JSAMR
Journal of the National Student Association of Medical Research
Volume 4, Issue 1

# The use of non-steroidal anti-inflammatory drugs in chronic kidney disease: a primary care audit

Kyriacou H[1α], Howard S[1], Hatoum A[1], Khan T[1], Hamblin F[1], Ranmuthu C[1], Durham H[1], Chowdhury M[1]

[1]Addenbrookes Hospital, University of Cambridge, Cambridge, UK

[α]Corresponding author: *hk417@cam.ac.uk*

Peer-reviewed
Received: 12$^{th}$ February 2020
Revised: 21$^{st}$ July 2020, 9$^{th}$ August 2020
Accepted: 10$^{th}$ August 2020
Available online: 27$^{th}$ December 2020

Keywords: Audit | Chronic Kidney Disease | Non-Steroidal Anti-Inflammatory Drug

## Abstract

The incidence of chronic kidney disease (CKD) is increasing alongside the use of non-steroidal anti-inflammatory drugs (NSAIDs). The use of these medications in patients with CKD is associated with an increased risk of renal impairment and disease progression. As a result, the latest guidance by the National Institution of Care Excellence cautions against the prescription of NSAIDs in these patients. With this in mind, the authors conducted a large primary care audit to identify patients with CKD that were prescribed an NSAID. This identified 53 cases out of 1490 patients with CKD (3.6%). The factors contributing to this result are discussed and proposals are given to build upon these findings in future.

## 1 Introduction

Chronic kidney disease (CKD) is a common condition with an estimated global prevalence of 11-13% (Hill et al., 2016). According to Kidney Care UK, 1 in 8 people will go on to develop it at some point in their lives (Kidney Care UK, n.d.). Unfortunately, CKD is also a significant cause of morbidity and mortality. In 2015 alone, 1.2 million people died from renal failure; an increase of 32% since 2005 (H. Wang et al., 2016). As a result, clinicians must be careful when managing these patients. This is especially true for the elderly who make up the largest proportion of CKD patients, and are at the highest risk of kidney injury (Public Health England, 2014; X. Wang, Bonventre, & Parrish, 2014).

Non-steroidal inflammatory drugs (NSAIDs) are also in very common use, with over 15 million prescriptions dispensed in England in 2014 (Davis & Robson, 2016). This is excluding private prescriptions and over-the-counter forms which are readily available in most pharmacies across the world. However, NSAIDs have been shown to rapidly decrease glomerular filtration rate (GFR) and long-term use is associated with the progression of renal disease (Davis & Robson, 2016; Hörl, 2010). It has been reported that in patients aged over 65 years, NSAIDs use can more than double the risk of acute kidney injury in the next 30 days (Schneider, Lévesque, Zhang, Hutchinson, & Brophy, 2006). In spite of this, 9% of patients aged over 70 were found to receive a prescription for NSAIDs for more than 3 months in 2016 (Hörl, 2010). Similar findings have been described by other authors internationally (Guirguis-Blake et al., 2018; Plantinga et al., 2011).

Given the frequency of both CKD and NSAID use,

even a small percentage overlap could lead to a large cumulation of patient harm. With this in mind, the authors performed a primary care audit of the number of patients with a diagnosis of CKD that were being prescribed NSAIDs. This took place at a large medical centre in England.

## 2 Criteria

The criteria for this study are based on the latest guidelines as set out by the National Institute for Care Excellence (NICE) in 2014 (NICE, 2014). Notably, these recommendations are reiterated in the 2019 revision of 'NSAIDs – prescribing issues', a part of the NICE Clinical Knowledge Summaries (CKS) (NICE, n.d.).

In addition, several other independent organisations have produced similar advice on NSAID use in CKD. This includes the UK's National Health Service (NHS) and international groups such as Kidney Disease: Improving Global Outcomes (Levin et al., 2013; NHS, n.d.). The guidance on this area therefore appears to be robust.

Specifically, we will be comparing our data set against the following two criteria (NICE, 2014):

1. 'NSAIDs should not be prescribed in people who have an eGFR of less than 30 mL/minute/1.73 $m^2$ i.e. severe renal impairment.'

2. 'For those with any renal impairment or even those at risk of developing renal impairment, prescribing NSAIDs should be avoided (if possible).'

## 3 Evidence

There is a plethora of evidence which supports the claim that NSAIDs, especially at a high dosage, may increase the risk of CKD and/or worsen kidney function (reviewed in (Nderitu, Doos, Jones, Davies, & Kadam, 2013; Yaxley, 2016)). In support of this, a literature search of the PubMed database in December 2019 for the terms 'non-steroidal anti-inflammatory drug' and 'chronic kidney disease' returned 7502 results. A selection of these are described in Table 1. Interestingly, different NSAID subtypes are associated with different risk values, but the guidance remains generalised.

## 4 Standards

After consultation with members of the primary care team, we decided on a standard of 90% against which we have compared our findings (Table 3). In other words, we expected to see that 90% of patients with CKD were not prescribed an NSAID. Whilst we would have liked this figure to be as high as possible, we realised this standard must consider a number of influencing factors.

Firstly, CKD comes in different stages Table 2 (Levey et al., 2003). Whilst all CKD patients should generally avoid NSAIDs, only stages 4-5 are absolute contraindications (Levin et al., 2013; NICE, 2014). Practitioners may therefore feel that in some cases, the benefits of NSAID use outweigh the risk. This is commonly the case with low-dose aspirin for cardiovascular risk control which has been reported to have no significant effect on kidney failure (Su et al., 2019).

Other GPs may be unconvinced by the latest guidelines which lump all types of NSAIDs and doses together, and want to form their own opinions based on their experience or the literature. It is also possible that some doctors may even be unaware of the most recent guidelines. Alternatively, patients may be intolerant or allergic to alternative analgesia such as opioids, or simply prefer NSAIDs due to other factors such as fear of addiction.

## 5 Methods

A search of the GP database (SystemOne) was performed to identify patients with CKD who had visited the practice in the last 12 months (from 01/01/2019 to 01/01/2020). The resultant patient list was then filtered to identify those which were also prescribed an NSAID at any point during this period. Patients were stratified by the stage of their CKD and the data was analysed as described below.

## 6 Results

At the time of this study, 1490 patients were found to be on the CKD register. Of these, 53 had been prescribed a NSAID on repeat prescription (3.6%). Nine were found to be CKD stage 3 but fortunately, no patients were stages 4 or 5. Out of these 9 patients with stage 3 disease, 5 were receiving aspirin for cardiovascular risk reduction. The distribution of NSAIDs prescribed in this sub-population are given in Figure 1.

Given these results, each patient was marked for review and the decision was made not to implement a second cycle at this time.

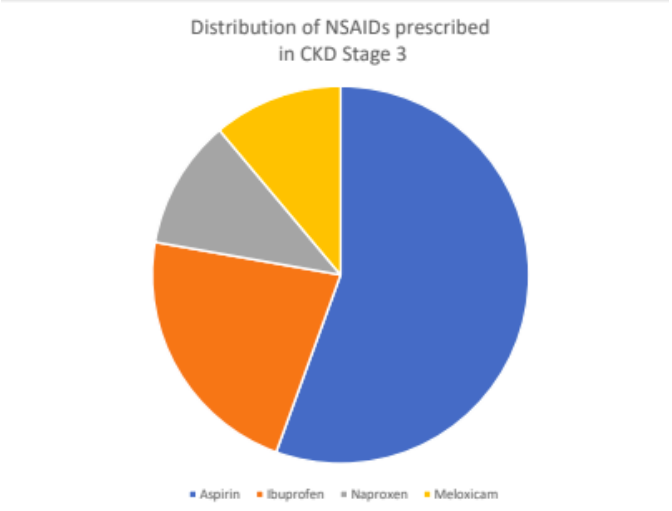


Figure 1: Pie chart of NSAID use in CKD stage 3 (n=9)

Table 1: Studies focusing on the effects of NSAIDs in CKD

| Study | Methods | Results |
|---|---|---|
| Nderitu et al 2013 | Systematic review and meta-analysis of NSAIDs and CKD progression. | High-dose NSAID use significantly increased the risk of accelerated CKD progression (OR: 1.26; 95% CI: 1.06– 1.50). |
| Hsu et al 2015 | Cohort study of 10184 subjects over 2.75 years using multiple regression analyses. | High-dose NSAID users experienced a 26% increased risk (OR: 1.26, 95% CI: 1.04-1.53). No risk differential was seen for selective and nonselective NSAID users. |
| Sandler et al 1989 | Multi-centre, retrospective case control study of 554 patients with newly diagnosed kidney disease. | Daily paracetamol ingestion was associated with higher risk of CKD compared with non-consumers (OR: 3.2; 95% CI: 1.05 to 9.80). |
| Ingrasciotta et al 2015 | Nested case-control study of 1989 CKD cases using multivariate models for NSAIDs. | Statistically significant increase in CKD risk for current users of oxicams (OR: 1.68; 95% CI: 1.15-2.44). |
| Fored et al 2001 | Case-control study of 926 CKD patients that regularly or sporadically used aspirin. | An average intake of 500g or more of aspirin per year during periods of regular use resulted in an increased risk of chronic renal failure (OR: 3.3; 95% CI: 1.4-8.0) |

*OR = odds ratio. CI = confidence interval.*

Table 2: Simplified staging system of CKD

| Stage | Description | GFR (ml/min/1.73m$^2$) |
|---|---|---|
| - | At increased risk | ≥60 |
| 1 | Kidney damage with normal or increased GFR | ≥90 |
| 2 | Kidney damage with mild decreased GFR | 60-89 |
| 3 | Moderately decreased GFR | 30-59 |
| 4 | Severely decreased GFR | 15-29 |
| 5 | Kidney failure | <15 (or dialysis) |

Table 3: Results on NSAID use in CKD

| | CKD + no NSAIDs | CKD + NSAIDs | Total |
|---|---|---|---|
| Number of patients | 1437 | 53 | 1490 |
| Patient percentage (%) | 96.4 | 3.6 | 100 |
| Pre-set standard (%) | 90 | 10 | 100 |

# 7 Discussion

96.4% of patients with CKD were not prescribed a NSAID in this GP practice which exceeded our standard of 90% 2. Moreover, no patients with CKD 4 or 5 were given an NSAID , in accordance with the latest evidence-based guidelines (NICE, 2014). After a period of observation, a number of factors were identified that contributed to this result.

Firstly, being a large practice, patients would often see a variety of clinicians of different grades over time (as well as medical students). This introduced a fresh perspective with every other consultation and enabled treatment plans to be double or triple checked.

Secondly, the computer system (SystemOne) automatically generates a 'pop-up' to warn against NSAID use in renal impairment. This creates the question as to why NSAIDs were given in 53 patients with CKD. One possible answer is that GPs might have been over-riding these prompts. This was observed on a number of occasions and one doctor explained to us that having so many different pop-ups for so many different things, actually made them all less effective. Another reason could be due to the perceived risk to benefit ratio of prescribing NSAIDs, as mentioned above.

Thirdly, the staff at the medical centre regularly meet to discuss topics such as prescribing issues and audit results. There is even a dedicated audit manager and an excess of keen medical students who are constantly evaluating the service provided.

However, this audit is not without its limitations and we realise that the results above are a gross underestimate of NSAID use in CKD. To better investigate this topic, one should also consider over-the-counter medication by conducting patient interviews. This is important as NSAIDs are commonly over-used in both dose and indication (Kaufman et al., 2018; Wilcox, Cryer, & Triadafilopoulos, 2005). During these interviews, one could also assess what patients with CKD know about NSAID use and whether they received any advice on diagnosis (e.g. verbally, as a leaflet, or from a website). Similarly, GPs could be interviewed and/or tested on NSAID prescribing issues. This could help establish why there were 53 cases of NSAID use in CKD identified.

# 8 Conclusions

This medical centre is exceeding standards with regards to NSAID use in CKD. There are multiple factors that have contributed to this and we advise that similar measures are employed by other practises. However, there is still room for improvement and as such, each case of NSAID use in CKD was followed up individually.

# Author statements

## Conflicts of interest statement

No conflicts of interest have been declared by any authors.

## Authorship statement

All authors fulfill ICMJE authorship criteria, which can be accessed at http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html. All authors have read and approved the final version, and accept responsibility for information published.

## Ethics statement

Authors declare that no ethical approval was required for this article.

## Editorial and peer review statement

The review process for this manuscript was double blind, where authors and peer reviewers were blinded to each others identity and institution.

## Open access and distribution statement



# References

Davis, A., & Robson, J. (2016, apr). *The dangers of NSAIDs: Look both ways* (Vol. 66) (No. 645). Royal College of General Practitioners. doi: 10.3399/bjgp16X684433

Guirguis-Blake, J., Keppel, G. A., Holmes, J., Force, R. W., Kriegsman, W., & Baldwin, L. M. (2018). Prescription of high-risk medications among patients with chronic kidney disease: A cross-sectional study from the washington, wyoming, Alaska, montana and idaho region practice and research network. *Family Practice*, *35*(5), 589–594. doi: 10.1093/fampra/cmy001

Hill, N. R., Fatoba, S. T., Oke, J. L., Hirst, J. A., O'Callaghan, C. A., Lasserson, D. S., & Hobbs, F. D. (2016, jul). *Global prevalence of chronic kidney disease - A systematic review and meta-analysis* (Vol. 11) (No. 7). Public Library of Science. doi: 10.1371/journal.pone.0158765

Hörl, W. H. (2010). *Nonsteroidal anti-inflammatory drugs and the kidney* (Vol. 3) (No. 7). Multidisciplinary Digital Publishing Institute (MDPI). doi: 10.3390/ph3072291

Kaufman, D. W., Kelly, J. P., Battista, D. R., Malone, M. K., Weinstein, R. B., & Shiffman, S. (2018, mar). Exceeding the daily dosing limit of nonsteroidal anti-inflammatory drugs among ibuprofen users. *Pharmacoepidemiology and Drug Safety*, *27*(3), 322–331. Retrieved from http://doi.wiley.com/10.1002/pds.4391 doi: 10.1002/pds.4391

Kidney Care UK. (n.d.). *Chronic kidney disease (CKD) | Kidney Care UK.* Retrieved from https://www.kidneycareuk.org/about-kidney-health/conditions/ckd/

Levey, A. S., Coresh, J., Balk, E., Kausz, A. T., Levin, A., Steffes, M. W., ... Willis, K. (2003, jul). *National Kidney Foundation Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification* (Vol. 139) (No. 2). American College of Physicians. doi: 10.7326/0003-4819-139-2-200307150-00013

Levin, A., Stevens, P. E., Bilous, R. W., Coresh, J., De Francisco, A. L., De Jong, P. E., ... Winearls, C. G. (2013, jan). *Kidney disease: Improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease* (Vol. 3) (No. 1). Nature Publishing Group. doi: 10.1038/kisup.2012.73

Nderitu, P., Doos, L., Jones, P. W., Davies, S. J., & Kadam, U. T. (2013, jun). Non-steroidal anti-inflammatory drugs and chronic kidney disease progression: a systematic review. *Family Practice*, *30*(3), 247–255. Retrieved from https://academic.oup.com/fampra/article-lookup/doi/10.1093/fampra/cms086 doi: 10.1093/fampra/cms086

NHS. (n.d.). *Chronic kidney disease - Treatment - NHS.* Retrieved from https://www.nhs.uk/conditions/kidney-disease/treatment/

NICE. (n.d.). *NSAIDs - prescribing issues - NICE CKS.* Retrieved from https://cks.nice.org.uk/nsaids-prescribing-issues{#}!scenario

NICE. (2014). *Chronic kidney disease in adults: assessment and management Clinical guideline.* Retrieved from www.nice.org.uk/guidance/cg182

Plantinga, L., Grubbs, V., Sarkar, U., Hsu, C. Y., Hedgeman, E., Robinson, B., ... Powe, N. (2011). Nonsteroidal anti-inflammatory drug use among persons with chronic kidney disease in the United States. *Annals of Family Medicine*, *9*(5), 423–430. doi: 10.1370/afm.1302

Public Health England. (2014). *Chronic kidney disease prevalence model.* Retrieved from www.facebook.com/PublicHealthEngland

Schneider, V., Lévesque, L. E., Zhang, B., Hutchinson, T., & Brophy, J. M. (2006, nov). Association of selective and conventional nonsteroidal antiinflammatory drugs with acute renal failure: A population-based, nested case-control analysis. *American Journal of Epidemiology*, *164*(9), 881–889. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17005625 doi: 10.1093/aje/kwj331

Su, X., Yan, B., Wang, L., Lv, J., Cheng, H., & Chen, Y. (2019, dec). Effect of antiplatelet therapy on cardiovascular and kidney outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. *BMC Nephrology*, *20*(1), 309. Retrieved from https://bmcnephrol.biomedcentral.com/articles/10.1186/s12882-019-1499-3 doi: 10.1186/s12882-019-1499-3

Wang, H., Naghavi, M., Allen, C., Barber, R. M., Carter, A., Casey, D. C., ... Zuhlke, L. J. (2016, oct). Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*, *388*(10053), 1459–1544. doi: 10.1016/S0140-6736(16)31012-1

Wang, X., Bonventre, J. V., & Parrish, A. R. (2014, sep). *The aging kidney: Increased susceptibility to nephrotoxicity* (Vol. 15) (No. 9). MDPI AG. doi: 10.3390/ijms150915358

Wilcox, C. M., Cryer, B., & Triadafilopoulos, G. (2005, nov). *Patterns of use and public perception of over-the-counter pain relievers: Focus on nonsteroidal anti-inflammatory drugs* (Vol. 32) (No. 11).

Yaxley, J. (2016). *Common analgesic agents and their roles in analgesic nephropathy: A commentary on the evidence* (Vol. 37) (No. 6). Korean Journal of Family Medicine. doi: 10.4082/kjfm.2016.37.6.310