NSAIDs and Kidney

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Prostaglandins and the Kidneys

✓NSAIDs provide their:

- Analgesic
- Anti-inflammatory
- Antipyretic actions
- Through inhibition of cyclooxygenase (COX) enzymes

✓COX enzymes convert arachidonic acid, liberated from the cell membrane, to various eicosanoids: **Thromboxane** and **prostaglandins**

✓These fatty acid derivatives act:

- Locally in a *paracrine* and *autocrine manner*
- Primarily as *modulators of the effects of systemic hormones*

✓Two isoforms of COX, COX-1 and COX-2:

- Have separate but overlapping roles

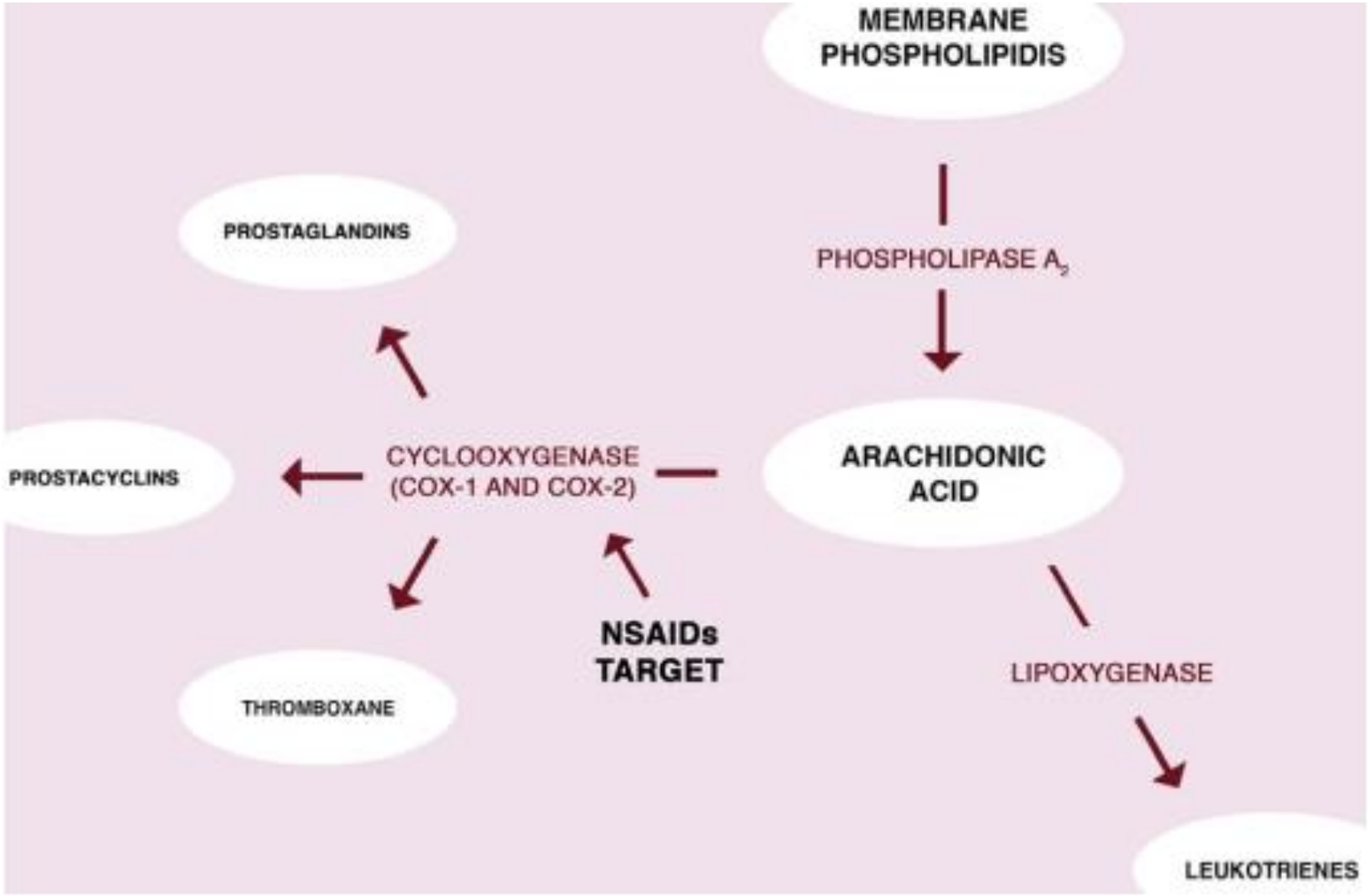
✓**COX-1** is expressed ***constitutively*** in many tissues and *maintains baseline physiologic functions*, including:

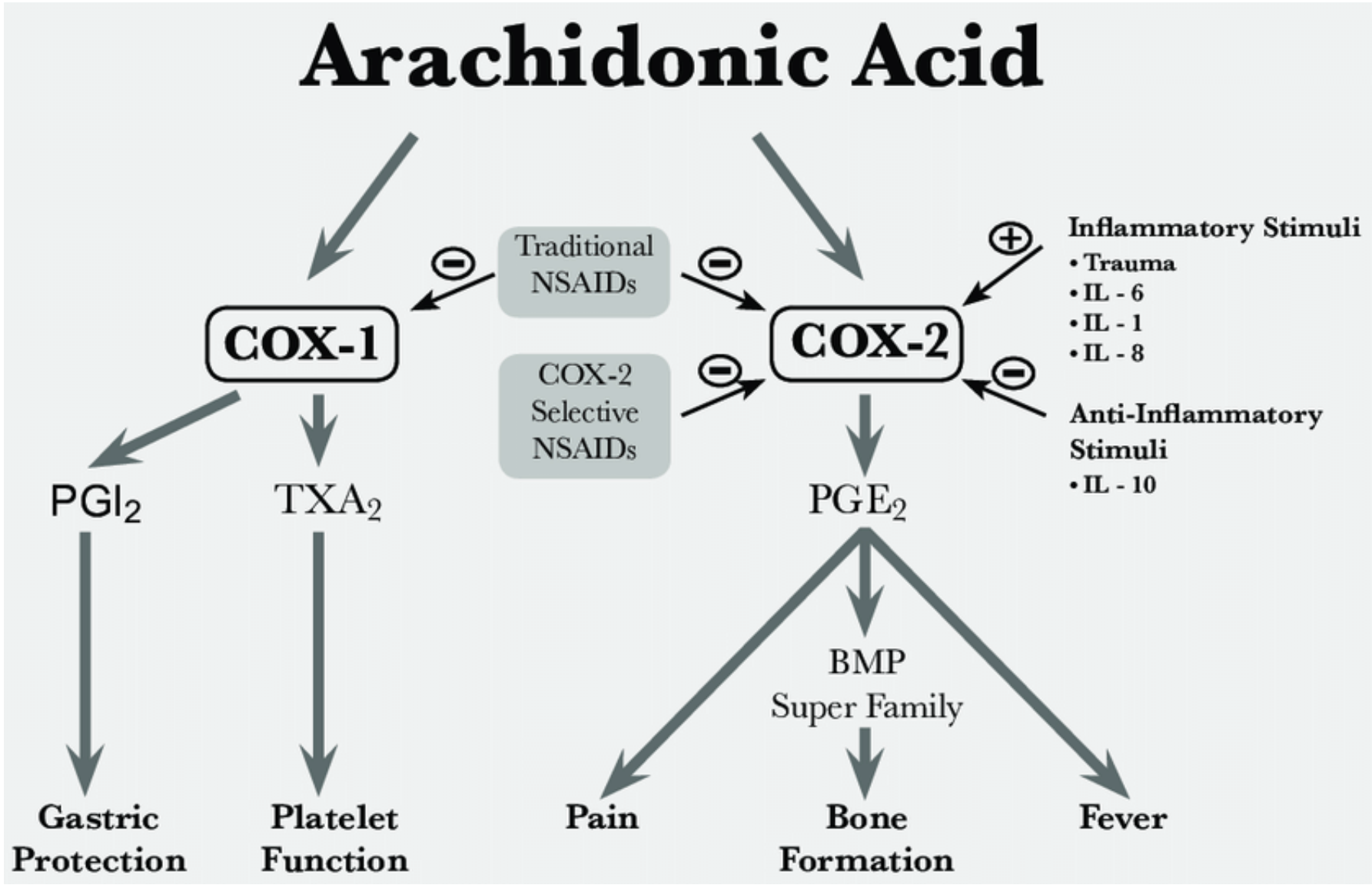
- Maintenance of kidney perfusion and function
- Regulation of platelet aggregation
- Protection of gastric mucosa

✓COX-2 expression is modified by (*inducible*):

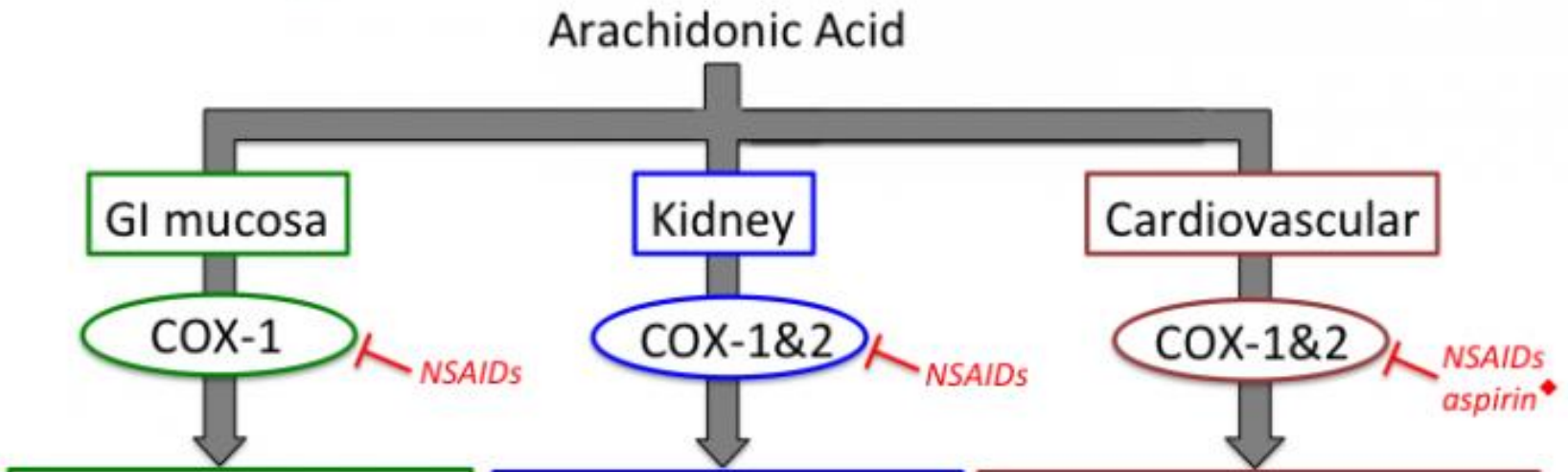
- Growth factors, cytokines, and other external signals
- And is *upregulated in response to inflammation*

The arachidonic acid cascade and NSAIDs biological target




Arachidonic Acid
Traditional NSAIDs
COX-1
COX-2
COX-2 Selective NSAIDs
Inflammatory Stimuli
• Trauma
• IL - 6
• IL - 1
• IL - 8
Anti-Inflammatory Stimuli
• IL - 10
PGI2
TXA2
PGE2
BMP Super Family
Gastric Protection
Platelet Function
Pain
Bone Formation
Fever

NSAID Side Effects:

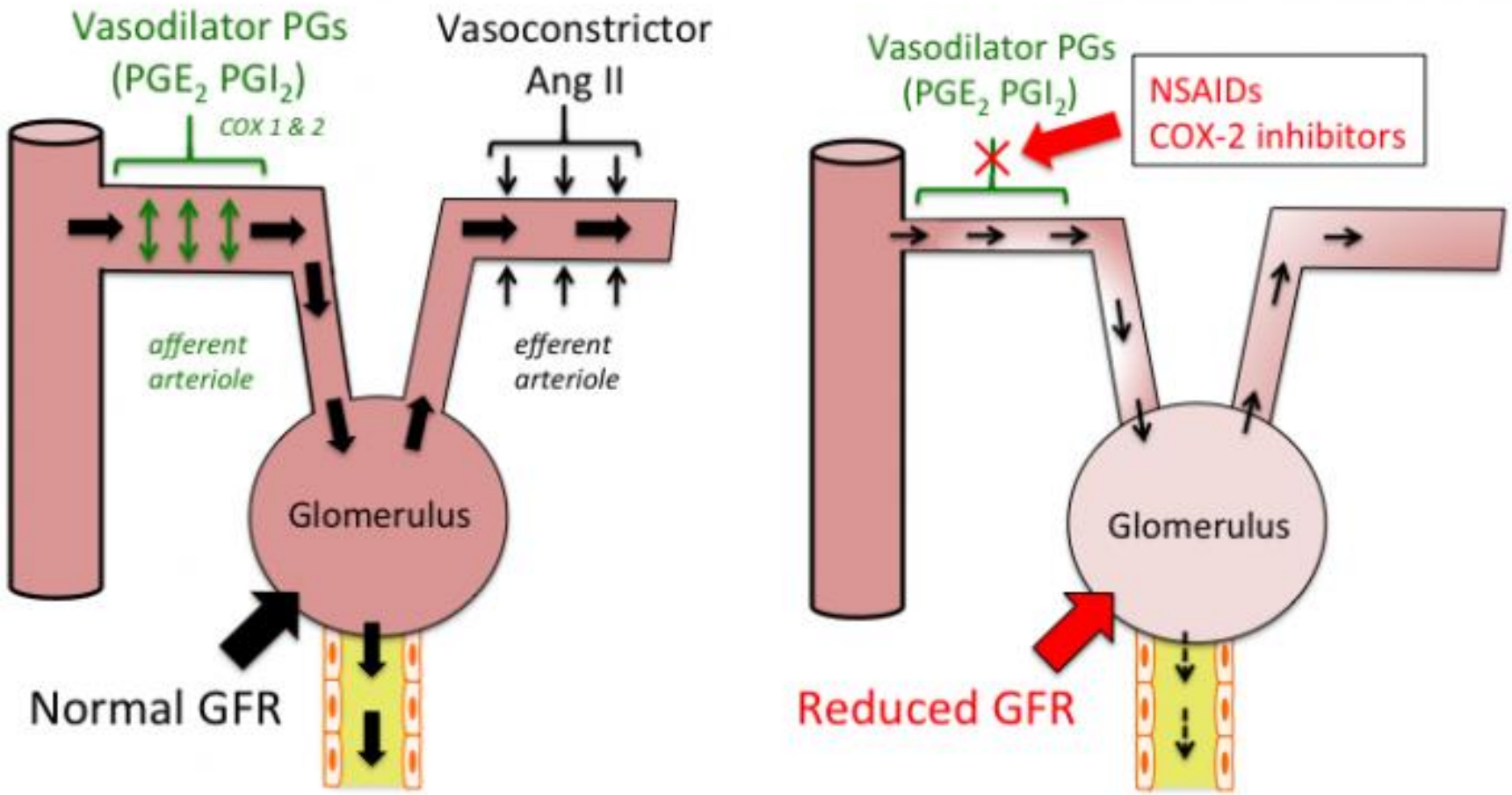


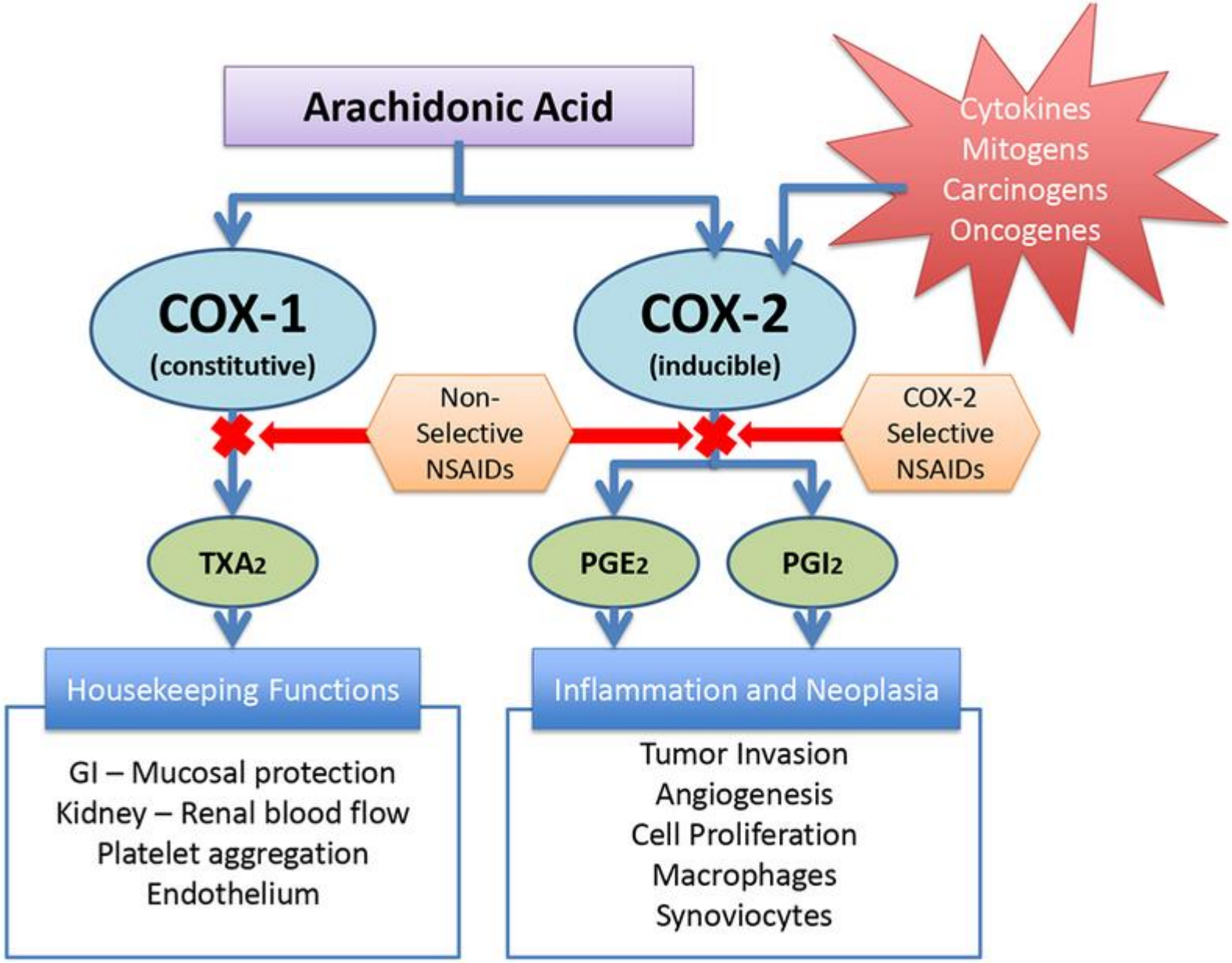
COX-1 inhibition:
- Peptic ulcers
- GI bleeding

COX inhibition:
- Na & water retention
- Hypertension
- Hemodynamic acute kidney injury

COX-2 > COX-1 inhibition:
- Stroke
- Myocardial infarction

◆ Low dose aspirin irreversibly inhibits platelet COX-1


Vasodilator PGs
(PGE2 PGI2)
COX 1 & 2
Vasoconstrictor
Ang II
afferent
arteriole
efferent
arteriole
Glomerulus
Normal GFR
Vasodilator PGs
(PGE2 PGI2)
NSAIDs
COX-2 inhibitors
Glomerulus
Reduced GFR


Arachidonic Acid
Cytokines
Mitogens
Carcinogens
Oncogenes
COX-1
(constitutive)
COX-2
(inducible)
Non-
Selective
NSAIDs
COX-2
Selective
NSAIDs
TXA2
PGE2
PGI2
Housekeeping Functions
GI – Mucosal protection
Kidney – Renal blood flow
Platelet aggregation
Endothelium
Inflammation and Neoplasia
Tumor Invasion
Angiogenesis
Cell Proliferation
Macrophages
Synoviocytes

✓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

✓COX-2 plays a critical role:

- In **adaptive** reno-protective measures
- Hence, NSAID inhibition of COX-2 is likely a major cause of nephrotoxicity

✓Vasodilating prostaglandins counteract vasoconstrictor effects:

- To maintain **RBF, GFR, and peritubular capillary perfusion**

✓Prostaglandins influence renal sodium, water, and potassium handling:

- Inhibition of sodium reabsorption and blunting of ADH effects result in **natriuresis** and **aquaresis**
- Stimulation of renin leads to aldosterone synthesis and **potassium secretion**

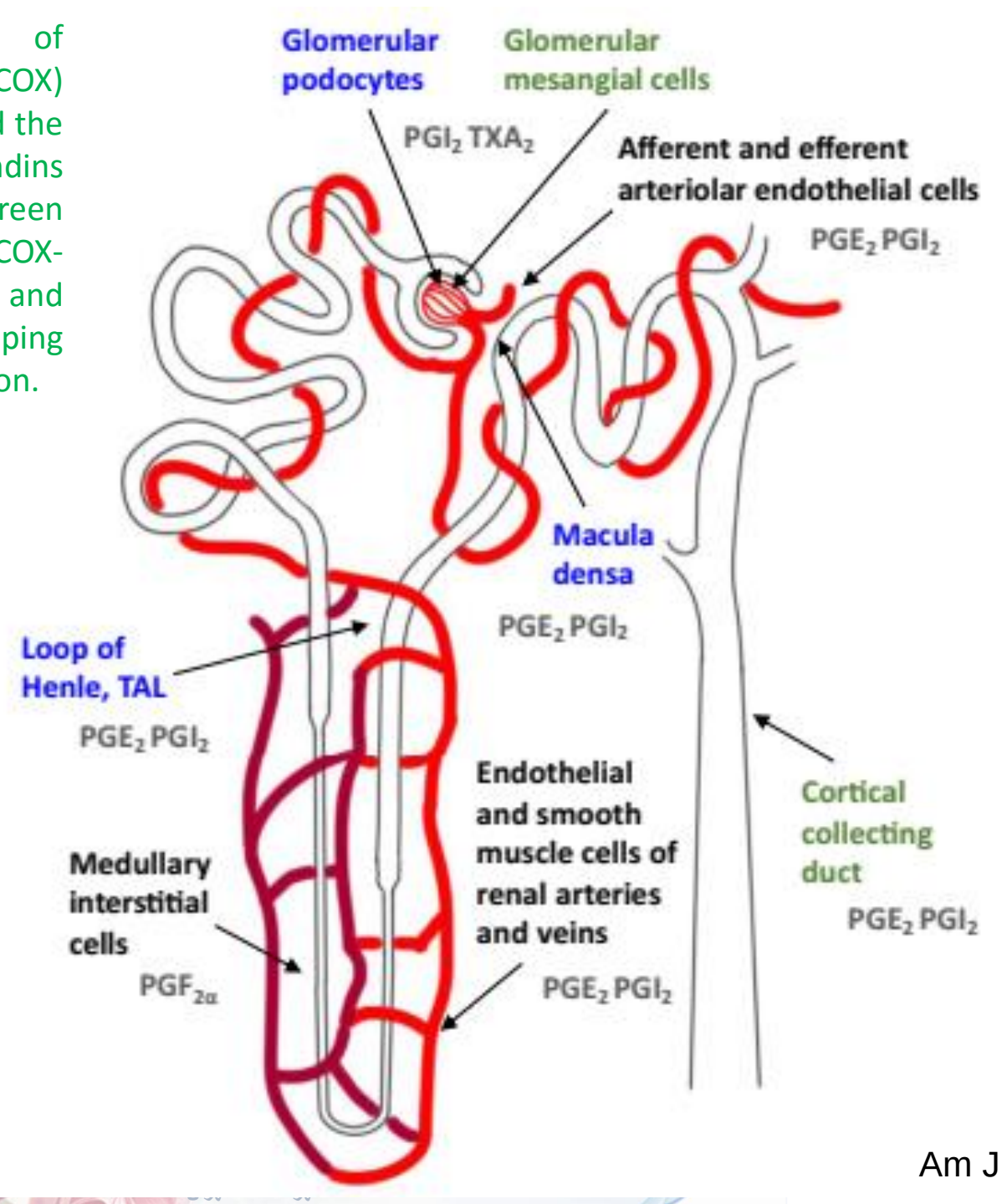
✓Unlike many systemic hormones that act unidirectionally to affect physiologic conditions, prostaglandins operating both:

- 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 *augment RBF, renin production, and sodium and water retention*

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.



It is suggested that both COX isoforms play opposing roles in renal function, with natriuresis increased by COX-1 inhibition followed by a drop in a blood pressure, whereas COX-2 inhibition increases blood pressure and promotes sodium retention.

J Clin Invest. 2002;110:61-69.

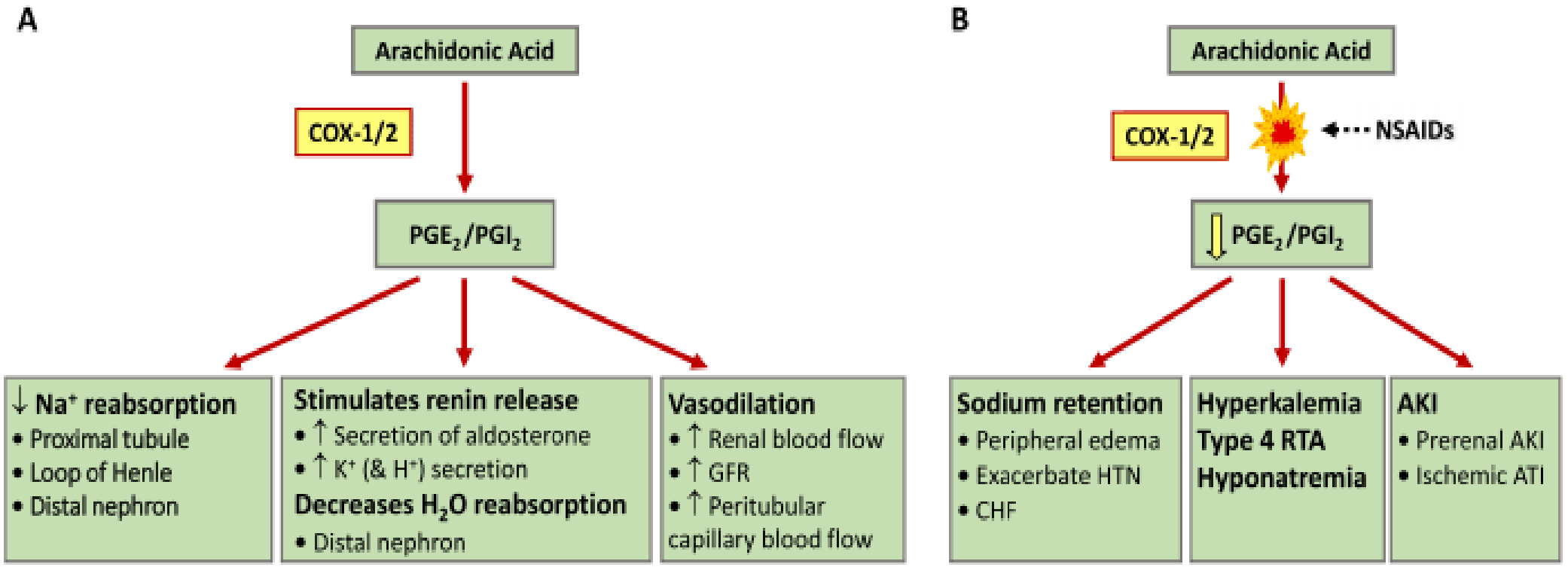
Am J Kidney Dis. 2020 Oct;76(4):546-557.

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

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; TXA_2, thromboxane A_2.

Prostaglandins and the Kidney



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.

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Clinical renal syndromes
Acute Kidney Injury

- AKI and other adverse effects such as fluid and electrolyte derangements *rarely* develop:
  - In patients with few or no risk factors for injury
  - with regular NSAID use
- Pooled risk ratios for AKI events for patients without CKD is 1.6 to 2.2.
- *Similar elevation in risk* among all agents:
  - Though *rofecoxib* demonstrated greatest risk.
  - Selective COX-2 inhibitors cause adverse kidney effects at *a rate and severity* comparable to nonselective NSAIDs

- NSAID-associated AKI is predominantly:
  - Hemodynamically mediated, and
  - Resulting in *reversible* reduction in GFR or ATN
- Patients at highest risk for AKI:
  - In whom *kidney perfusion is dependent* on prostaglandin-induced vasodilation to combat vasoconstrictors:
    - *True volume depletion* and
    - *Reduced ECV:*
      - *CHF*
      - *Nephrotic syndrome*
      - *Cirrhosis*

- Conditions associated with vascular dysfunction with increase AKI risk:
  - *Advancing age* and *hypertension*
  - Due to reduced vascular reserve:
    - Atherosclerosis and narrowing of renal arterioles
- Increase risk of AKI *in CKD*:
  - Reduced renal reserve in CKD and
  - Increase PG dependence for perfusion of *remnant nephrons*

- Risk for NSAID-associated AKI appears higher in:
  - More advanced stages of CKD
  - Older age
  - Specific medication coadministrations
  - Multimorbidity of patients with CKD rather than CKD itself

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

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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)

Summary of Effects of Nonsteroidal Anti-inflammatory Drugs (NSAIDs) on Renal Function

Renal Syndrome	Mechanism	Risk Factors	Prevention or Treatment
Sodium retention and edema	Decreased PGs	NSAID therapy (most common adverse effect)	Stop NSAID
Hyperkalemia	Decreased PGs	Renal disease	Stop NSAID
	Decreased delivery of K^+ to distal tubule	Heart failure	Avoid indomethacin in high-risk patients
	Decreased RAA axis activity	Type 2 diabetes mellitus	
		Potassium supplementation	
		K^+-sparing diuretic	
Acute deterioration of renal function	Decreased PGs and disruption of hemodynamic balance	Hepatic disease (e.g., cirrhosis)	Stop NSAID
		Renal disease	Avoid use in high-risk patients
		Heart failure	
		Dehydration	
		Old age	
Nephrotic syndrome with interstitial nephritis	Increased lymphocyte recruitment and activation through formation of leukotrienes	Fenoprofen	Stop NSAID; support with dialysis and steroids (?) PRN
Acute renal papillary necrosis	Direct toxicity	Massive NSAID ingestion	Stop NSAID
	Decreased PG	Dehydration	Rehydrate
Chronic renal papillary necrosis	Direct toxicity	Phenacetin abuse	Stop NSAID; avoid chronic "compound" analgesic use
	Decreased PGs	Aspirin–acetaminophen combination abuse (?)	

Hypervolemia

- NSAIDs increase sodium and water retention, promoting:
  - Edema formation
  - Exacerbating CHF
  - Worsening hypertension
  - Most pronounced in patients with underlying sodium- and water-avid states such as:
    - CHF, nephrotic syndrome, and cirrhosis
  - In CKD, increased ADH secretion and RAAS activation act to augment blood flow to hypo-perfused nephrons through
  - In hypertension and diabetes mellitus (2 main causes of CKD)

Hyponatremia

- Two mechanisms promote net free-water absorption and hyponatremia by inhibiting PGs:
  - Amplification of antidiuretic effect of ADH
  - Intensification of medullary interstitial osmotic gradient
- Patients at higher risk for hyponatremia with NSAIDs:
  - Cirrhosis, nephrotic syndrome, and CHF, and SIADH
  - Older adults to thiazide diuretic–induced hyponatremia
- Incidence of clinically symptomatic hyponatremia is low
- Even mild forms of hyponatremia are associated with:
  - Increased mortality, longer hospitalizations, readmissions, falls, osteoporosis, and cognitive impairment

Hyperkalemia

- Prostaglandin deficiency induces hyporeninism hypoaldosteronism:
  - Impaired principal cell potassium secretion
- Decreased sodium chloride delivery to distal tubule reduces:
  - Electrochemical gradient for potassium secretion
- AKI can further exacerbate hyperkalemia
- Hyperkalemia with NSAID use is related to:
  - Underlying comorbid conditions
  - Exposure to medications that impair renal potassium handling
- Mild to moderate CKD does not increase hyperkalemia risk with NSAIDs

Hypertension

- NSAIDs may worsen blood pressure (BP) control:
  - By approximately *3 to 6 mm Hg* through
  - Renal sodium and water retention
  - Increased peripheral vascular resistance
- NSAIDs render several classes of antihypertensives less effective (*ACI/ARB*, *diuretics*) by:
  - Decreased renin production
  - Increased sodium avidity (TAL segment)
- Patients with *underlying hypertension* and *sodium-avid states* are at higher risk for hypertension with NSAIDs

Acute Interstitial Nephritis and Glomerulonephritis

- NSAIDs also cause kidney injury through:
  - Idiosyncratic reactions, including *acute interstitial nephritis (AIN)*
  - Due to shunting of arachidonic acid into the *lipo-oxygenase pathway*
  - Leading to increased production of *proinflammatory leukotrienes*
  - Approximately *2-fold increase in risk for AIN*, though absolute risk is very low
- Proteinuria and nephrotic syndrome:
  - *Membranous nephropathy*
  - *Minimal change disease*
  - Well-established but more infrequent complications
  - May occur alone or with AIN
  - Occurs weeks to months after initial NSAID exposure

Progression of CKD

- ✓Chronic pain is common in patients with CKD
- ✓Its management is limited by drug related adverse effects
- ✓Patients with reduced GFR are at increased risk for drug-related toxicity
  - due to *impaired metabolism* and *excretion*
- ✓Increasing risk for the classic “clinical renal syndromes” with NSAIDs in patients with CKD

✓Underlying CKD is a

- “Prostaglandin-dependent” state
- Which makes NSAID use potentially more risky

✓NSAID avoidance has led to:

- Increased opioid administration to manage pain
- Often at excessive doses for the degree of GFR
- Opioid use poses many risks regardless of GFR

- Risk for CKD progression due to NSAID use:
  - Although is not insignificant
  - It appears to be small
  - Related to *cumulative dose*
  - *Modifiable by appropriate patient selection* in patients with mild to moderate CKD

✓Prostaglandin production is increased *in CKD*

- As a mechanism to improve perfusion of remaining nephrons

✓This is important in maintaining baseline GFR

- Even in the setting of modestly reduced glomerular filtration

- Strong modifiers of NSAIDs to cause nephrotoxicity in CKD:
  - Severity underlying health conditions
  - Burden of chronic disease
  - Concomitant medication exposures

- In the medical community, NSAIDs are regarded as

harmful for patients with CKD

- Clinical guidelines currently recommend:
  - Avoidance of prolonged NSAID use in CKD with GFR > 30 mL/min/1.73 m2
  - Complete avoidance with GFR < 30 mL/min/1.73 m2

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[e]	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[e]	Daypro	38-44 h	1,200 mg (1×/d)	Avoid
Enolic Acids				
Piroxicam[e]	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[e]	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

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Recommendations of NSAIDs use in CKD

- *For patients with CKD stages 1 and 2:*
  - Which are stable
  - Without predisposing risk factors
  - Monitoring can be similar to patients without kidney disease
- *In patients with Stage 3 CKD:*
  - In whom predisposing risk factors 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
- 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.

Recommendations

- *Short-acting agents* are preferred over long-acting agents:
  - Along with optimization of volume status and
  - Cardiac function before and during treatment
  - Adjustment of NSAIDs dosing interval
- NSAIDs should likely be avoided in those with *prostaglandin-dependent RBF*, including:
  - States of true and ECV depletion:
  - Cirrhosis, CHF, nephrotic syndrome
- Additional caution with NSAID use is with *potassium handling issues*:
  - Who are prescribed RAAS inhibitors, diuretics, mineralocorticoid inhibitors and trimethoprim

Recommendations

- *Patients with stage 4 CKD:*
  - Require a more judicious approach to NSAID therapy
  - If NSAIDs are to be used in patients with stable CKD 4
  - Low doses of short half-life preparations
  - With an appropriate dosing interval
  - For 5 or fewer days and
  - Close monitoring within the treatment period
- *In patients with stage 5 CKD:*
  - Except under circumstances prioritizing palliation over prolongation of life
  - Patients with stage 5 CKD should never receive these drugs
  - Because risk for lethal renal complications is high
  - Despite the absence of data

Recommendations

- *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

Conclusion

- ***NSAIDs*** are associated with adverse renal outcomes
- Their risk must be weighed against benefit of improved pain control
- An accurate risk assessment must be highly individualized based on:
  - CKD stage
  - Age
  - Comorbid conditions
  - Concomitant medication use

Thank You for Your Attention