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

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The debate in this issue of Kidney360 addresses the quandary that exists regarding the safety of nonsteroidal anti-inflammatory drug (NSAID) use in patients with CKD. This is an important issue because pain syndromes are common in patients with CKD. Whereas NSAIDs are a widely used and effective analgesic, they can be associated with several adverse clinical kidney syndromes (Table 1), particularly in patients with underlying CKD (1,2). Clinicians struggle to achieve adequate analgesia while also avoiding toxicity in this group. However, is avoiding NSAIDs in patients with CKD too restrictive and unnecessary? Our two expert debaters Erin Baretto and Bruce Guthrie tackle the conundrum of whether NSAIDs can be safely used in patients with nondialysis CKD. They will present the PRO and CON sides of the debate. We provide background on NSAID therapy in patients with CKD to set the stage for the debate.

Pain management in patients with CKD is limited by a number of analgesic drug-related adverse effects (3). Reduced GFR and impaired tubular secretion put patients with AKI or CKD at increased risk of drug-related nephrotoxicity because of increased accumulation of parent drugs, and their metabolites, from impaired metabolism and excretion (4). A significant number of drugs with potential toxicity are concomitantly prescribed to patients with advanced CKD (5). As such, NSAIDs are considered a class of drugs that should be avoided in patients with CKD, particularly those with advanced CKD (6,7). This approach has led to increased opioid administration and use of adjuvant therapies to manage pain (8,9). Importantly, opioid use poses many risks and data regarding the safety of even commonly used agents in patients with CKD are markedly limited (8). In fact, a recent publication noted that NSAIDs were safer than opioids in this group of patients (10). In light of this, a more nuanced approach encompassing CKD stage and other risk-enhancing comorbidities should be used given the difficulty in managing pain in this population. Let us see what our two expert faculty debaters have to say about this issue.

Dr. Barreto, on the PRO side of the debate provides perspective regarding the relative risk of NSAID use compared with the use of alternative analgesics. Her article cites multiple studies demonstrating noninferiority of NSAIDs compared with opioids in causing worsening kidney disease and hospitalization, and the higher risk of death with use of opioids compared with NSAIDs in patients with CKD. Multiple studies cited for this side of the debate offer evidence that NSAID use is not associated with a greater risk of AKI or worsening kidney disease in patients with CKD, and Dr. Barreto argues that the idea that non-NSAID analgesics are consistently safer for patients with CKD is not supported by data. Dr. Barreto concludes that the appropriateness of NSAID use in patients with CKD should be on the basis of an individualized evaluation encompassing type of pain, expected dose and duration, patient risk profile including stage of CKD, suitability of alternative therapies, and goals of care.

On the CON side of the debate, Dr. Guthrie highlights the physiologic underpinnings of NSAID-related adverse effects and how the “CKD kidney” may be more susceptible to these processes. He highlights that the risk of development of adverse clinical kidney syndromes with use of these agents is made higher in the setting of certain risk factors, such as dehydration and illness. Selected observational studies, which he outlines, have demonstrated the increased risk of AKI with NSAID use in the general population, and that although there is a similar absolute increased risk of AKI with NSAID use in patients with CKD, their baseline risk of developing AKI from any cause is greater because of many factors. His article suggests that between the combined risks of gastrointestinal, kidney, and cardiovascular adverse events and the high burden of comorbid risk factors in the CKD population, NSAID use is almost never safe in this population, although he acknowledges that in real clinical practice, we are frequently faced with the decision to choose between options that are all unsafe in some respect.

So what should clinicians caring for patients with CKD suffering with pain take away from this debate? Both debaters make strong arguments for their respective sides and as they both point out, the strength of the current data available on this subject in the literature is fairly weak because of the observational nature of the vast majority of the studies. In our view, in patients with CKD stages 1–3 in whom predisposing

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nephrotic risk factors are adequately addressed, use of short-acting NSAIDs for ≤5–7 days is a reasonable pain-management strategy with an acceptably low risk of significant nephrotoxicity. In this setting, routine laboratory testing and follow-up within 2–3 weeks should be undertaken to monitor for adverse effects. Long-term therapy may be used in patients cognizant of those conditions (vomiting, diarrhea, volume depletion, etc.) that should prompt immediate NSAID discontinuation. Patients must also be willing to participate in close medical follow-up. NSAIDs should likely be avoided in those with PG-dependent states, including states of uncorrected volume depletion, advanced cirrhosis, decompensated heart failure, or nephrotic syndrome (11). In addition, NSAID therapy should be used cautiously in patients with CKD who are prescribed renin-angiotensin inhibitors, diuretics, and other hyperkalemia-promoting drugs.

In contrast with patients with early-stage CKD, the risk of nephrotoxicity has not been adequately studied in patients with stage 4 and 5 CKD. As such, patients with stage 4 CKD require a more judicious approach to NSAID therapy because they often struggle with increased AKI events, electrolyte and acid-base abnormalities, hyperkalemia, and hypervolemia in the absence of NSAID therapy. NSAID use will exacerbate these complications, especially in patients with underlying heart failure, nephrosis, cirrhosis, hypertension, and type 4 renal tubular acidosis. Furthermore, concomitantly prescribed medications noted above will enhance risk of these complications. When stable patients with stage 4 CKD necessitate therapy with NSAIDs, low doses of short t1/2 preparations for ≤5 days and with close monitoring are required. In patients with nondialysis-dependent stage 5 CKD, these drugs should be avoided because of the significant risk of potentially severe complications. However, if palliation and patient comfort are the primary goals, then NSAIDs can be used judiciously recognizing the potential risk of adverse outcomes.

NSAIDs are clearly associated with adverse kidney outcomes. As such, the benefit of improved pain control must be weighed against toxicity. The most judicious approach is one that is highly individualized on the basis of CKD stage, age, comorbidities, and concomitant medication use. Ultimately, cautious use of NSAIDs in patients is reasonable with the major focus on avoiding iatrogenic life-threatening NSAID-related complications such as severe AKI, hyperkalemia, and hypervolemia. Whereas NSAIDs are generally avoided in patients with kidney disease, their use in this population after appropriate patient selection is reasonable, especially after weighing the risks posed by currently available alternative therapies.

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Author Contributions
M. Perazella was responsible for validation and visualization; M. Baker and M. Perazella were responsible for conceptualization, writing the original draft, and reviewing and editing the manuscript.

References
1. Nath KA, Chmielewski DH, Hostetter TH: Regulatory role of prostanooids in glomerular microcirculation of remnant nephrons. Am J Physiol 252: F829–F837, 1987
2. Gambardino G, Perazella MA: Adverse renal effects of anti-inflammatory agents: Evaluation of selective and nonselective cyclooxygenase inhibitors. J Intern Med 253: 643–652, 2003 https://doi.org/10.1046/j.1365-2796.2003.01146.x
3. Wu J, Ginsberg JS, Zhan M, Diamantidis CJ, Chen J, Woods C, Fink JC: Chronic pain and analgesic use in CKD: Implications for patient safety. Clin J Am Soc Nephrol 10: 435–442, 2015 https://doi.org/10.2215/CJN.06520714
4. Perazella MA: Pharmacology behind common drug nephrotoxicities. Clin J Am Soc Nephrol 13: 1897–1908, 2018 https://doi.org/10.2215/CJN.00150118
5. Bilge U, Sahin G, Unluoglu I, Ipek M, Durdu M, Keskin A: Inappropriate use of nonsteroidal anti-inflammatory drugs and other drugs in chronic kidney disease patients without renal replacement therapy. Ren Fail 35: 906–910, 2013 https://doi.org/10.3109/0886022X.2013.801272
6. Koncicki HM, Umruh M, Schell JO: Pain management in CKD: A guide for nephrology providers. Am J Kidney Dis 69: 451–460, 2017 https://doi.org/10.1053/j.ajkd.2016.08.039
7. The 2019 American Geriatrics Society Beers Criteria® Update Expert Panel: American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc 67: 674–694, 2019 https://doi.org/10.1111/jgs.15767
8. Davison SN: Clinical pharmacology considerations in pain management in patients with advanced kidney failure. Clin J Am Soc Nephrol 14: 917–931, 2019 https://doi.org/10.2215/CJN.05180418
9. Zhan M, St Peter WL, Doerfler RM, Woods CM, Blumenthal JB, Diamantidis CJ, Hsu CY, Lash JP, Lustigova E, Mahone EB, Ojo AO, Slaven A, Strauss L, Talerico JJ, Winkelmayer WC, Xie D, Fink JC; Chronic Renal Insufficiency Cohort (CRIC) Study

Table 1. Clinical kidney syndromes of nonsteroidal anti-inflammatory drugs

| Clinical Syndrome                                                                 |
|-----------------------------------------------------------------------------------|
| AKI (reduced renal PGs)                                                          |
| Hemodynamic kidney failure                                                       |
| Ischemic acute tubular injury                                                     |
| Hyperkalemia ± nonanion gap metabolic acidosis                                    |
| Hyponatremia                                                                      |
| Hypervolemia and sodium avidity                                                  |
| Edema, congestive heart failure                                                  |
| Diuretic resistance                                                              |
| Increased BP                                                                      |
| Exacerbation of underlying hypertension                                           |
| Acute tubulointerstitial nephritis (idiopathic reaction)                         |
| Nephrotic syndrome                                                               |
| Membranous nephropathy                                                           |
| Minimal change disease                                                           |
| Acute or chronic papillary necrosis                                              |
| Progression of CKD                                                               |

KIDNEY360 1: 1192–1194, November, 2020 NSAID Safety in CKD, Baker and Perazella 1193
Investigators: Patterns of NSAIDs use and their association with other analgesic use in CKD. *Clin J Am Soc Nephrol* 12: 1778–1786, 2017 https://doi.org/10.2215/CJN.12311216

10. Zhan M, Doerfler RM, Xie D, Chen J, Chen HY, Diamantidis CJ, Rahman M, Ricardo AC, Sondheimer J, Strauss L, Wagner LA, Weir MR, Fink JC; CRIC Study Investigators: Association of opioids and nonsteroidal anti-inflammatory drugs with outcomes in CKD: Findings from the CRIC (Chronic Renal Insufficiency Cohort) study. *Am J Kidney Dis* 76: 184–193, 2020 https://doi.org/10.1053/j.ajkd.2019.12.010

11. Baker M, Perazella MA: NSAIDs in CKD: Are they safe? *Am J Kidney Dis* 76: 546–557, 2020

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See related debates, “Can NSAIDs Be Used Safely for Analgesia in Patients with CKD?: PRO” and “Can NSAIDs Be Used Safely for Analgesia in Patients with CKD?: CON” on pages 1184–1188 and 1189–1191, respectively.