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Can NSAIDs be used safely in CKD patients? : Pro

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Introduction

- Nearly **60%** of patients with CKD suffer pain. Of those patients with CKD who have pain, most rate their pain as **moderate** or **severe** in intensity.
- Undermanaged pain is associated with higher rates of mood disorders, maladaptive coping, and decreased quality of life for patients with CKD ¹.
- NSAIDs are recommended as first-line for analgesia and also act as antipyretic and anti-inflammatory medications.

1. Koncicki HM, et al. Am J Kidney Dis. 2017

Introduction

- Estimates indicate that **98 million patients** annually are prescribed NSAIDs ¹.
- In the **National Health and Nutrition Examination Survey**, routine NSAID use was common in patients with CKD and use increased with increasing CKD severity ².

1. Pai AB, et al. Ann Pharmacotherapy. 2019.

2. Plantinga L, et al. BMC Nephrol. 2016.

NSAIDs Nephrotoxicity

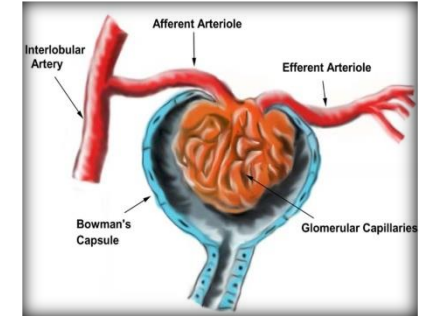
A. Direct Nephrotoxicity: from NSAIDs include **interstitial nephritis, papillary necrosis, and GN** ¹.

- Although these risks of NSAIDs have been **reproducibly demonstrated**, on a per patient level they **remain rare**.
< 1% – 5% of all NSAID users experience such side effects ².
- Most nephrotoxicity related to NSAIDs **recovers** after drug withdrawal; however, the likelihood of recovery may depend on renal reserve.

1. Sriperumbuduri S, Hiremath S. Curr Opin Nephrol Hypertens. 2019.

2. Bakhriansyah M, et al. Clin J Am Soc Nephrol . 2019.

NSAIDs Nephrotoxicity

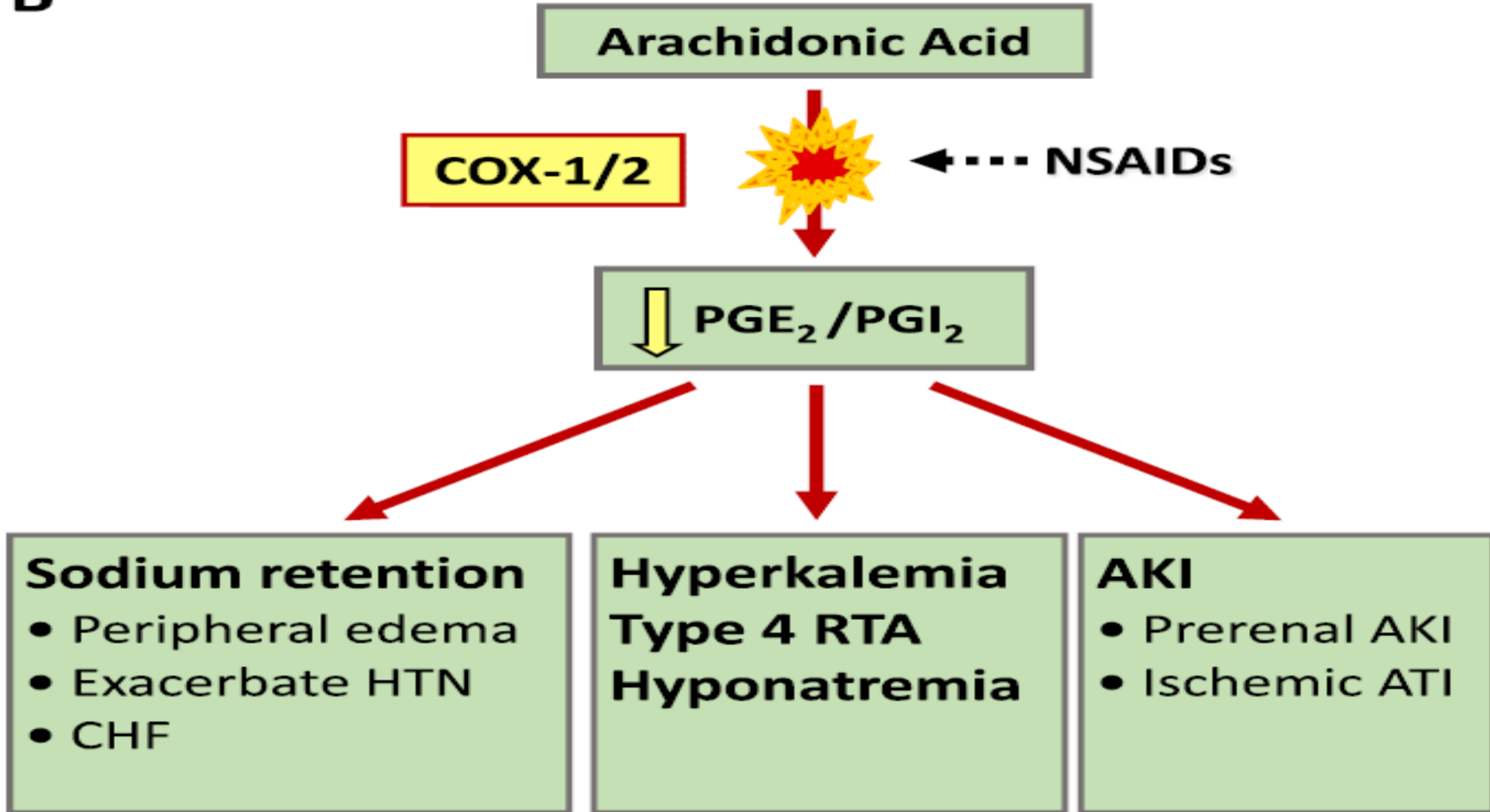


B. Indirect Nephrotoxicity: from **NSAIDs** is linked to altered intraglomerular hemodynamics.

- **NSAIDs inhibit PG synthesis**, which decreases afferent arteriolar vasodilation and can reduce glomerular pressure.
- This is especially prominent in patients with already jeopardized renal perfusion as in shock or intravascular volume depletion.
- For this reason, use of NSAIDs in acutely ill patients with AKI, acute kidney disease, or in the midst of renal recovery remains **ill advised**.

Erin F, et al. KIDNEY360.2020.

B



NSAIDs and the Kidneys

- **Risk factors** for **NSAID**-associated nephrotoxicity included higher drug doses, longer durations, concurrent use of renin-angiotensin system (RAS) inhibitors or diuretics, preexisting CKD, and advanced age ¹.
- **Recent evidence** has refuted that some of these risks may be less profound than once thought ².
- **Historically**; This is likely to be due to withdrawal of **acetaminophen** from the market, an often coadministered agent with NSAIDs that increased the nephrotoxicity of the drug combination.

1. Rivosecchi RM, et al. Ann Pharmacother.2016.

2. Miano TA, et al. Kidney360 . 2020.

NSAIDs and the Kidneys

- A multicenter propensity-matched cohort of **25,571** hospitalized adults evaluated the risk of nephrotoxicity associated with **NSAID** use in the presence or absence of RAS inhibitors.
- The mean duration of NSAID exposure was **2.4** days.
- Compared with patients treated with **alternate analgesic** or antihypertensive agents not known to affect glomerular hemodynamics (oxycodone and amlodipine, respectively).
- This combination of NSAID and RAS inhibitor did not worsen AKI incidence, severity, or duration ¹.

1. Miano TA, et al. Kidney360. 2020.

NSAIDs and the Kidneys

- In a case control study that evaluated the odds of *nephrotic syndrome* in **13,074** primary care patients, NSAID exposure for **< 15 days** was not associated with greater risk ¹.
- In a study of patients with **rheumatoid arthritis**, patients with a baseline **eGFR > 30** ml/min per 1.73 m² treated with **NSAIDs** for **> 3.2 years**, experienced *comparable kidney function decline* compared with those **not exposed to NSAIDs** ².

1. Bakhriansyah M, et al. Clin J Am Soc Nephrol . 2019.

2. Mo¨ller B, et al. Ann Rheum Dis. 2015.

NSAIDs and the Kidneys

- In the **Nurse's Health Study and the Physician's Health Study**¹, greater cumulative exposure to NSAIDs > 10 – 20 years was not associated with *long-term adverse kidney outcomes*.
- Abandoning the use of NSAIDs in patients with kidney disease will lead to consequences from the therapeutic alternatives.

1. Rexrode KM, et al. JAMA. 2001.

Opioids Use in CKD

- In the **Chronic Renal Insufficiency Cohort (CRIC)**, **opioid** use was associated with a *greater risk for adverse events including kidney failure requiring dialysis and death*, even after adjustment for potential confounders including baseline kidney function. ¹
- In a head-to head comparison of the *risk of death* in patients with CKD receiving **opioids** versus those receiving **NSAIDs**, **opioids** were associated with a dose-dependent higher risk of death at every quintile of CKD. ²

1. Zhan M, et al. *Am J Kidney Dis.* 2020.

2. Novick TK, et al. *Clin J Am Soc Nephrol.* 2019.

Gabapentinoids Use in CKD

- **Gabapentinoids**, common agents used for the treatment of neuropathic pain especially in patients with diabetic kidney disease, can lead to worrisome **neurotoxicity**.
- In patients with an **eGFR < 90** ml/min per 1.73 m² treated with **gabapentinoids**, approximately **6%** experienced **neurotoxicity**, which manifested *as encephalopathy, ataxia, myoclonus, and generalized weakness* ¹.
- The assumption that **non- NSAID** therapies are consistently safer alternatives in patients with CKD is not supported by data.

1. Zand L, et al. Am J Med. 2010.

Pain Management

- Pain is classified as **nociceptive** (relating to tissue damage) or as **neuropathic** (relating to injury to nerves).
- **The Centers for Disease Control and Prevention** published guidelines in **2016** that recommend **nonpharmacologic interventions** as first line in all patients for the management of chronic pain regardless of type.
- **Nonpharmacologic interventions** such as physical therapy, acupuncture, behavior management techniques, mindfulness, and music therapy are evidenced-based for the management of chronic pain ¹.

1. Paice JA, et al. J Clin Oncol. 2016.

Pain Management

- When **nonpharmacologic** interventions are not possible or not effective, **pharmacologic** modalities are entertained.
- **The World Health Organization (WHO)** developed a **pain ladder** for the **pharmacologic** management of pain, which has been suggested for use in CKD and validated in ESKD ¹⁻².
- The **first step** of the **WHO** pain ladder includes acetaminophen, and topical or oral NSAIDs, **Step 1** also can include adjuvant medications that predominately target neuropathic pain such as tricyclic antidepressants, serotonin-NE reuptake inhibitors, gabapentinoids.
- **Steps 2** and **3** of the WHO **pain ladder** include the use of opioid pain relievers.

1. Koncicki HM, et al. Am J Kidney Dis. 2017.

2. Barakzoy AS, et al. J Am Soc Nephrol. 2006.

Pain Management

- For nociceptive pain, **topical NSAIDs** should be considered first line.
- **A Cochrane review** shows **topical NSAIDs** to be as effective as **oral NSAIDs**, for both acute and chronic pain, with no more GI or cardiac side effects than placebo¹.
- Although **topical NSAIDs** are limitedly absorbed, there have been no reports of clinically meaningful kidney injury with the products available on the market.
- **Topical NSAIDs** are impractical for patients with widespread pain. In these cases **acetaminophen** is typically used before **oral NSAIDs** in patients with CKD.

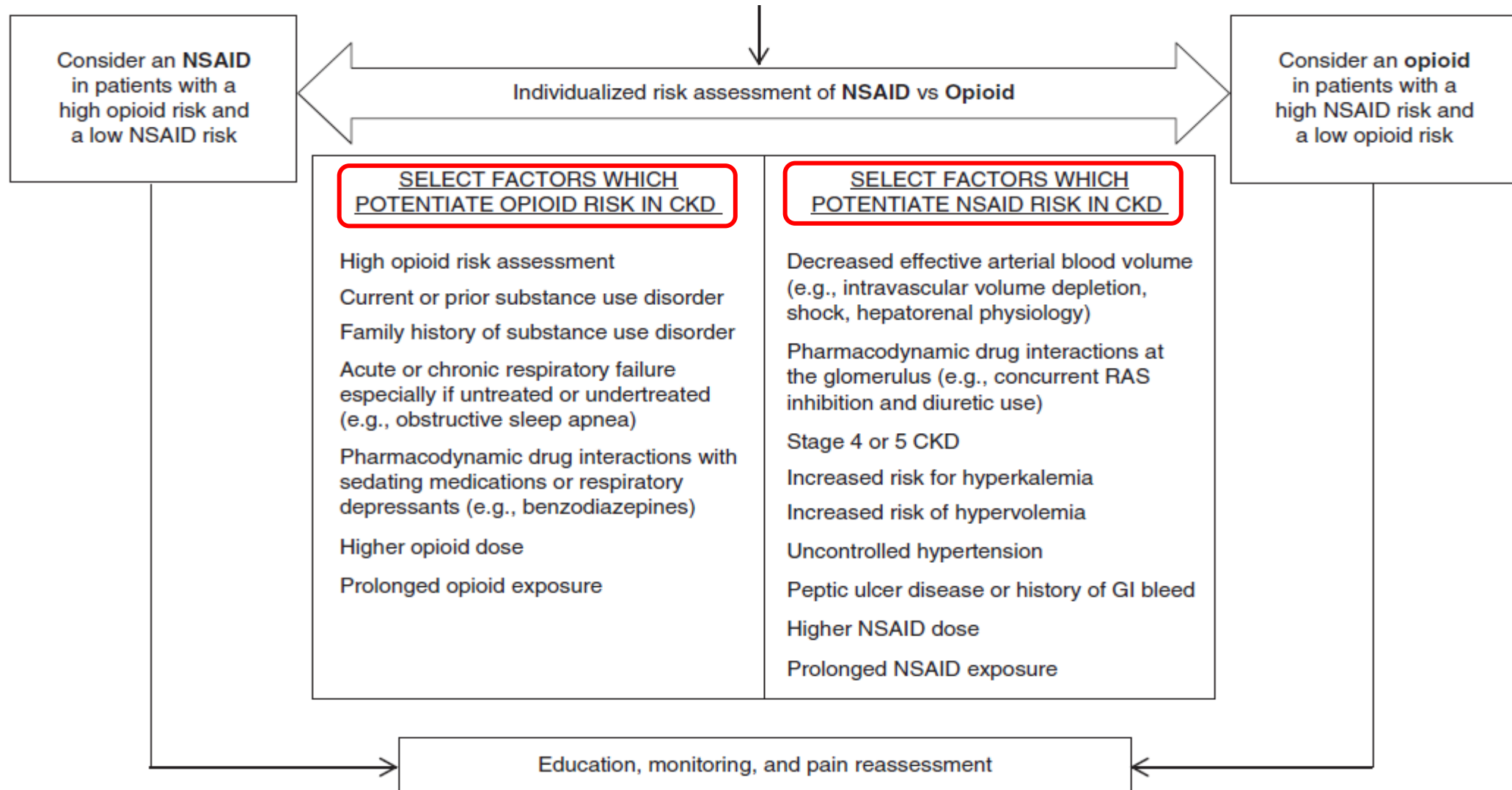
1. Derry S, et al. Cochrane Database Syst Rev. 2017.

Pain Management

- If pain is inadequately controlled by these measures, clinicians face the crux of the clinical challenge: how to select between an oral **NSAID** or an **opioid**.
- The **nephrotoxicity** risk, **GI** and **cardiovascular** side effects of **NSAIDs** is just one facet of this decision. Alongside the potential for **respiratory depression, central nervous system depression, and dependence** with **opioids**. ¹

1. Derry S, et al. Cochrane Database Syst Rev. 2017.

Proposed algorithm for analgesic selection in patients with CKD



NSAIDs vs Opioids in Pain Management in CKD

- In patients with stages 1 through 3 CKD, evidence from **large cohorts** indicate that use of NSAIDs does not accelerate CKD progression ¹.
- For these reasons and the known risk of opioids, in patients with stages 1 through 3 CKD, we generally favor a trial of oral **NSAIDs** for the next step in pain management.

1. Mo¨ller B, et al. Ann Rheum Dis. 2015.

NSAIDs vs Opioids in Pain Management in CKD

- **For example**, consider a 69-year-old man with stage 3 CKD from nephrotic syndrome, a prior myocardial infarction, active alcohol substance use disorder, and untreated obstructive sleep apnea.
- Despite at least two expected risks associated with **NSAIDs** (kidney and cardiovascular), the potential complications of **opioids**, particularly the risks for respiratory depression and additive central nervous system depression, are likely more substantial.
- This balance must be considered as part of shared decision making.

Erin F, et al. KIDNEY 360.2020.

NSAIDs vs Opioids in Pain Management in CKD

- Patients with stage 4 and 5 CKD likely represent a subpopulation at increased risk for complications from **NSAIDs**.
- These patients may have diminished renal reserve and a decreased ability to recover from a nephrotoxic event.
- These patients also exhibit heightened risks with **opioids** so the decision remains challenging.

Erin F, et al. KIDNEY360.2020.

NSAIDs vs Opioids in Pain Management in CKD

- We propose two illustrative cases to highlight the need for individualization.
- **The first case** is a 34-year-old woman with stage **4 CKD** from FSGS and prior heroin addiction who needs pain management for menstrual cramps. In her situation, the risk-benefit analysis likely favors once-monthly **NSAID** use rather than use of an **opioid** despite her stage 4 CKD.
- **The second case** is a 70-year-old man with stage **5 CKD**, prior peptic ulcer disease, and resistant hypertension struggling with calciphylaxis would likely be better suited to treatment with an **opioid**.

Erin F, et al. KIDNEY360.2020.

NSAIDs Dosage in CKD

- **NSAIDs** should be appropriately dosed on the basis of kidney function.
- The lowest dose should be used for the shortest duration possible.
- Dose equivalence across **NSAIDs** may be estimated with the Assessment of **Spondyloarthritis International Society NSAID Equivalent Score**¹.

1. Dougados M, et al. Ann Rheum Dis. 2011.

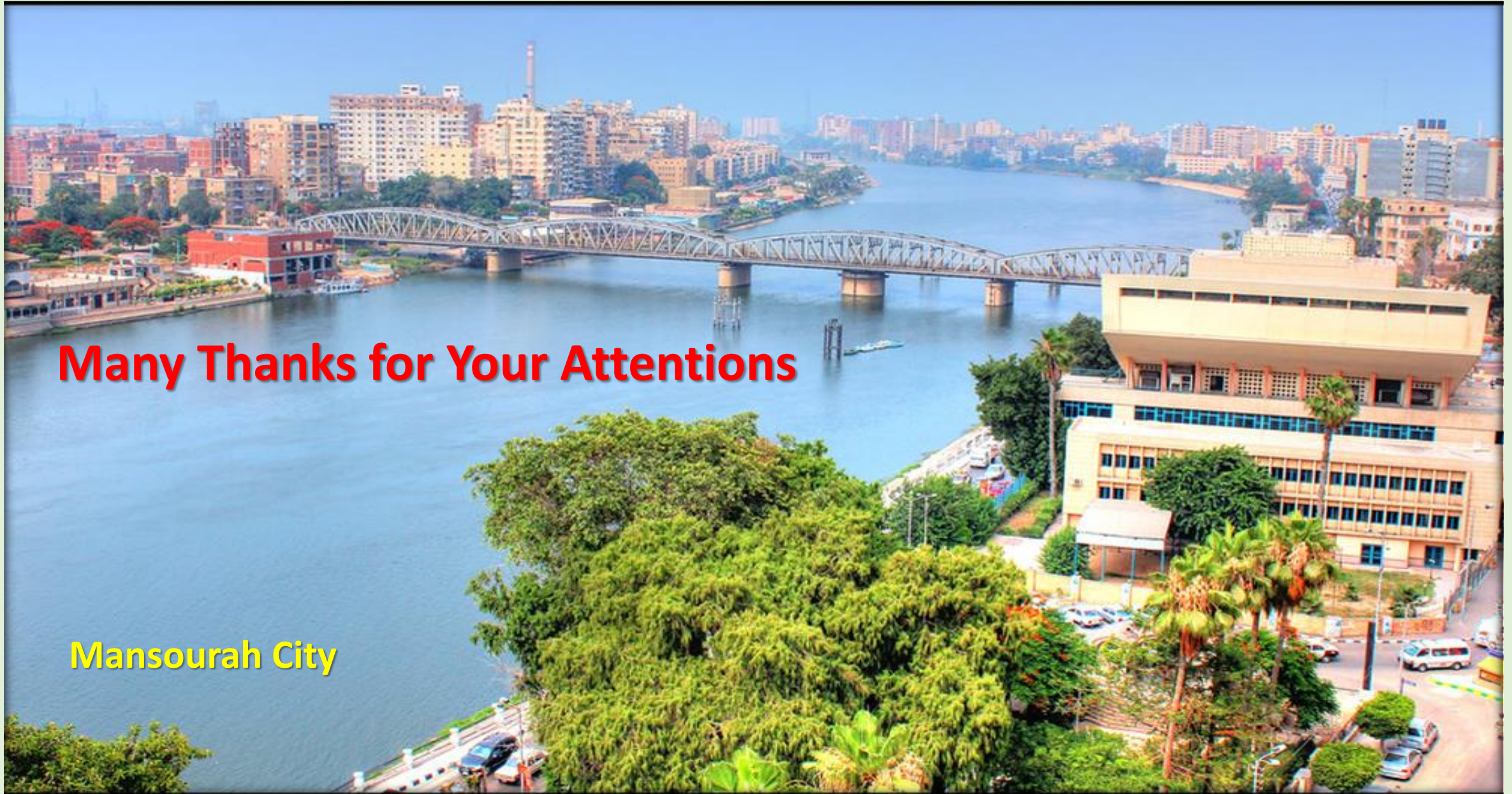
Renal Function Monitoring During NSAID Usage

- Intensity of monitoring should be **tailored to risk**.
- **In low-risk scenarios** (i.e., short duration of therapy or less-severe kidney disease), approximately yearly kidney function and electrolytes, similar to the non-CKD population, is likely sufficient.
- **In high-risk scenarios**, monitoring (to include kidney function, electrolytes, and clinical assessment of ongoing benefit versus harm), should mirror the approach to opioids (e.g., monthly for 3 months and then every 3 months thereafter if stable).

Erin F, et al. KIDNEY360.2020.

Conclusions

- Pharmacologic pain management for patients with CKD requires a careful individualized risk-benefit analysis.
- Although it is tempting to avoid NSAIDs in patients with CKD altogether, the counterbalance of exposure to alternative analgesics such as opioids may be to the patient's detriment.
- Clinicians must recalibrate their risk barometer for pharmacologic pain management in patients with CKD.
- Oral NSAIDs remain an essential and highly efficacious class of medication for pain management in appropriately selected individuals with CKD.



Many Thanks for Your Attentions

Mansourah City