Can NSAIDs be used safely in CKD patients?: CON

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NSAID

- Non-steroidal 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.
- NSAIDs are a common cause of drug-related emergency hospital admission and drug related death, from GI bleeding, AKI, and serious cardiovascular events .

Vascular and upper GIT effects of NSAID: Meta-analyses of data from randomized trials.
Lancet 382: 769–779, 2013

NSAID

- **International consensus guidelines** recommend avoiding NSAIDs in people with eGFR 30 ml/min per 1.73 m2, and to avoid prolonged use in those with eGFR 30–59 ml/min per 1.73 m2 .
- 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.
- **A systematic review of NSAID** use in people with CKD in seven cross sectional studies found that 8%–21% were currently taking NSAIDs .
- **Randomized controlled trials** examining NSAID effectiveness routinely exclude people with CKD, and often do not evaluate renal outcomes or other potential harms.

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NSAID

- 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.
- **COX-2** expression is modified by growth factors, cytokines, and other external signals and is upregulated in response to inflammation.
- **COX-2** is also constitutively expressed in the kidneys. 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.

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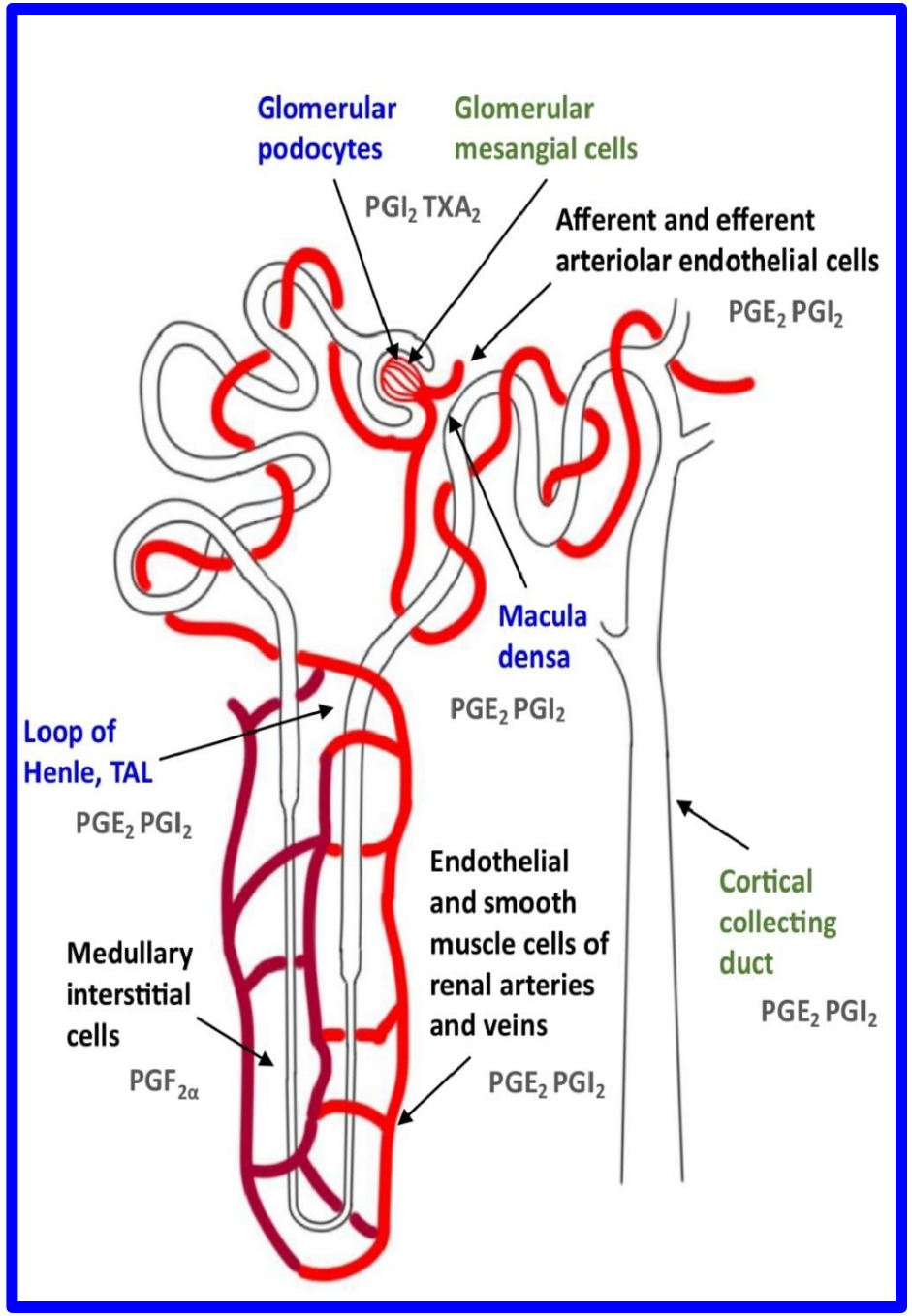
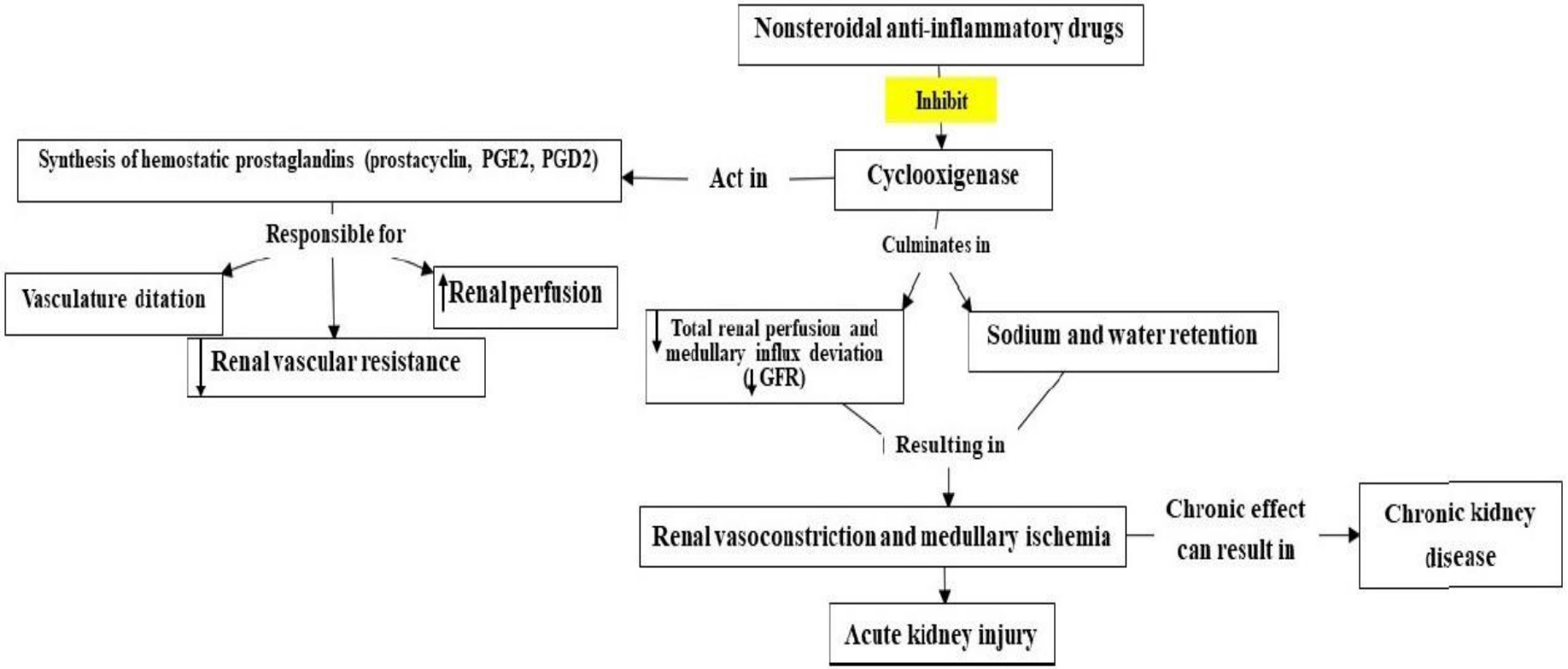
Location of expression of (COX) isoforms in the kidney and the predominant (PGs) produced



Text in green denotes locations where COX-1 expressed; **blue**, COX-2; and **black**, locations of overlapping COX-1 and COX-2 expression.

TAL, thick ascending limb; TXA2, thromboxane A2

NSAID-induced kidney injury pathophysiology



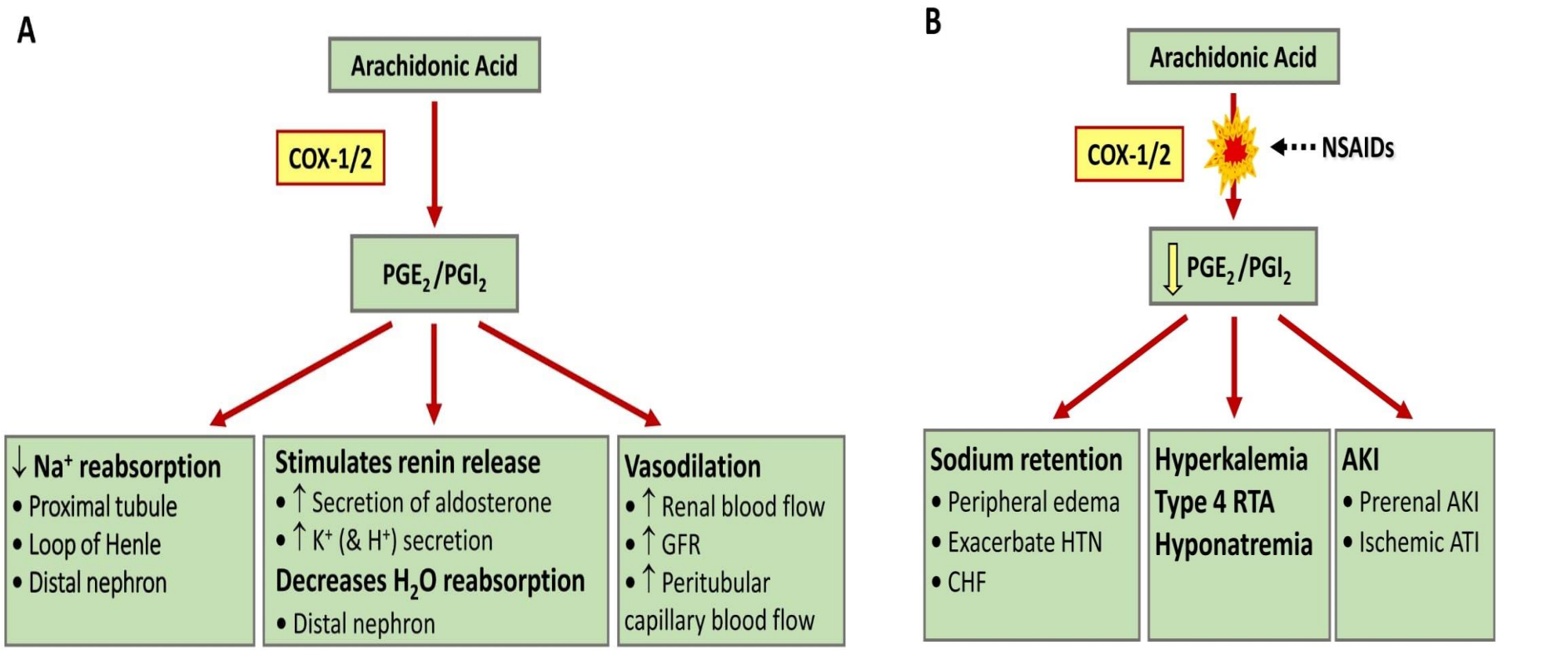
Braz. J. Nephrol. (J. Bras. Nefrol.) 2019;41(1):124-130

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	Augmentation of postglomerular perfusion
		Inhibition of cAMP synthesis	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
$PGF_{2\alpha}$	Medullary interstitial and tubular cells	Modulation of water reabsorption and transcellular transport of sodium	Adaptive sodium and water handling

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.

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.

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

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

Risk Factors for NSAID Nephrotoxicity

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
- 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)

NSAIDs and AKI

- **NSAID-associated AKI** is predominantly hemodynamically mediated, resulting in reversible reduction in GFR or ischemic tubular injury.
- 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 postglomerular capillary perfusion, increasing risk for ischemic tubular injury.

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NSAIDs and AKI

- Although more advanced stages of CKD, older age, and specific medication co-administrations can lead to greater NSAID-related AKI risk, the mult-imorbidity 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.

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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.
- **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.

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Hyperkalemia

- Hyperkalemia with NSAID use in clinical practice is related to underlying comorbid conditions and exposure to medications that impair renal potassium handling.
- **A nested case-control study** by Lafrance and Miller 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.
- The strongest risk factors for developing hyperkalemia include a prior episode of hyperkalemia, hospitalization within the past month, diabetes, and AKI.

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Hypertension

- NSAIDs may worsen blood pressure (BP) control by approximately 3 to 6 mm Hg through renal sodium and water retention and increased peripheral vascular resistance.
- **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.
- **A meta-analysis** that included more than 1,200 patients found that the NSAIDs increased BP primarily in patients with underlying hypertension, including patients on effective antihypertensive treatment. Patients with advancing age, diabetes, and CKD also appear to be at increased risk for worsening hypertension with NSAIDs.

Acute Interstitial Nephritis and Glomerulonephritis

- NSAIDs also cause kidney injury through idiosyncratic reactions, including acute interstitial nephritis (AIN).
- **AIN** may occur in part due to shunting of arachidonic acid into the lipo-oxygenase pathway, leading to increased production of pro-inflammatory leukotrienes.
- 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.

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Progression of CKD

- **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 nonusers.
- **A large randomized 3- year trial** comparing the use of celecoxib, naproxen, and ibuprofen in more than 24,000 patients with arthritis with early or no CKD showed a low incidence of composite acute and long-term decrease in GFRs with all 3 agents.
- **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.

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Progression of CKD {CON}

- **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, NSAID-treated patients with CKD stages 4-5 developed a significantly steeper GFR decline.
- **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.
- 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.

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Summary of potential (NSAID) nephrotoxicity in chronic kidney disease (CKD)

*Nephrotoxicity**	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
Recommen-dations	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.

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) IV 60-120 mg (4×/d)	Reduced dose 1-2×/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	Ansaid	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

- **a** Dosing in healthy patients.
- **b** GFR > 30 < 60 mL/min, limited/no data for GFR < 30 mL/min.
- **c** Biliary excretion of 30% to 40%.
- **d** Nabumetone and sulindac are metabolized to active metabolites

CONCOLUSION

- 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

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Thank you