

NSAIDs in CKD: Are They Safe?

Megan Baker and Mark A. Perazella



The management of pain in patients with chronic kidney disease (CKD) is challenging for many reasons. These patients have increased susceptibility to adverse drug effects due to altered drug metabolism and excretion, and there are limited safety data for use in this population despite a high pain burden. Nonsteroidal anti-inflammatory drugs (NSAIDs) have long been regarded as dangerous for use in patients with CKD because of their risk for nephrotoxicity and thus alternative classes of analgesics, including opioids, have become more commonly used for pain control in this population. Given the well-established risks that opioids and other analgesics pose, further characterization of the risk posed by NSAIDs in patients with CKD is warranted. NSAID use has been associated with acute kidney injury, progressive loss of glomerular filtration rate in CKD, electrolyte derangements, and hypervolemia with worsening of heart failure and hypertension. The risk for these nephrotoxicity syndromes is modified by many comorbid conditions, risk factors, and characteristics of use, and in patients with CKD, the risk differs between levels of glomerular filtration rate. In this review, we offer recommendations for the cautious use of NSAIDs in the CKD population after careful consideration of these risk factors on an individualized basis.

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Introduction

Chronic pain is common in patients with chronic kidney disease (CKD), and its management is limited by drug-related adverse effects across analgesic classes.¹ Patients with reduced glomerular filtration rates (GFR) are at increased risk for drug-related toxicity due to impaired metabolism and excretion and increased accumulation of parent drugs and their metabolites.

Medications that have adverse side effects specifically associated with their use in CKD are prescribed more frequently as patients progress to more severe stages of CKD.² This is likely a reflection of both increasingly complex prescribing considerations with worsening GFR and polypharmacy related to advanced disease. For decades, nonsteroidal anti-inflammatory drugs (NSAIDs) have been at the top of the list of potentially harmful medications in patients with CKD, and this consensus continues to affect practice patterns today.^{3,4} Concern for increasing risk for the classic “clinical renal syndromes” associated with NSAIDs (Box 1) in patients with CKD underlies this thought process.⁵ Underlying CKD is considered a “prostaglandin-dependent” state, which makes NSAID use potentially more risky.⁶

Although patients with advancing CKD are exposed to more NSAIDs from combined over-the-counter and prescription use, health care provider prescribing of NSAIDs recently has been decreasing in a stepwise fashion with higher CKD stage in accordance with prescription guidance.^{7,8} NSAID avoidance has ultimately led to increased opioid administration and other adjuvant therapies to manage pain, often at excessive doses for the degree of GFR reduction.^{9,10} Opioid use poses many risks regardless of GFR, and data regarding the safety of even commonly used agents in patients with CKD are markedly limited.⁹ A review of the evidence surrounding NSAID use in patients with CKD suggests a more nuanced approach

encompassing CKD stage and other risk-enhancing comorbid conditions given the difficulty managing pain in this population.

Prostaglandins and the Kidneys

NSAIDs provide their analgesic, anti-inflammatory, and antipyretic actions through inhibition of cyclooxygenase (COX) enzymes. COX enzymes convert arachidonic acid, liberated from the cell membrane, to various eicosanoids, namely thromboxane and prostaglandins. These fatty acid derivatives act locally in a paracrine and autocrine manner, primarily as modulators of the effects of systemic hormones.¹¹

Two isoforms of COX, COX-1 and COX-2, have separate but overlapping roles. COX-1 is expressed constitutively in many tissues and maintains baseline physiologic functions, including maintenance of kidney perfusion and function, regulation of platelet aggregation, and protection of gastric mucosa.¹² COX-2 expression is modified by growth factors, cytokines, and other external signals and is upregulated in response to inflammation.¹¹ Although differences in their gene regulation lead to more constitutive expression of COX-1 and inducible expression of COX-2 in many tissues, COX-2 is also constitutively expressed in the kidneys.^{11,13}

COX-2 is largely responsible for increased prostaglandin production under circumstances requiring augmentation of renal blood flow (RBF), including in cases of reduced effective circulating volume (ECV) and reduced GFR.¹¹ The sites of COX-1 and COX-2 expression and prostaglandin action in human kidneys are shown in Figure 1.¹⁴ COX-2 is upregulated in animal kidneys in response to volume contraction and circulating angiotensin II, which increases prostaglandin synthesis, leading to local adaptation.¹⁵⁻¹⁸ Although differences in COX-2 localization exist between humans and animals, the strategic locations of this enzyme

Box 1. Adverse Effects of NSAIDs on the Kidney

- Acute kidney injury
 - ◊ Hemodynamic and acute tubular injury
- Hyperkalemia ± metabolic acidosis
- Hyponatremia
- Hypervolemia and sodium avidity
 - ◊ Edema, congestive heart failure
 - ◊ Diuretic resistance
- Exacerbation of hypertension
- Acute interstitial nephritis
- Nephrotic syndrome
 - ◊ Membranous nephropathy
 - ◊ Minimal change disease
- Acute or chronic papillary necrosis
- Progression of chronic kidney disease

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

and its upregulation under physiologic stress in both models suggest that COX-2 plays a critical role in adaptive renoprotective measures.¹¹ Hence, NSAID inhibition of COX-2 is likely a major cause of the nephrotoxicity of this drug class.^{11,19}

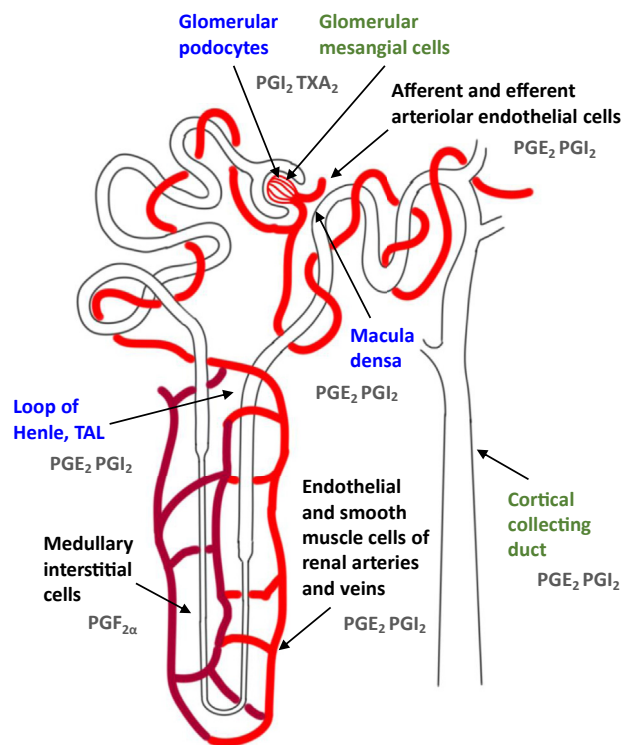


Figure 1. Location of expression of cyclooxygenase (COX) isoforms in the kidney and the predominant prostaglandins (PGs) produced. Text in green denotes locations where COX-1 expressed; blue, COX-2; and black, locations of overlapping COX-1 and COX-2 expression. Abbreviations: TAL, thick ascending limb; TXA₂, thromboxane A₂.

The primary eicosanoids in the kidney are prostaglandin I₂ (PGI₂), PGE₂, thromboxane A₂, and PGF_{2α}.¹¹ Prostaglandins play a significant role in modulating RBF and GFR (Table 1; Fig 2A). Vasodilating prostaglandins counteract vasoconstrictor effects to maintain RBF, GFR, and peritubular capillary perfusion.^{5,20} Prostaglandins also influence renal sodium, water, and potassium handling (Fig 2A).^{5,20} Their inhibition of sodium reabsorption and blunting of antidiuretic hormone (ADH) effects result in natriuresis and aquaresis, whereas prostaglandin stimulation of renin leads to aldosterone synthesis and potassium secretion.^{5,20} Unlike many systemic hormones that act unidirectionally to affect physiologic conditions, prostaglandins control a delicate balance, operating both under conditions requiring excretion and those calling for retention of sodium, water, and potassium and therefore their effects are complex and highly localized.

Under various circumstances of ECV depletion, prostaglandin production is increased to augment RBF, renin production, and sodium and water retention.²¹ Prostaglandin production is increased in CKD as a mechanism to improve the perfusion of remaining nephrons, even in the absence of volume depletion.⁶ This is important in maintaining baseline GFR even in the setting of modestly reduced glomerular filtration.¹¹

NSAIDs and the Kidneys

Overview

In the medical community, NSAIDs are regarded as harmful for patients with CKD. Clinical guidelines currently recommend the avoidance of prolonged NSAID use in CKD with GFR > 30 mL/min/1.73 m² and complete avoidance with GFR < 30 mL/min/1.73 m².²²⁻²⁴ Concern for NSAID-associated nephrotoxicity in patients with CKD arose from an era of combination analgesics (a mixture of NSAIDs with phenacetin, paracetamol, or salicylamide and caffeine or codeine) and is founded physiologically on concern for lack of renal reserve in the “CKD kidney.”²⁵

Epidemiologic studies have suggested increased nephrotoxicity risk with noncombination NSAID use in patients with CKD. However, epidemiologic studies examining the risk for CKD progression from NSAIDs are tasked with comparing unique sets of populations that are defined by their use of NSAIDs. Knowledge about NSAID nephrotoxicity leads to altered drug use, leading to selection and confounding biases.²⁶ Patients with CKD ingesting NSAIDs despite their well-publicized risk for nephrotoxicity represent a population that is inherently different than nonusers. Incompatible conclusions between many well-designed studies likely result from differences in study population, study design, study size, and methods used for attempting to adjust for confounders. These contradictory findings suggest a propensity for NSAIDs to cause nephrotoxicity in CKD, but also the presence of strong modifiers of this effect, such as severity of underlying health

Table 1. Prostaglandins and the Kidney

Eicosanoid	Site	Action	Effect in the Kidney
PGE ₂ and PGI ₂	JGA of glomerulus	Activation of RAAS	Sodium and water retention by the PCT, and sodium retention and potassium wasting by the DCT through the effects of aldosterone
	Medulla, inner cortex	Arteriolar vasodilation Inhibition of cAMP synthesis	Augmentation of postglomerular perfusion Decreased ADH effect and increase diuresis
	Loop of Henle	Decreases transcellular transport of sodium	Increased sodium excretion and decreased medullary osmotic gradient
	Glomerulus	Attenuates podocyte cell contraction and arteriolar vasoconstriction induced by angiotensin II, endothelin, ADH, platelet activating factor	Attenuation of podocyte cell contraction leads to preservation of glomerular surface area and GFR
TXA ₂	Glomerulus	Vasoconstriction and podocyte contraction	Decreased renal blood flow, glomerular filtration, and perfusion pressure
PGF _{2α}	Medullary interstitial and tubular cells	Modulation of water reabsorption and transcellular transport of sodium	Adaptive sodium and water handling

Abbreviations: ADH, antidiuretic hormone; cAMP, cyclic adenosine monophosphate; DCT, distal collecting tubule; GFR, glomerular filtration rate; JGA, juxtaglomerular apparatus; PCT, proximal convoluted tubule; PG, prostaglandin; RAAS, renin-angiotensin-aldosterone system; TXA₂, thromboxane A₂.

conditions, burden of chronic disease, and concomitant medication exposures (Box 2). Many studies also have lack of stratification by CKD stage or exclusion of advanced CKD (stages 4-5) altogether.

Prescribing NSAIDs raises the concern for increased risk for the development of one of the serious “clinical renal syndromes.” The risk for each of these effects is discussed next.

Acute Kidney Injury

The major concern associated with NSAID use is acute kidney injury (AKI). Despite this, AKI and other adverse effects such as fluid and electrolyte derangements rarely develop in patients with few or no risk factors for injury (Box 2) with regular NSAID use.²⁷⁻³² Pooled risk ratios for AKI events among individual NSAIDs for patients without CKD are reported to be within a range of 1.6 to 2.2.¹² Although the nephrotoxicity of individual NSAIDs may

vary to a certain degree, a meta-analysis characterizing AKI risk with the use of many common agents demonstrated a relatively similar elevation in risk among all agents, though rofecoxib demonstrated the greatest risk.³³ Importantly, selective COX-2 inhibitors cause adverse kidney effects at a rate and severity comparable to nonselective NSAIDs.^{19,33-36}

NSAID-associated AKI is predominantly hemodynamically mediated, resulting in reversible reduction in GFR or ischemic tubular injury (Fig 2B). Patients at highest risk for AKI are those in whom kidney perfusion is dependent on prostaglandin-induced vasodilation to combat circulating systemic and local vasoconstrictors. In states of reduced ECV, angiotensin II and endothelin reduce GFR and post-glomerular capillary perfusion, increasing risk for ischemic tubular injury. True volume depletion and reduced ECV as seen with congestive heart failure (CHF), nephrotic syndrome, and cirrhosis increase the risk for hemodynamic

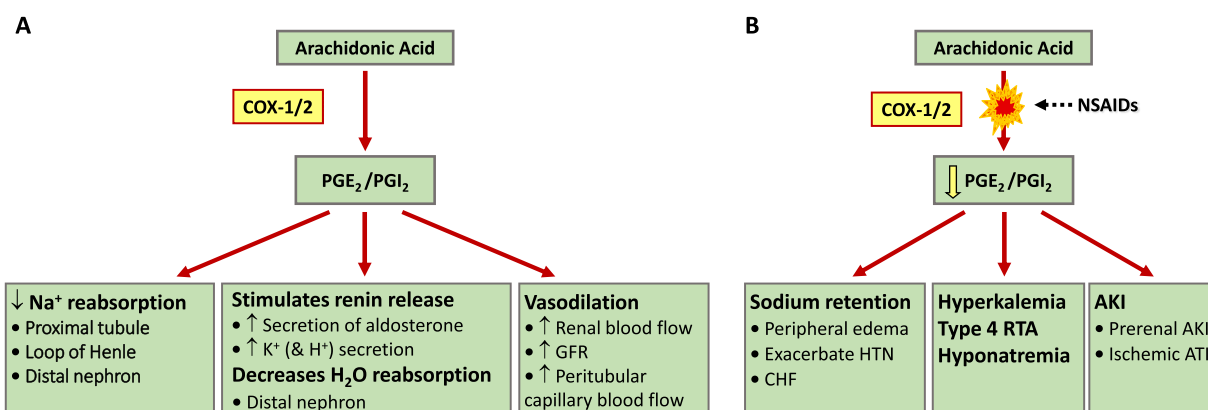


Figure 2. Prostaglandins (PGs) and the kidney. (A) Prostaglandin production and downstream effects in the kidneys. Synthesis of various prostaglandins from arachidonic acid by cyclooxygenase (COX) enzymes has a number of effects in the kidneys. (B) Adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on kidney function. NSAID therapy causes a number of adverse effects in the kidney through inhibition of prostaglandin production. Abbreviations: AKI, acute kidney injury; ATI, acute tubular injury; CHF, congestive heart failure; GFR, glomerular filtration rate; HTN, hypertension; RTA, renal tubular acidosis.

Box 2. Risk Factors for NSAID Nephrotoxicity**Acute Kidney Injury**

- True circulating volume depletion
 - ◊ Exercise-induced, diarrhea, vomiting, excessive diuresis, poor oral intake
- Effective circulating volume depletion
 - ◊ Nephrotic syndrome, cirrhosis, CHF, hypoalbuminemia
- High cumulative dose exposure
- Concurrent calcineurin inhibitors and other vasoconstrictors
- Concurrent therapy with RAAS inhibitors, diuretics, or both

Hyperkalemia

- Concurrent use of medications promoting hyperkalemia
 - ◊ RAAS inhibitors, trimethoprim, heparin, other drugs
- Exposure to radiocontrast with concomitant RAAS inhibitor
- Age > 65 y
- Hyporeninemic hypoaldosteronism
- Type 4 RTA

Hyponatremia

- True or effective circulating volume depletion (outlined above)
- Conditions associated with SIADH
- Increased free water intake ± increased sodium losses (eg, with extreme exercise)
- Thiazide use in elderly patients

Hypervolemia

- Underlying comorbid conditions promoting sodium avidity, including CHF, cirrhosis, and nephrotic syndrome

Worsened hypertension

- Underlying hypertension, including on effective treatment
- Hyporeninemic states, as seen in elderly and diabetes mellitus

Progression of CKD

- Age > 65 y
- High cumulative dose exposure
- Coronary artery disease
- Combination analgesics (banned)

Note: Risk posed by kidney disease outlined in Figure 3; excluded from this table. Abbreviations: CHF, congestive heart failure; CKD, chronic kidney disease; NSAID, nonsteroidal anti-inflammatory drug; RAAS, renin-angiotensin-aldosterone system; RTA, renal tubular acidosis; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

AKI with NSAIDs.^{37,38} Conditions associated with vascular dysfunction such as advancing age and hypertension are associated with increased AKI risk with NSAIDs, likely reflecting reduced vascular reserve due to atherosclerosis and narrowing of renal arterioles, effecting heavier reliance on prostaglandin for perfusion.^{6,39,40,41}

The biological plausibility of CKD conferring an increased risk for NSAID-associated AKI is based on the concept of reduced renal reserve in CKD and increased prostaglandin dependence for perfusion of remnant nephrons.^{6,39,40} Although overall studies show that NSAIDs confer AKI risk in patients with CKD, quantification of this risk varies greatly between studies examining populations with differing baseline characteristics and use patterns.

A retrospective cohort study including more than 35,000 matched elderly patient pairs with hypertension, CKD, or CHF showed no difference in kidney complications between those exposed and not exposed to prescription NSAIDs.⁴² However, diagnosis codes were used to define these outcomes and CKD stages were not stratified.^{43,44} A systematic meta-analysis of high-quality observation-based population studies found that NSAID-related AKI risk in patients with CKD was similar to the general population. However, there was significant study heterogeneity, suggesting significant modifiers to the risk.³⁵ Although informative for moderate (stage 3) CKD, many large trials and meta-analyses to date characterize CKD as a homogeneous group of patients with any GFR < 60 mL/min/1.73 m² and therefore conclusions regarding NSAID risk based on these studies cannot be applied to patients with more advanced stage 4–5 CKD, who are often either excluded or vastly under-represented.

The risk for NSAID-associated AKI appears higher in elderly patients with CKD, though elderly patients without CKD are also at increased risk, as previously mentioned. A large population-based study of an elderly cohort found no impact of baseline GFR on risk for NSAID-associated AKI. However, there was a trend toward higher absolute increase in AKI risk with lower baseline GFR.⁴¹ Another study demonstrated similar risk for reversible hemodynamic AKI between elderly patients with moderate CKD and without CKD using NSAIDs, but NSAIDs significantly increased the risk for intrinsic AKI only among patients with CKD.³⁹

AKI risk with NSAIDs also increases with use alongside interacting medications. Concomitant NSAID use with renin-angiotensin-aldosterone system (RAAS) inhibitors, diuretics, or both has been associated with increased AKI risk, especially within the first 30 days of combined use.^{40,45} The AKI risk of double or triple therapy is suggested to be even more pronounced in patients with stages 1–3 CKD and is likely elevated in advanced stages as well.⁴⁰ Prostaglandins attenuate angiotensin II-mediated afferent arteriole vasoconstriction, and COX-2 expression is upregulated with angiotensin-converting enzyme inhibitor use,⁴⁶ providing a physiologic model explaining why RAAS inhibitors increase NSAIDs' AKI risk. Other prominent examples include calcineurin inhibitors, whose vasoconstrictive effects increase the risk for ischemic injury in transplant recipients.^{47,48}

Although more advanced stages of CKD, older age, and specific medication coadministrations can lead to greater NSAID-related AKI risk, the multimorbidity of patients with CKD rather than CKD itself should be considered the greatest risk to NSAID therapy. The CKD population is a complex patient cohort with significant comorbid disease burden, and these comorbid conditions, their complications, and their management frequently lead to significant AKI risk factors.

Hypervolemia

NSAIDs also affect fluid and electrolyte balance. By preventing the natriuretic and aquaretic effects of prostaglandins, NSAIDs increase sodium and water retention, thereby promoting edema formation, exacerbating CHF, and worsening hypertension (Fig 2B).²⁶ These effects are most pronounced in patients with underlying sodium- and water-avid states such as CHF, nephrotic syndrome, and cirrhosis (Box 2). A recent meta-analysis of randomized placebo-controlled trials found 70% increased risk for CHF and edema with selective COX-2 inhibitor use versus placebo, even when excluding particularly high-risk agents such as rofecoxib.⁴⁹ Additionally, NSAIDs are associated with an increased dose-dependent risk for CHF hospitalization.^{50–52}

In the setting of CKD, increased ADH secretion and RAAS activation act to augment blood flow to hypoperfused nephrons through sodium and water retention.⁵³ NSAID-induced increased sodium avidity worsens this underlying process and its propensity for adverse effects, though specific data for this population are lacking. Epidemiologically, patients with CKD are at increased risk for hypervolemia even outside the physiology of their kidney disease because of their burden of comorbid conditions. Hypertension and diabetes mellitus are the 2 main causes of CKD in the United States and they are also 2 prominent risk factors for NSAID-associated hypervolemia and hypertension.

Hyponatremia

NSAID-associated hyponatremia occurs largely as a result of the mechanisms that lead to water and sodium retention. The antidiuretic effect of ADH is amplified in the absence of prostaglandins' regulatory effect on this hormone, whereas intensification of the medullary interstitial osmotic gradient with prostaglandin inhibition enhances free-water absorption. Both these mechanisms produce conditions that promote net free-water absorption and hyponatremia.⁵⁴

Patients with underlying conditions (Box 2) that promote water retention are at higher risk for hyponatremia with NSAID exposure. This includes cirrhosis, nephrotic syndrome, and CHF, as well as conditions associated with syndrome of inappropriate ADH secretion.⁵⁵ NSAIDs blunt the inhibitory effects of prostaglandins on ADH and under circumstances of elevated ADH levels, the effect is further exacerbated. NSAIDs will also lower the threshold for the development of hyponatremia under conditions that promote non-ADH-mediated hyponatremia. Exercise-associated hyponatremia in endurance athletes can develop from increased free-water intake in combination with NSAIDs.⁵⁶ NSAIDs may also increase the susceptibility of older adults to thiazide diuretic-induced hyponatremia.⁵⁷

Finally, several reports suggest an association between NSAID use and syndrome of inappropriate ADH secretion-mediated hyponatremia.^{58,59} ADH levels can be persistently

elevated in patients with CKD, particularly in those with underlying diabetes mellitus.⁶⁰ Individuals with CKD also have comorbid conditions such as CHF, nephrotic syndrome, and cirrhosis, which increase nonosmotic ADH production, predisposing to NSAID-induced hyponatremia. Similar to the literature on other NSAID adverse effects, studies performed to date that characterize hyponatremia with NSAIDs are confounded by these underlying predisposing factors. Although the incidence of NSAID-associated clinically symptomatic hyponatremia is likely low, even mild forms of hyponatremia are associated with increased mortality, longer hospitalizations, readmissions, falls, osteoporosis, and cognitive impairment.^{55,61}

Hyperkalemia

Because prostaglandins modulate renal potassium handling, their inhibition contributes to NSAID-associated hyperkalemia. Prostaglandin-mediated renin release facilitates aldosterone-driven potassium excretion in the distal nephron. Prostaglandin deficiency induces hypoaldosteronism, which leads to impaired principal cell potassium secretion, likely the primary driver of NSAID-induced hyperkalemia.⁶² Decreased sodium chloride delivery to the distal tubule also reduces the electrochemical gradient for potassium secretion,⁶² while reduced principal cell potassium channel activity also contributes.⁶³ Finally, NSAID-associated AKI can further exacerbate hyperkalemia. However, under most circumstances, there is a low absolute risk for hyperkalemia with NSAIDs.⁴¹

Hyperkalemia with NSAID use in clinical practice is related to underlying comorbid conditions and exposure to medications that impair renal potassium handling (Box 2), and NSAIDs are rarely the sole cause of hyperkalemia in studies to date.⁶⁴ A nested case-control study by Lafrance and Miller⁶⁴ that quantified the risk for the development of hyperkalemia with potassium levels > 6.0 mEq/L imposed by NSAIDs alone in a patient population of veterans demonstrated no increased risk with either single or multiple NSAID use. However, certain individual agents were reported to have elevated risk unrelated to COX-2 selectivity, including rofecoxib (odds ratio, 1.37) and indomethacin (odds ratio, 1.36).⁶⁴ The strongest risk factors for developing hyperkalemia include a prior episode of hyperkalemia, hospitalization within the past month, diabetes, and AKI.⁶⁴ Heart failure also appears to increase the risk posed by NSAIDs.⁶⁵ The combination of RAAS inhibitors and contrast media with NSAIDs has a positive additive risk.⁶⁴ Unsurprisingly, combination therapy with multiple hyperkalemia-inducing medications such as RAAS inhibitors and trimethoprim is associated with significant hyperkalemia.⁶² Thus, NSAIDs contribute to hyperkalemia in at-risk patients with CKD but rarely cause it in the absence of risk factors.

Although CKD itself may be a risk factor for hyperkalemia, current evidence does not support that mild to moderate CKD increases hyperkalemia risk with NSAIDs.

Lafrance and Miller⁶⁴ found that the hyperkalemia risk with NSAIDs in patients with moderate CKD was less than the combined risks of NSAID use and CKD individually, suggesting that moderate CKD does not increase the risk for NSAID-associated hyperkalemia. A retrospective cohort study of elderly patients found no significant association between CKD and hyperkalemia with NSAIDs, though elderly age has been linked with a 50% increased risk for hyperkalemia with NSAID use compared with younger patients.⁴¹ Patients with CKD frequently develop hyperkalemia due to additional comorbid conditions such as hyporeninemic hypoaldosteronism, type 4 renal tubular acidosis, and advanced age or due to RAAS blockers or other drugs that impair renal potassium handling. However, moderate CKD alone does not appear to increase the risk for NSAID-associated hyperkalemia.

Hypertension

NSAIDs may worsen blood pressure (BP) control by approximately 3 to 6 mm Hg^{66,67} through renal sodium and water retention and increased peripheral vascular resistance.¹⁹ In addition, NSAID-associated decreased renin production and increased sodium avidity appears to render several classes of antihypertensives less effective, particularly angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and diuretics.^{67–70} A double-blinded randomized cardiovascular safety trial showed that 3% of patients using NSAIDs developed average systolic BPs 3 mm Hg higher than baseline after 4 months.⁷¹ Although single-digit BP elevations appear inconsequential for individual patients, from an epidemiologic standpoint, BP increases as low as 5 mm Hg increase cardiovascular morbidity.⁷²

Patients with underlying hypertension and sodium-avid states are at higher risk for hypertension with NSAIDs (Box 2). A meta-analysis that included more than 1,200 patients found that the NSAIDs increased BP primarily in patients with underlying hypertension,⁶⁶ including patients on effective antihypertensive treatment.⁶⁷ Patients with advancing age, diabetes, and CKD also appear to be at increased risk for worsening hypertension with NSAIDs.⁷³

Acute Interstitial Nephritis and Glomerulonephritis

NSAIDs also cause kidney injury through idiosyncratic reactions, including acute interstitial nephritis (AIN). In this setting, AIN may occur in part due to shunting of arachidonic acid into the lipo-oxygenase pathway, leading to increased production of proinflammatory leukotrienes.⁶⁹ As a class, NSAIDs confer an approximate 2-fold increase in risk for AIN, though the absolute risk is very low.⁷⁴ Proteinuria and nephrotic syndrome due to either membranous nephropathy or minimal change disease are other well-established but more infrequent complications of NSAIDs, which may occur alone or with AIN.^{75–77} These glomerulopathies occur weeks to months after initial NSAID exposure.^{5,78}

Progression of CKD

Concern about CKD progression has been another barrier to NSAID use in patients with CKD, and the literature on this subject is proportionally vast and filled with incompatible conclusions. Many early often-cited studies charted the correlation between patient-reported prior NSAID consumption and the presence of CKD.^{29,30,79–81} These studies are highly subject to recall bias and also demonstrated conflicting findings.^{29,30,79–81}

A prospective observational study of 10,184 individuals older than 65 years with GFR > 60 mL/min/1.73 m² reported that NSAID users had a small but significant risk for increased rate of CKD progression compared with non-users.⁸² However, there was no association between NSAID use and CKD progression with GFR < 60 mL/min/1.73 m².⁸² This and other similar studies are affected by the design's inability to exclude a protopathic bias away from greater NSAID use in patients with CKD knowledgeable about NSAID risk, as well as under-representation of more advanced-stage CKD that renders such studies underpowered to detect an effect.

To reduce confounding, some studies have examined the effect of NSAIDs in populations requiring long-term anti-inflammatory medications. A large randomized 3-year trial comparing the use of celecoxib, naproxen, and ibuprofen in more than 24,000 patients with arthritis and with early or no CKD showed a low incidence of composite acute and long-term decrease in GFRs with all 3 agents.⁸³ However, this study was affected by drug discontinuation by 70% of patients at the time of follow-up. Using a controlled multivariable analysis, a retrospective cohort study of nearly 2,000 patients using ibuprofen and 4,000 using acetaminophen found that age of 65 years and older and coronary artery disease, but not underlying CKD, were risk factors for worsening kidney disease with ibuprofen use.⁸⁴ Although CKD stage was not collected in this study, it demonstrated that ibuprofen does not cause CKD progression, at least in moderate CKD.⁸⁴ Another prospective cohort study of more than 4,000 patients with rheumatoid arthritis showed no difference in the rate of GFR change between NSAID users and nonusers with CKD stages 1–3 at baseline. However, 17 NSAID-treated patients with CKD stages 4–5 developed a significantly steeper GFR decline.⁸⁵

Similar to other nephrotoxic manifestations, the risk for CKD progression appears to be dose-dependent. A meta-analysis targeting the strength of the association between NSAID use and CKD progression in moderate to severe CKD showed no association with regular-dose NSAID use.⁸⁶ At undefined higher doses, there was a statistically significant increase in risk for CKD progression, but the absolute risk was small.⁸⁶ A retrospective longitudinal cohort study of US Army soldiers without pre-existing kidney disease demonstrated 20% greater risk for CKD progression among patients receiving more than 7 World Health Organization–defined daily doses per month of

total NSAIDs compared with nonusers.⁸⁷ Similarly, a case-control study found an association between stage 5 CKD development and NSAIDs only in users of the highest quantities.⁷⁹

In summary, although the risk for CKD progression due to NSAID use is not insignificant, it appears to be small, related to cumulative dose, and modifiable by appropriate patient selection in patients with mild to moderate CKD.

Recommendations

Based on the somewhat incomplete data for NSAID nephrotoxicity in patients with advanced CKD, we make recommendations for cautious use of NSAIDs in patients with CKD under certain circumstances (Fig 3). It is most important to avoid causing potentially life-threatening NSAID-related complications such as AKI, hyperkalemia, and hypervolemia

<i>Nephrotoxicity*</i>	Stage 1-2 CKD	Stage 3 CKD	Stage 4 CKD	Stage 5 CKD, No KRT
AKI	Low risk, similar to general population [†] .	Low risk, similar to non-elderly general population [†] , mildly increased in elderly.	At least moderately increased risk compared with general population.	High risk compared with general population.
	Risk posed by concurrent RAASi and/or diuretic use greater than in general population.			
Hyperkalemia	Low risk, similar to general population [†] .	Low risk, similar to general population [†] .	Moderately increased risk compared with general population.	High risk compared with general population.
Hyponatremia	Low risk, similar to general population [†] . Risk may be increased with DM.	Low risk, similar to general population [†] . Risk may be increased with DM.	Risk may be elevated compared with general population, but data lacking.	Risk may be elevated compared with general population, but data lacking.
Hypervolemia	Risk similar to general population [†] .	Risk similar to general population [†] .	Increased risk due to risk for Na ⁺ and water retention and reduced GFR.	High risk due to risk for Na ⁺ and water retention and reduced GFR.
Hypertension	Likely increased risk compared with general population based on level of underlying hyporeninemia.	Mildly increased risk compared with general population based on level of underlying hyporeninemia.	Increased risk due to risk for precipitating hypervolemia and systemic vasoconstriction.	High risk due to risk for precipitating hypervolemia and systemic vasoconstriction.
Progression of CKD	No increased risk with NSAID use [†] .	No increased risk with NSAID use [†] .	Likely moderate increased risk.	Moderate to high increased risk.
Data Strength	Strong-moderate	Moderate	Weak	Weak
Recommendations	Short-term use for ≤5 days acceptable**. Long-term use also acceptable on case-by-case basis**, with close monitoring for nephrotoxicity and for development of risk factors for nephrotoxicity as in Table 3.		Consider short-term, low-dose NSAID use on a case-by-case basis with close monitoring**. In patients with underlying hyperkalemia, should consider NSAIDs contraindicated.	Would consider NSAIDs as absolutely contraindicated except under circumstances of palliative care.

Figure 3. Summary of potential nonsteroidal anti-inflammatory drug (NSAID) nephrotoxicity in chronic kidney disease (CKD). *Outlines additional risk for each nephrotoxicity posed by CKD at different stages, as well as any risk factors (including those in Box 2) that pose a greater risk in these populations. The burden of Box 2 risk factors is high, especially with increasing CKD stage, and this must be considered in conjunction with the risk outlined in this table, which is reflected in these Recommendations. †In the absence of other risk factors as noted in Box 2. **With minimization of risk factors outlined in Box 2, as able. Abbreviations: AKI, acute kidney injury; DM, diabetes mellitus; GFR, glomerular filtration rate; KRT, kidney replacement therapy; RAASi, renin-angiotensin-aldosterone system inhibitor.

Table 2. NSAID Dosing

NSAID Class	Trade Name	t _{1/2}	Total Dose/d (Dosing) ^a	Recommendation for CKD Dosing ^b
Carboxylic Acids				
Salsalate	Disalcid	1 h	1.5-3.0 g (2×/d)	Reduced dose 2×/d
Choline Mg ⁺⁺ trisalicylate	Trilisate	0.25 h	1.5-3.0 g (2-3×/d)	Reduced dose 2×/d
Diflunisal	Dolobid	7.5-8 h	0.5-1.5 g (2×/d)	Reduced dose 1×/d
Acetic Acids				
Indomethacin ^c	Indocin	5-10 h	75-150 mg (2-4×/d)	Normal dose 1-2×/d
Tolmetin	Tolectin	1 h	400-2,400 mg (2-3×/d)	Reduced dose 2×/d
Sulindac ^d	Clinoril	16.4 h	200-400 mg (2×/d)	Reduced dose 1×/d
Diclofenac ^c	Voltaren, Cataflam	1-2 h	100-150 mg (2×/d)	Reduced dose 2×/d
	Arthrotec	2 h	100 mg (2×/d)	Reduced dose 2×/d
Etodolac	Lodine	6.4 h	400-1,200 mg (2-4×/d)	Normal dose 1-2×/d
Ketorolac	Toradol	5-6 h	Oral 40 mg (4×/d)	Reduced dose 1-2×/d
			IV 60-120 mg (4×/d)	Reduced dose 1-2×/d
Propionic Acids				
Ibuprofen	Motrin, Rufen	1.8-2 h	800-3,200 mg (4×/d)	Normal dose 2×/d
Naproxen	Naprosyn, Anaprox	12-17 h	500-1,000 mg (2×/d)	Reduced dose 1×/d
	Aleve		450 mg (2×/d)	Reduced dose 1×/d
Ketoprofen	Orudis	2-4 h	225 mg (3×/d)	Reduced dose 1-2×/d
Flurbiprofen	Ansaïd	5-7 h	200-300 mg (2-3×/d)	Reduced dose 1×/d
Fenoprofen	Nalfon	2.5-3 h	1,200-2,400 mg (4×/d)	Reduced dose 2×/d
Oxaprozin ^c	Daypro	38-44 h	1,200 mg (1×/d)	Avoid
Enolic Acids				
Piroxicam ^c	Feldene	45-50 h	10-20 mg (1×/d)	Avoid
Fenamates				
Mefenamic acid	Ponstel	2 h	1,000 mg (4×/d)	Reduced dose 2-3×/d
Meclofenamate ^c	Meclomen	1-5 h	150-400 mg (3-4×/d)	Reduced dose 1-2×/d
Naphthylkanones				
Nabumetone ^d	Relafen	23-30 h	1,000-1,500 mg (2-3×/d)	Reduced dose 1-2×/d
COX-2 Inhibitors				
Celecoxib	Celebrex	11 h	100-400 mg (1-2×/d)	Reduced dose 1-2×/d

Note: NSAIDs undergo hepatic metabolism. Kidney excretion of inactive metabolites predominates for most.

Abbreviations: CKD, chronic kidney disease; COX, cyclooxygenase; GFR, glomerular filtration rate; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; t_{1/2}, half-life.

^aDosing in healthy patients.

^bGFR > 30 < 60 mL/min, limited/no data for GFR < 30 mL/min.

^cBiliary excretion of 30% to 40%.

^dNabumetone and sulindac are metabolized to active metabolites.

in at-risk patients with CKD. Worsening BP control and increasing CKD progression are other possible adverse effects to consider before NSAID therapy initiation.

For stable patients with CKD stages 1 and 2 without predisposing risk factors, monitoring can be similar to that for patients without kidney disease. In patients with stage 3 CKD in whom predisposing risk factors have been minimized, short-term NSAID use for up to 5 days is an acceptable pain management strategy with an acceptably low nephrotoxic risk. Routine laboratory testing and follow-up within 2 to 3 weeks of use are adequate for surveillance for adverse effects. Long-term NSAID use in these patients carries more risk for adverse outcomes; however, this relates to a longer exposure period over which additional risk factors for NSAID toxicity may develop. Therefore, long-term therapy is acceptable in

patients amenable to education regarding higher risk conditions that may arise under which NSAIDs should be withheld and to continued close follow up with medical care. Short-acting agents are preferred over long-acting agents (Table 2), along with optimization of volume status and cardiac function before and during treatment.⁸⁸ Adjustment of the NSAID dosing interval should be made to account for reduced elimination of the drug with CKD.⁸⁹ NSAIDs should likely be avoided in those with prostaglandin-dependent RBF, including states of true and ECV depletion, cirrhosis, CHF, or nephrotic syndrome.⁵ Additional caution with NSAID use should be undertaken in patients with CKD with potassium handling issues who are prescribed RAAS inhibitors, diuretics, and other hyperkalemia-promoting drugs such as mineralocorticoid inhibitors and trimethoprim.

Patients with stage 4 CKD require a more judicious approach to NSAID therapy because the risk for nephrotoxicity has not been adequately studied in this cohort. Because many of these patients struggle with increased AKI events, electrolyte and acid-base abnormalities (particularly hyperkalemia and metabolic acidosis), and hypervolemia, an individualized approach to NSAID use is mandated. NSAID exposure will likely exacerbate all these problems in many patients with stages 4–5 CKD, especially in the setting of common comorbid conditions (CHF, nephrosis, cirrhosis, hypertension, and type 4 renal tubular acidosis) and concomitant medications (RAAS blockers, diuretics, and mineralocorticoid antagonists). If NSAIDs are to be used in patients with stable stage 4 CKD, low doses of short half-life preparations with an appropriate dosing interval for 5 or fewer days and close monitoring within the treatment period are required.

Except under circumstances prioritizing palliation over prolongation of life, patients with stage 5 CKD should never receive these drugs because the risk for lethal renal complications is high despite the absence of data. The decision to avoid NSAIDs for pain management in patients receiving maintenance hemodialysis or peritoneal dialysis to preserve GFR (residual renal function) should be individualized but is outside the scope of this review. Similarly, the decision to use NSAIDs in patients with a kidney transplant should be individualized based on GFR and concomitant risk factors for adverse effects. Because these patients lack normal autoregulatory mechanisms to protect against reduced prostaglandin levels and are often using immunosuppressive agents that amplify the potential toxicity posed by NSAIDs, judicious use and close monitoring is mandated.

Topical NSAID formulations have little systemic absorption, with peak concentrations no greater than 1.5% of oral NSAID formulations, and should be considered a viable alternative or adjunctive pain management strategy in all patients with CKD, particularly in addressing musculoskeletal and arthritic pain.⁹⁰ Although studies of topical formulations consistently demonstrate significantly reduced kidney-related adverse effects compared with oral formulations, use in patients with stages 4–5 CKD, especially those with other prostaglandin-dependent conditions, should be accompanied by close monitoring at the onset of use.^{91,92}

Conclusion

NSAIDs are associated with adverse renal outcomes, and their risk must be weighed against the benefit of improved pain control. An accurate risk assessment must be highly individualized based on CKD stage, age, comorbid conditions, and concomitant medication use. Although historically avoided in kidney disease, NSAIDs should be considered for use in this population alongside other therapies after appropriate patient selection.

Article Information

Authors' Full Names and Academic Degrees: Megan Baker, MD, and Mark A. Perazella, MD.

Authors' Affiliations: Department of Medicine (MB), and Section of Nephrology, Department of Medicine (MAP), Yale University School of Medicine, New Haven, CT; and Department of Medicine, Veterans Affairs Medical Center, West Haven, CT (MAP).

Address for Correspondence: Mark A. Perazella, MD, Section of Nephrology, Department of Medicine, Yale University School of Medicine, BB114, 330 Cedar St, New Haven, CT 06410. E-mail: mark.perazella@yale.edu

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