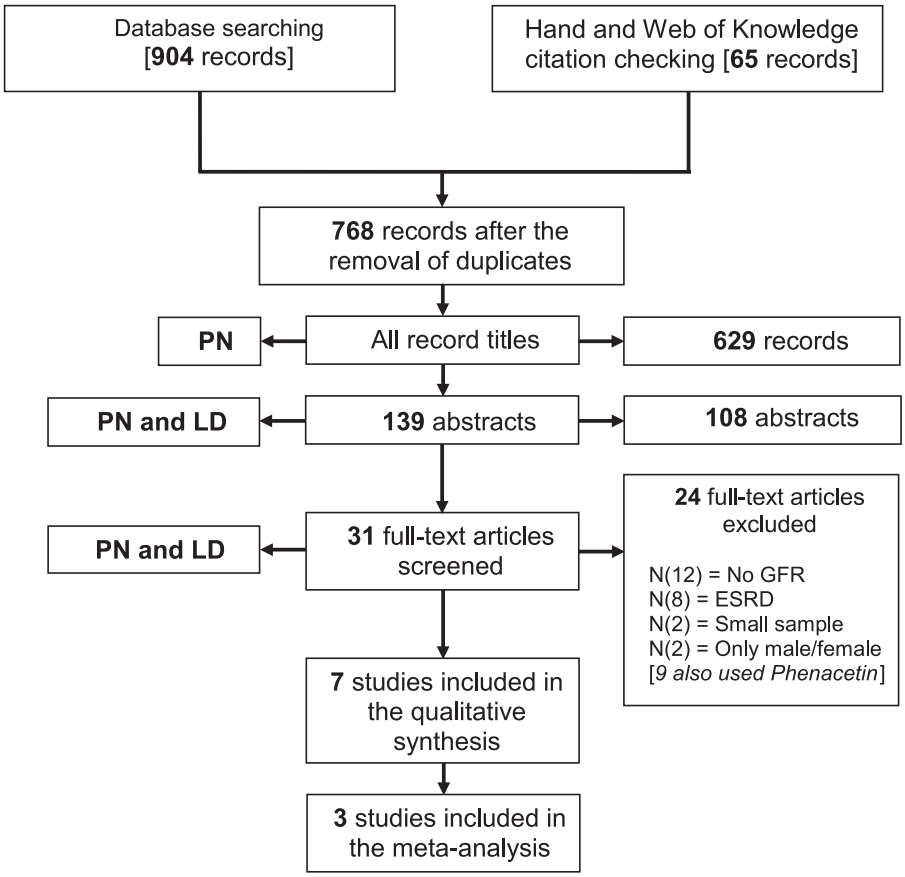

FIGURE 1 *Flow chart of identifying relevant studies.*

on an incompatible continuous outcome measure of CKD progression.[23] Figure 2 shows that there is no significant association between overall NSAID use and accelerated CKD progression; pooled OR = 1.04 (95%CI: 0.90–1.20), $P = 0.63$, $I^2 = 52\%$ (moderate heterogeneity). Exploring the moderate heterogeneity, sub-group analysis revealed that regular-dose NSAID use was not significantly associated with accelerated CKD progression, pooled OR = 0.96 (95%CI: 0.86–1.07), $P = 0.43$, $I^2 = 0\%$ (insignificant heterogeneity) but high-dose NSAID use significantly increased the risk of accelerated CKD progression, pooled OR = 1.26 (95%CI: 1.06–1.50), $P = 0.009$, $I^2 = 0\%$.

NSAIDs and the risk of developing moderate to severe CKD

The studies by Fored,[10] Hippisley-Cox[25] and Agodoa[24] varied in design and focused on the risk of developing moderate to severe CKD but not CKD progression. Fored *et al*. recruited patients with stage 4–5 CKD cases along with matched controls (1:1 ratio).[10] Compared with the control group, stage 4–5 CKD patients were significantly more likely to have had regular aspirin use.[10]

In the cross-sectional Agodoa *et al*. study, the prevalence of moderate to severe CKD (estimated to be 8.3%) was not significantly associated with habitual ibuprofen or aspirin use.[24]

Hippisley-Cox and Coupland, using a cohort design, found that stage 3B CKD was significantly associated with NSAID use in males and females.[25] The overall incidence rate of stage 3B CKD was 58.46 and 42.02 per 10 000 person years for women and men, respectively.[25]

Methodological quality

Presented below is a summary of the CASP assessment of bias. The included studies had large population-based samples (801–1,574,749 participants) with selection criteria that were appropriate for our objectives. The use of the eGFR using MDRD or BSA-CG equations minimized the risk of selection bias and accurately categorized moderate to severe CKD.[27]

The NKF-KDOQI criteria for diagnosing CKD requires there to be renal dysfunction in two consecutive measurements over ≥ 3 months.[1] The minimum duration of follow-up used in the inclusion criteria was ≥ 6 months. Therefore, CKD progression studies (Gooch,[20] Yarger,[21] Hemmelgarn[22] and Evans[23]) with two or more measurements of the eGFR included in this review would have had chronic renal dysfunction by the given definition. However, participants in the Hippisley-Cox and Coupland,[25] Fored[10] and Agodoa[24]

TABLE 2 *Research design characteristics*

Study	Study type and location	Inclusion criteria	Exclusion criteria	Study sample	NSAID data	Definition of NSAID use	Outcome
Fored *et al.* 2001[10]	Case–control, Sweden	18–74 year, creatinine, men > 300 µmol/l, women > 250 µmol/l; age (±10 years) and sex-matched controls	Pre- or post-renal failure, transplant patients	926 CRF versus 998 controls	Questionnaire; standardized interview	Regular use, twice a week for 2 months; non-users <20 tablet lifetime use	OR for CKD 4–5 aspirin, 2.50 (95%CI, 1.90–3.30); acetaminophen, 2.50 (95%CI, 1.70–3.60)
Gooch *et al.* 2007[20]	Cohort, Canada	≥66 years, ≥2 serum creatinine measurements	≥12 or hospital serum creatinine, eGFR >90 ml/min/1.73 m^2	10 184 patients	Prescription data	Use, ≥1 Rx 1 year before first creatinine measurement. High-dose use ≥90th percentile.	OR for accelerated eGFR decline (≥15 ml/min/1.73 m^2); any NSAID use (CKD 3), 0.82 (95%CI, 0.59–1.15); high dose (CKD 1–5), 1.26 (95%CI, 1.04–1.53)
Hemmelgarn *et al.* 2007[22]	Cohort, Canada	≥66 years, ≥2 serum creatinine measurements	≥12 or hospital serum creatinine, eGFR >90 ml/min/1.73 m^2	10 184 patients	Prescription data	Use, ≥1 Rx in 6 months before first creatinine measurement.	OR for accelerated eGFR decline (≥15 ml/min/1.73 m^2); any NSAID use (CKD 1–5), 1.00 (95%CI, 0.90–1.20)
Agodoa *et al.* 2008[24]	Cross-sectional, USA	>20 years old, ≥1 serum creatinine measurement	Missing data, dialysis, pregnancy and menses	8057 residents	Standardized survey	Habitual use, ever intake of an analgesic every day for at least 1 month	OR for CKD stage 3 (or worse) (<60 ml/min/1.73 m^2); ibuprofen,1.21 (95%CI, 0.70–2.10); aspirin,0.95 (95%CI, 0.70–1.20)
Evans *et al.* 2009[23]	Cohort, Sweden	18–74 years, creatinine permanently >300 µmol/l (men), >250 µmol/l (women)	Pre- or post-renal failure, transplant patients	801 patients	Questionnaire; standardised interview	Regular use, twice a week for 2 months; non-users <20 tablet lifetime use	Difference in the mean eGFR; decline coefficient; aspirin, +0.80 ml/min/1.73 m^2; (95%CI, 0.10–1.50)
Hippisley-Cox and Coupland 2010[25]	Cohort, England and Wales	35–74, no pre-existing CKD	Evidence of CKD	799 658 men and 775 091 women	Prescription data	Use, ≥2 Rx 6 months before study inclusion	HR for CKD stage 3B (<45 ml/min/1.73 m^2); men,1.30 (95%CI, 1.27–1.34); women,1.29 (95%CI, 1.25–1.33)
Yarger *et al.* 2011[21]	Cohort, USA	≥67 years, ≥2 serum creatinine measurements, CKD 2–3, continually eligible for TRICARE, received treatment at a military facility	CKD 1,4 or 5, ineligible for TRICARE, never received treatment at a military health facility	34 295 patients	Prescription data	No use, low-medium and high NSAID use (dose and criteria not defined)	OR for eGFR decline (≥15 ml/min/1.73 m^2); low-medium dose (CKD 3), 0.94 (95%CI, 0.78–1.12); high dose (CKD 3), 1.28 (95%CI, 0.84–1.93)

Shaded = CKD progression studies. NSAID, non-steroidal anti-inflammatory drug; CRF, chronic renal failure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; OR, odds ratio; HR, hazard ratio; Rx, prescription(s).

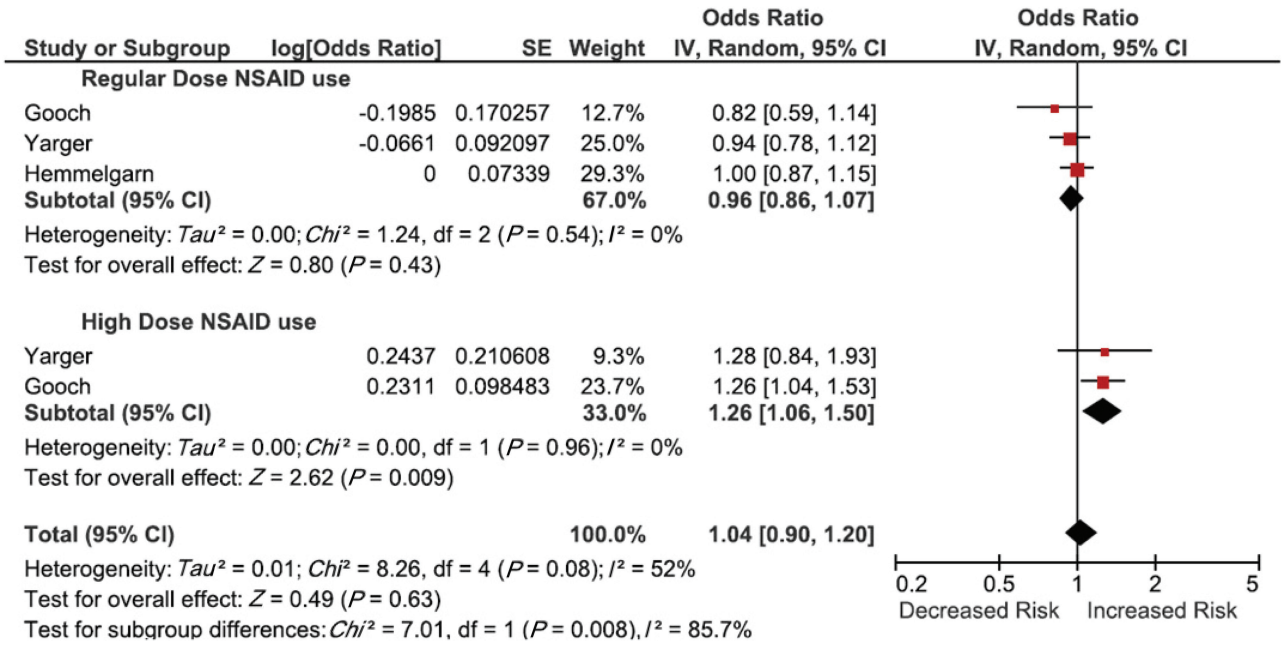

FIGURE 2 *Meta-analysis of non-steroidal anti-inflammatory drugs and the odds ratio for accelerated chronic kidney disease progression. SE, standard error; IV, inverse variance; random, random effects model; CI, confidence interval.*

studies, which looked at the development of moderate to severe CKD, may have had only a single eGFR measurement. Therefore, there is a risk that the single eGFR measurement corresponding to moderate to severe CKD may simply have been due to measurement error or an acute change in the participants' renal function at the time of the measurement. However, the large sample sizes, the use of the MDRD/BSA-CG equations and the clear renal dysfunction definitions employed, especially in the Hippisley-Cox and Coupland (stage 3B CKD)[25] and Fored (stage 4–5 CKD)[10] studies minimizes this risk.

The definition of accelerated CKD progression (eGFR decline ≥ 15 ml/min/1.73 m2 over a 2-year time period) was large enough such that any observed effect would be clinically significant and not merely due to measurement error or biological variation.[3] However, the definition also meant that the degree of change may be disproportionately large for patients with stage 4 CKD and may not be physiologically possible in stage 5 CKD patients. On the other hand, only 4% of patients in the Gooch[20] or Hemmelgarn[22] studies had stage 4 or 5 CKD and such participants were excluded from the Yarger study.[21] Moreover, the Gooch study[20] subdivided participants into stage 1–2, stage 3 and stage 4–5 CKD allowing the data on stage 3 CKD patients with normal-dose NSAID use to be extracted. Although the Hemmelgarn study[22] did not provide sub-group data, the effect of the remaining patients with stage 4 or 5 CKD is limited and is unlikely to significantly affect the meta-analysis findings.

Studies using computerized prescription data were unable to capture the level of over-the-counter NSAID use but studies using self-reported data would capture both over-the-counter and prescription use. However, the reliability of self-reported analgesia use behaviour was not assessed. Only Gooch *et al.*[20] used a standardized measure of cumulative NSAID use, others relied on subjective measures[10,21,23,24] or did not measure cumulative use at all.[22,25] There is a risk of confounding if pathologies (e.g. gout) that promote increased NSAID use also exacerbate CKD progression.[28] NSAID use may also be prompted by prodromal symptoms of worsening renal function.

Six studies presented the adjusted ORs featuring the covariates of age, gender and at least one co-morbidity.[10,20,21,23–25] However, given the array of possible confounding factors in CKD patients, especially amongst NSAID users who may have multi-morbidity, the risk of bias to significantly affect the results is ever present.

Discussion and conclusions

Summary of main findings

Our systematic review showed that regular-dose NSAID use was not associated with accelerated progression of CKD. However, high-dose NSAID use may significantly increase the risk of accelerated renal function decline by 26%. Within this systematic review, there is no clear evidence on whether NSAID use is associated with an increased risk of developing moderate to severe CKD.

Strengths and limitations of the review

In this review, we have quantified the risk posed by regular- and high-dose NSAID use on CKD progression.

The meta-analysis findings were based on three of the four eligible studies (Gooch,[20] Yarger[21] and Hemmelgarn[22]) looking at the effects of NSAIDs on CKD progression. Although not included in the meta-analysis, the results of the study by Evans *et al*.[23] were concordant with the meta-analysis findings. NICE guidelines define significant GFR decline as that >5.0 ml/min/1.73 m2 per year or >10.0 ml/min/1.73 m2 over 5 years.[3] Therefore, the definition of accelerated CKD progression (≥15 ml/min/1.73 m2 over 2 years) is clinically significant. Compared with earlier systematic reviews by McLaughlin *et al*.[17] and Delzell *et al*.[18] (1998), our findings include recent studies (2001–2011) with improved methodological designs as the studies featured in their reviews did not measure the progression of CKD (hence, they were not included in this review). The selection criteria were designed to allow the findings to be generalizable to clinical practice. The review tries to answer two distinct questions: whether NSAID use is associated with CKD progression and whether NSAID use increases the risk of developing moderate to severe CKD.

Publication bias was minimized as we had no language or date of publication restrictions and we conducted a thorough search for unpublished literature. Due to the limited number of studies, an objective assessment of publication bias through the use of funnel plots would not be reliable.[29]

Limitations of our systematic review are the lack of a standardized measure of 'high-dose' NSAID use and the unknown duration of safe NSAID use. In addition, the outcome measure of CKD progression did not account for the time period over which the decline took place; a more accurate measure of CKD progression would be the rate of eGFR decline per year,[30] which was used only in a study by Evans *et al*.[23] Studies within the systematic review looking at the development of moderate to severe CKD used a single eGFR measure; hence, some participants might not have had CKD as defined by the NKF-KDOQI criteria.[1] The primary outcome definition of an eGFR decline of >15 ml/min/1.73 m2 employed in the studies by Gooch,[20] Yarger[21] and Hemmelgarn[22] may have been disproportionately large for patients with stage 4 or 5 CKD. Finally, the meta-analysis is based on a relatively small number of cohort studies but with large sample populations. Only three of the seven included studies had enough methodological and statistical similarities to be included in the meta-analysis. One must always be cautious about interpreting findings from observational studies as they can be liable to the effects of bias and confounding.

Comparison with existing literature

NSAIDs and CKD progression. We compared our results to identified full-text studies reporting on NSAID use and CKD that, although not fulfilling our inclusion criteria (see Supplementary data, Web Supplement 2 for more detail on the reasons for exclusion), closely matched the included studies. Our findings on NSAID use and CKD progression are consistent with the Nurses' Health Study by Curhan *et al*.[31] and the Physicians Health Study by Kurth *et al*.[32] who found no significant association between NSAID use and renal function decline in females or males, respectively. However, both also found no significant association between high-dose NSAID use and worsening renal function.[31,32] This contradiction with our own findings may be due to the differences in the age and genders of the study participants as both factors affect the levels of NSAID use and CKD prognosis.[33–35] The mean age in the studies by Gooch *et al*.[20] and Yarger *et al*.[21] was 74 and 76 compared with 57 and 49 in the Nurses'[31] and the Physicians'[32] health studies, respectively. The Nurses'[31] and the Physicians'[32] health studies included only female or male participants and hence did not fulfil the inclusion criteria for the systematic review. Although our review shows that high-dose NSAID use may lead to an increased risk of CKD progression, the absolute risk attributable to high-dose NSAID use is likely to be small. In the Yarger study, high-dose NSAID users made up just 4.2% of the total sample population and only 13.4% of these patients had accelerated CKD progression.[21]

In our review, Evans *et al*.[23] found no significant association between aspirin use and renal function decline. Equally, most studies have found no significant association between aspirin use and renal dysfunction.[31,32,36–40] Only three published studies have reported significant renal dysfunction with aspirin use.[8,9,41] The majority of studies looking at the effects of aspirin use on CKD progression used ESRD as the primary outcome or did not measure the eGFR and hence were not suitable for inclusion.[8,9,36–41]

NSAIDs and the risk of developing moderate to severe CKD. As reported in our review, Agodoa *et al*.[24] found no significant association between regular NSAID use and an increased risk of developing moderate to severe CKD, consistent with other similar studies in the literature by Murray *et al*.[42] Rexrode *et al*.[38] and Stürmer *et al*.[43] (not included in the systematic review as they reported on creatinine clearance). However, the included studies by Hippisley-Cox and Coupland[25] and Fored *et al*.[10] did find a significant association as have other studies by Sandler *et al*.[37,44] and Segasothy *et al*.[45] However, these studies[37,44,45] had smaller sample sizes, recruited older patients and had higher levels of NSAID use compared with the studies which did not find a significant association.[24,38,42,43] Moreover, the study by Hippisley-Cox and Coupland[25] was not primarily designed to investigate the association between NSAID use and renal dysfunction. Overall, the most robust evidence indicates that NSAID use is not significantly associated with an increased risk

of developing moderate to severe CKD, which is consistent with the meta-analysis findings.

Implications for future research and clinical practice

As the definition of high-dose use is unclear and the fact that NSAIDs have other detrimental effects on kidney function, such as acute kidney injury, they should always be used with caution and given at the lowest effective dose. Annual screening is advocated in CKD patients with continued NSAID use. Future research should quantify the level of high-dose use in CKD patients and explore the effects of co-morbidity and co-prescription.

Acknowledgements

We are grateful to Prof. Danielle van der Windt (Primary Care Epidemiology) and Dr Olalekan Uthman (Research Associate/Systematic Reviewer) for their invaluable comments on the paper and meta-analysis.

Declaration

Funding: Wolfson Foundation; North Staffordshire Medical Institute.
Ethical approval: none.
Conflict of interest: none.

Supplementary material

Supplementary material is available at *Family Practice* online.

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