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Can NSAIDs Be Used Safely for Analgesia in Patients with CKD?: CON

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Nonsteroidal anti-inflammatory drugs (NSAIDs) reversibly inhibit cyclooxygenase (COX) and therefore alter PG synthesis in many tissues with a range of effects beyond their intended one. NSAIDs have a number of well-known adverse effects on the kidney, gastrointestinal (GI) tract, and cardiovascular system. Adverse effect profiles vary by drug, in part depending on relative selectivity for the COX-1 and COX-2 isozymes, with more COX-2 selective inhibitors having lower risk of GI bleeding but higher risk of cardiovascular disease. Therefore, all NSAIDs have potentially serious adverse effects, and NSAIDs are a common cause of drug-related emergency hospital admission and drug-related death, from GI bleeding, AKI, and serious cardiovascular events (1,2).

International consensus guidelines recommend avoiding NSAIDs in people with eGFR <30 ml/min per 1.73 m^2, and to avoid prolonged use in those with eGFR 30–59 ml/min per 1.73 m^2 (3). Despite this, NSAIDs are commonly prescribed to people with CKD. One in ten people with CKD in the Chronic Renal Insufficiency Cohort Study were prescribed an NSAID annually, with 24% exposed at some point during 8 years of follow-up. Exposure was common in all subgroups examined, but was somewhat less likely in people with more severe CKD and those seeing nephrologists (4). A systematic review of NSAID use in people with CKD in seven cross-sectional studies found that 8%–21% were currently taking NSAIDs (5). One likely reason for liberal prescribing is that NSAID prescribing has rapidly observable benefits on pain, whereas harms are merely theoretical risks at the point of prescribing. In addition, the prescriber will often not observe the harmful outcome because the patient presents with adverse effects elsewhere in the health care system.

Randomized controlled trials examining NSAID effectiveness routinely exclude people with CKD, and often do not evaluate renal outcomes or other potential harms (6). Most of our evidence for NSAID harms in people with CKD therefore comes from observational studies. Although this means that causality cannot always be proved, there is no doubt that NSAID prescribing in people with CKD has a number of important adverse effects on the kidney and on other body systems.

Renal Adverse Effects

PGs play an important role in maintaining or increasing renal blood flow in the face of extracellular volume depletion or reduced filtration, and have effects on renal handling of sodium, potassium, and water. NSAID inhibition of renal PG synthesis can therefore cause abnormalities of serum sodium and potassium, fluid retention, and AKI in the face of dehydration and intercurrent illness.

There is consistent evidence from observational studies that NSAIDs are associated with increased risk of AKI. A systematic review estimated a pooled odds ratio (OR) of 1.63 (95% confidence interval [95% CI], 1.22 to 2.19) for AKI for current NSAID exposure in people with CKD (6). This relative risk is similar to that observed in the general population, but baseline risk of AKI is higher in people with CKD meaning that absolute risk of NSAID exposure is higher (6). A population study in Canada published since the review found ORs of 1.41 (95% CI, 1.20 to 1.65) and 1.50 (95% CI, 1.20 to 1.89) for AKI and hyperkalemia, respectively, for new NSAID use in older adults irrespective of renal function. Estimated ORs were similar in those with and without CKD, but baseline risk and therefore absolute risk of AKI associated with NSAID exposure was higher in people with CKD (7). People with CKD are commonly prescribed diuretics and/or renin-angiotensin system inhibitors (Table 1), which is a further risk factor for AKI. The risk of NSAID exposure for AKI in people taking renin-angiotensin system inhibitors and/or diuretics is somewhat larger in people with CKD (OR 2.51 [95% CI, 1.09 to 5.78]) compared with those without (OR 1.60 [95% CI, 1.31 to 1.95]). However, the absolute risk of AKI is four times greater in people with CKD because their baseline risk of AKI is higher (8).

In contrast, the evidence that NSAID exposure is associated with progression of CKD is more mixed. Some studies show a dose-related increased risk of incident CKD in people with hypertension (9). However, a systematic review of seven studies found no association with progression of CKD for regular-dose NSAID use, although a significantly increased risk of progression from high-dose use (pooled OR 1.26; 95% CI, 1.06 to 1.50) (10).

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Table 1. Prevalence of selected prescribing and comorbidities in people with CKD (reanalysis of existing dataset)

Drug or Condition with Clinically Important NSAID Interaction	Aged <65 yr (*N*=5159)[a] (%)	Aged ≥65 yr (*N*=28,412) (%)
Current diuretic[b]	38.5	57.8
Current RASI[b]	52.6	57.3
Current diuretic and RASI[b]	26.8	37.0
Current antiplatelet[b]	32.7	52.6
Current oral anticoagulation[b]	3.8	8.3
Cardiovascular disease[c]	24.7	50.6
Heart failure	6.0	14.3
Any of the above	73.8	90.8
Two or more of the above	48.0	73.7

RASI, renin-angiotensin system inhibitor.
[a]Reanalysis of data for 33,571 people recorded as having CKD in primary care medical records in Scotland (9).
[b]Current prescribing = prescription issued in last 84 d (either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker).
[c]Coronary heart disease, stroke, transient ischemic attack, or peripheral vascular disease.

GI and Cardiovascular Adverse Effects

There are many other reasons to be concerned about NSAID exposure in people with CKD, because NSAIDs cause GI bleeding, cardiovascular disease, and worsening of heart failure (2). People with CKD are at higher risk of GI bleeding. Compared with people with eGFR ≥60 ml/min per 1.73 m^2 and after adjustment for age, sex, comorbidity, and coprescribing, risk of hospitalization with GI bleeding is 50% higher in people with CKD stage 3, and seven times higher people with CKD stage 4 or 5 (11). NSAIDs can cause GI bleeding in anyone, but their risks are therefore potentiated in people with CKD because of higher baseline risk, and further potentiated by the frequent coprescribing in people with CKD of other drugs that increase bleeding risk (Table 1) (12).

Many, but not all, NSAIDs are also associated with increased risk of major vascular events, particularly COX-2 inhibitors and diclofenac, where risk is increased by one third (2). Ibuprofen is associated with some increased cardiovascular risk in high doses, but has lower risk of GI bleeding. In contrast, naproxen appears safe from a cardiovascular perspective but is associated with higher rates of GI bleeding (2). NSAIDs are associated with a doubling of risk of heart failure hospitalization in randomized clinical trials (2), with evidence of increased mortality associated with NSAID prescription in people with established heart failure, particularly at higher doses (13). People with CKD have higher cardiovascular risk, and commonly have established CVD and/or heart failure (Table 1), meaning that absolute risk of harm from NSAID exposure will be larger than in the general population.

Summary

NSAIDs have a number of adverse renal effects in people with CKD, and in particular are associated with clinically significant increased risks of AKI. People with CKD (and particularly older people with CKD) are very commonly prescribed other nephrotoxic drugs or other drugs that increase bleeding risk, very commonly have established cardiovascular disease, and fairly commonly have heart failure (Table 1). More than three-quarters have at least one additional reason to avoid NSAIDs, and more than one half have two or more additional reasons. In addition to renal risks, there will therefore often be good reasons to avoid NSAIDs in people with CKD. Although it is possible to mitigate NSAID risks by choosing NSAIDs that are safer for one outcome (such as naproxen for cardiovascular risks, or COX- 2 inhibitors for GI bleeding risks) there is no NSAID that is consistently safer across all outcomes.

Similarly, although coprescribing of gastro-protective drugs can mitigate (but not abolish) GI bleeding risks, there is growing evidence that proton pump inhibitors are themselves associated with both incident CKD and with AKI in established CKD (14).

There is therefore no safe way to prescribe NSAIDS for people with CKD. NSAID use in people with CKD always carries some risk, and that risk accrues across multiple domains (AKI, electrolyte disturbance, GI bleeding, cardiovascular disease, fluid retention, and exacerbation of heart failure), which are all more common in people with CKD than the general population. NSAIDs can therefore never be considered safe in people with CKD. However, they are sometimes indicated when baseline risk of all adverse effects is low and the indication is sufficiently strong that the expected benefit outweighs all expected risk. In this context, untreated pain is clearly suboptimal. Other analgesics are not always effective and opioids in particular have significant problems of their own. If you must prescribe NSAIDs, then consider and aim to mitigate all potential adverse effects of NSAIDs in an individual.

Gastroprotection with proton pump inhibitors should be used where indicated, interacting drugs should be stopped where possible, and patients should be instructed to stop NSAIDs and other nephrotoxic drugs should they develop diarrhea or vomiting, or febrile illnesses with reduced fluid intake (3). NSAIDs *cannot be used safely* in people with CKD because they are always risky. However, risk of NSAID use varies between individuals. NSAID use is therefore *not always wrong* because clinical practice not infrequently requires choosing the least-bad option in situations where every option is problematic.

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Author Contribution

B. Guthrie was responsible for project administration, and review and editing the manuscript.

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See related debate, "Can NSAIDs Be Used Safely for Analgesia in Patients with CKD?: PRO" and commentary, "Can NSAIDs Be Used Safely for Analgesia in Patients with CKD?: COMMENTARY" on pages 1184–1188 and 1192–1194, respectively.