

NSAIDs & Glucocorticoids

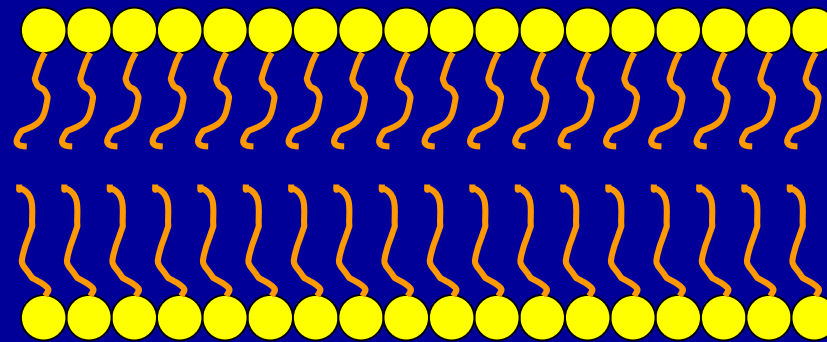
Monitoring

Alimohammad Fatemi

Associate Professor of Rheumatology

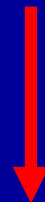
A Glance to the Action of NSAIDs

Cell Membrane Phospholipids

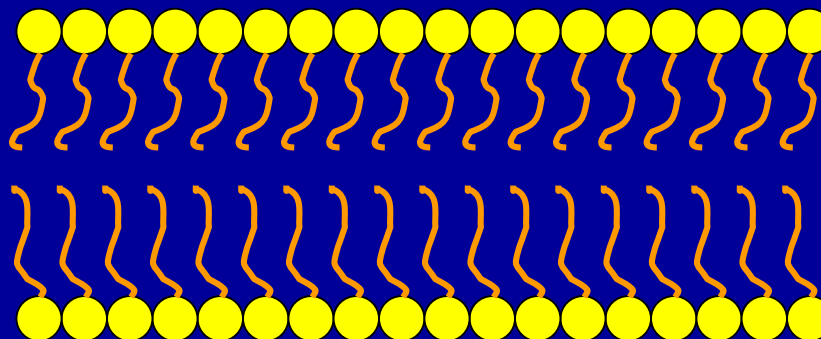


**Diverse
Physical,
Chemical and
Inflammatory
Stimuli**

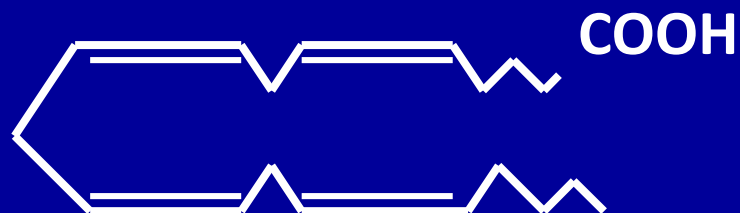
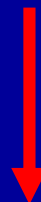
.....▶ **Phospholipase A2**



Cell Membrane Phospholipids



Phospholipase A2

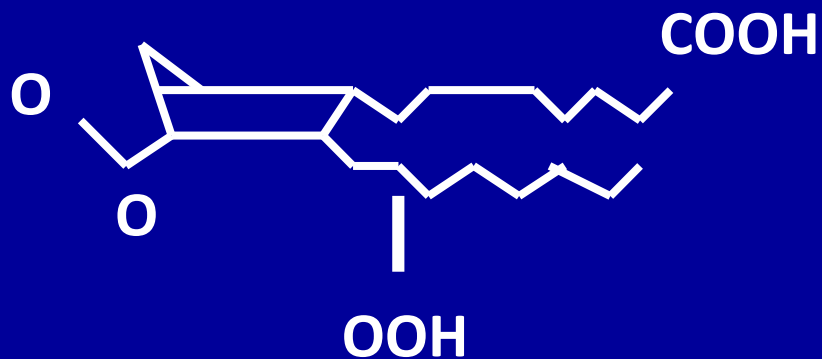


Arachidonic Acid

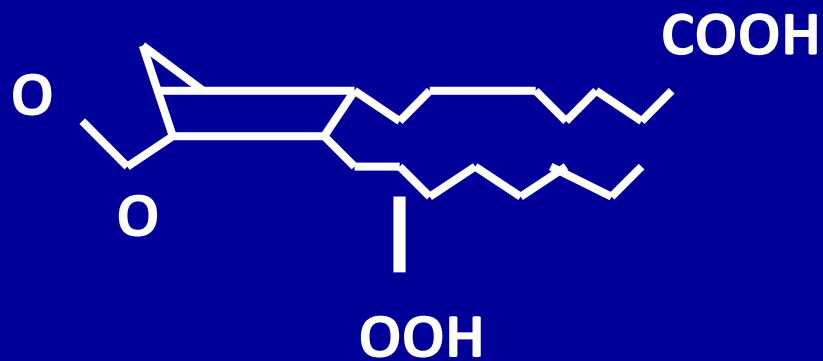


Arachidonic Acid

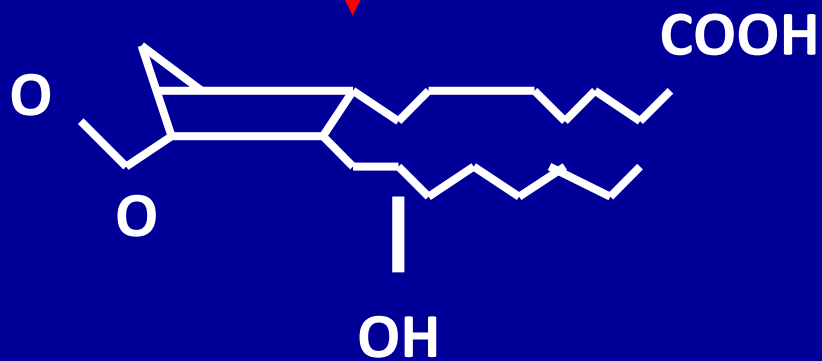
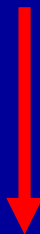
COX-1
COX-2



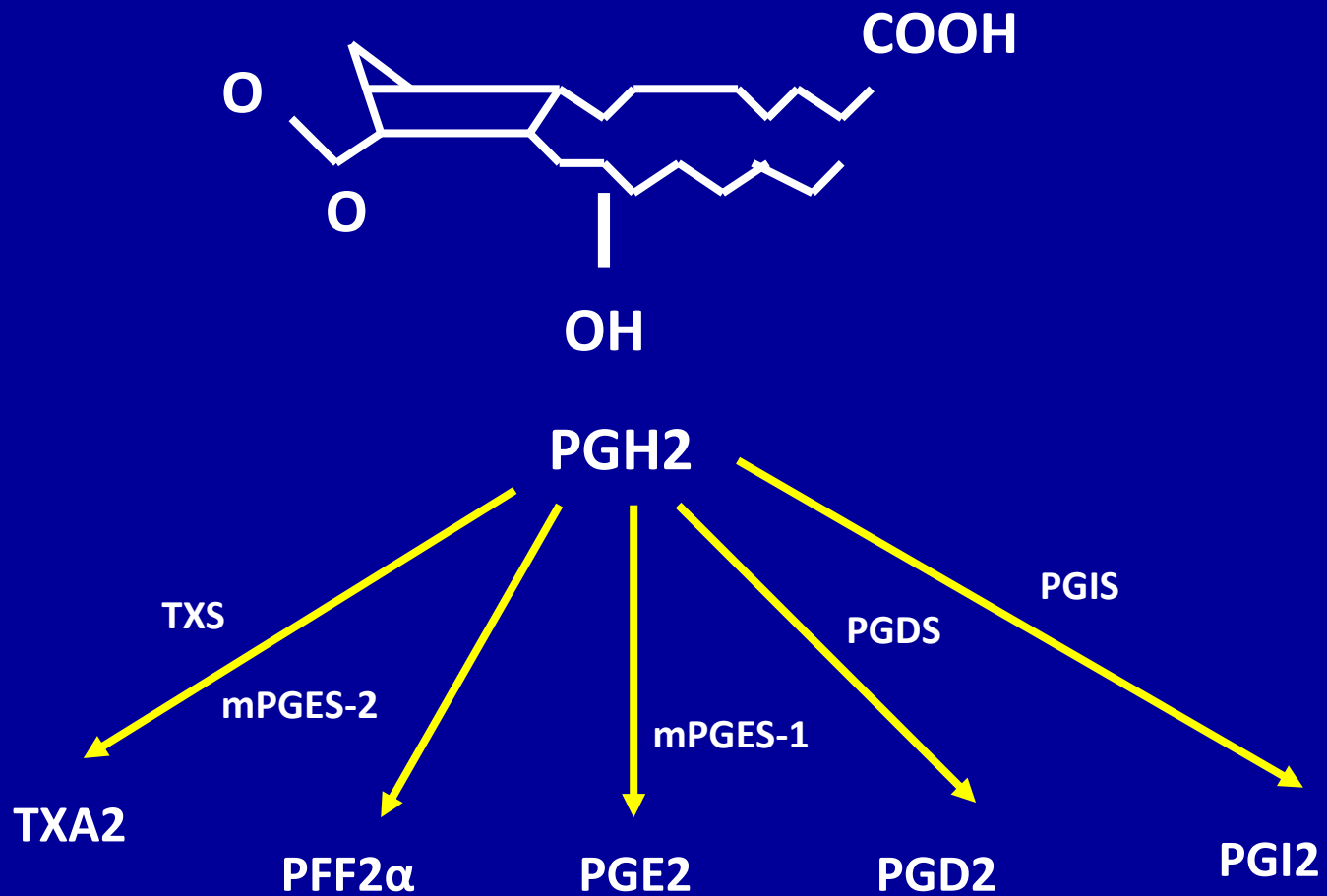
PGG2



PGG₂

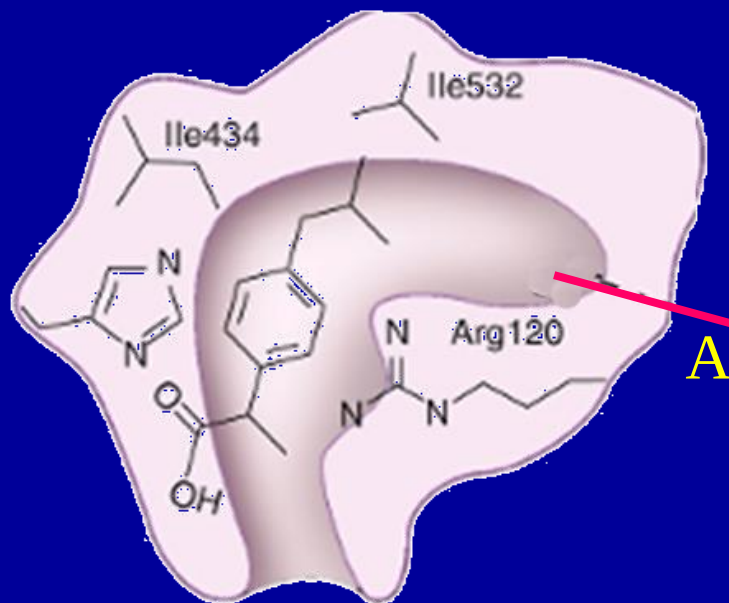


PGH₂



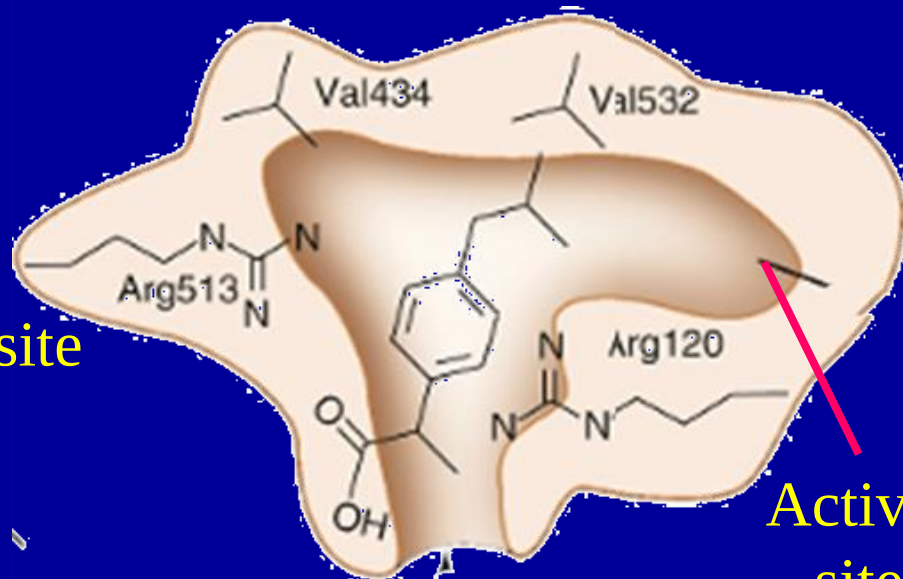
COX Structure

Cox-1



Active site

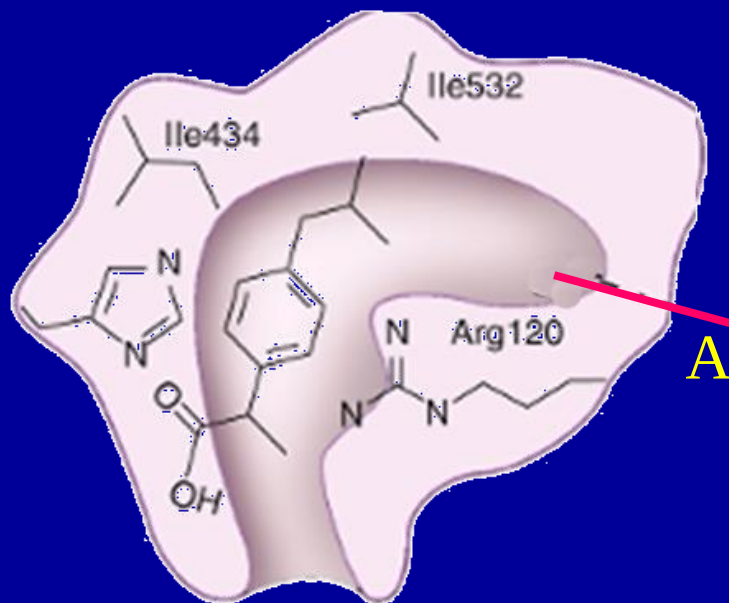
Cox-2



Active site

COX Structure

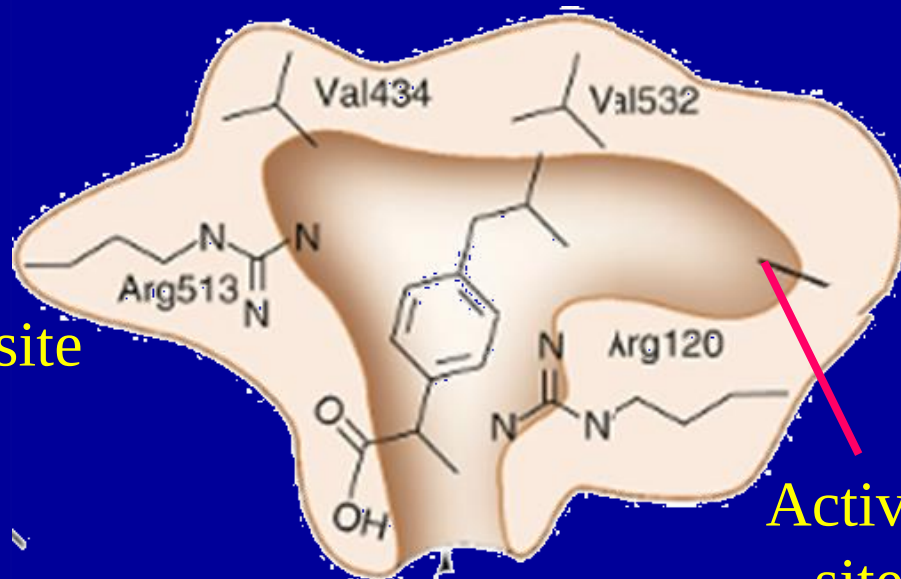
Cox-1



Active site

Normal GI Mucosa
Platelet
Kidney

Cox-2

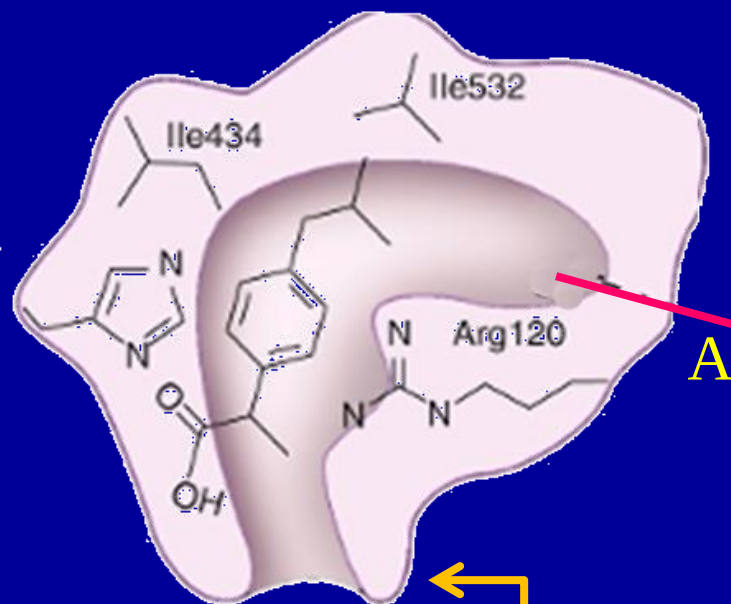


Active site

Brain
Kidney
Inflammatory Sites

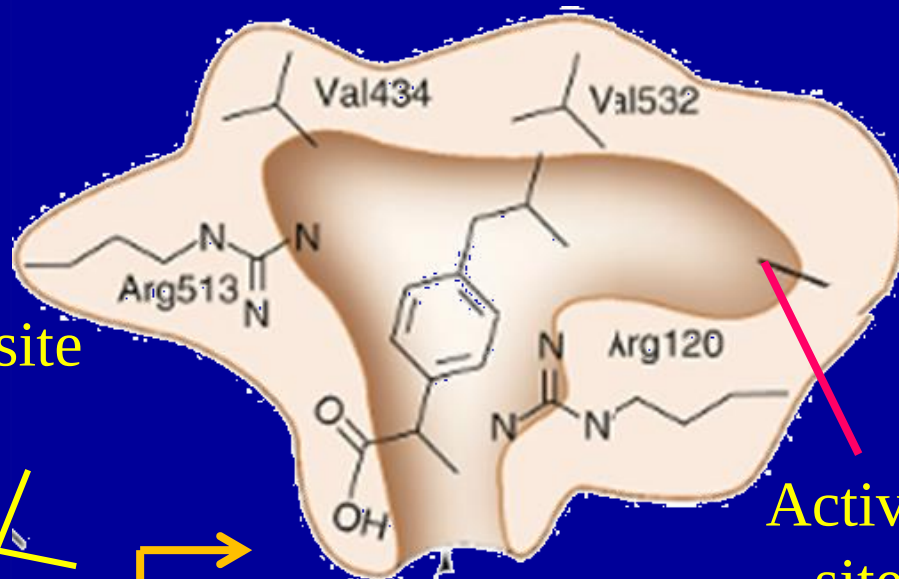
COX Structure

Cox-1

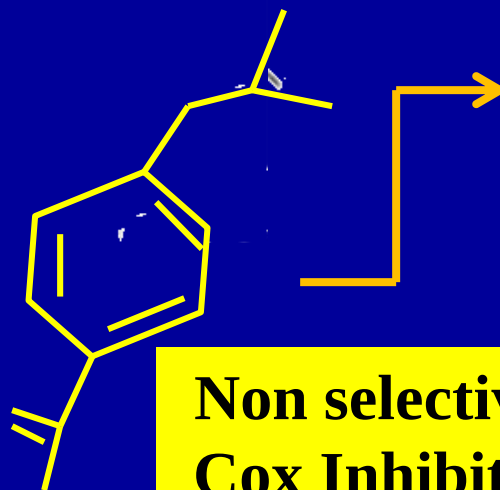


Active site

Cox-2



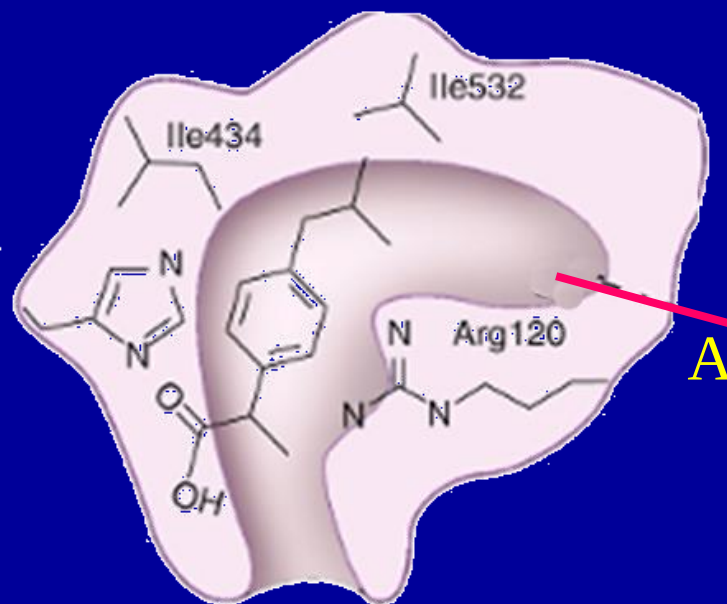
Active site



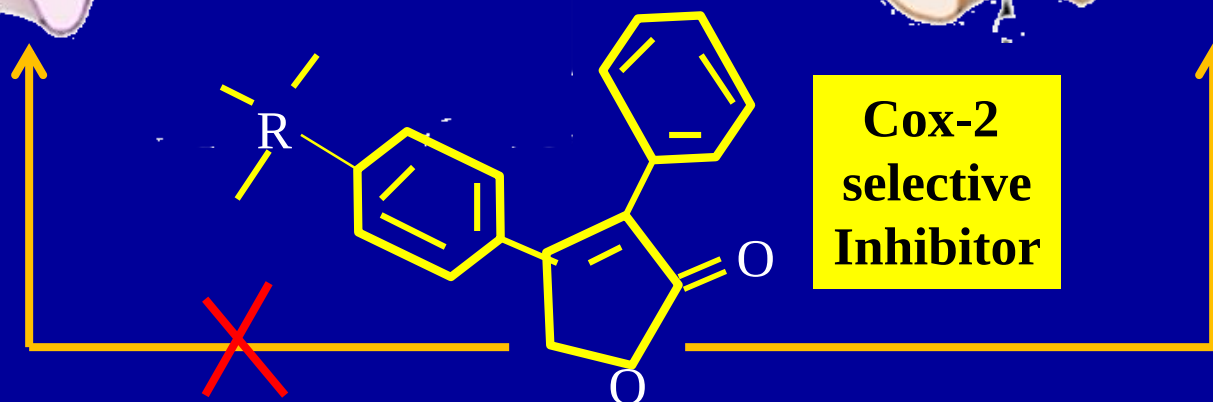
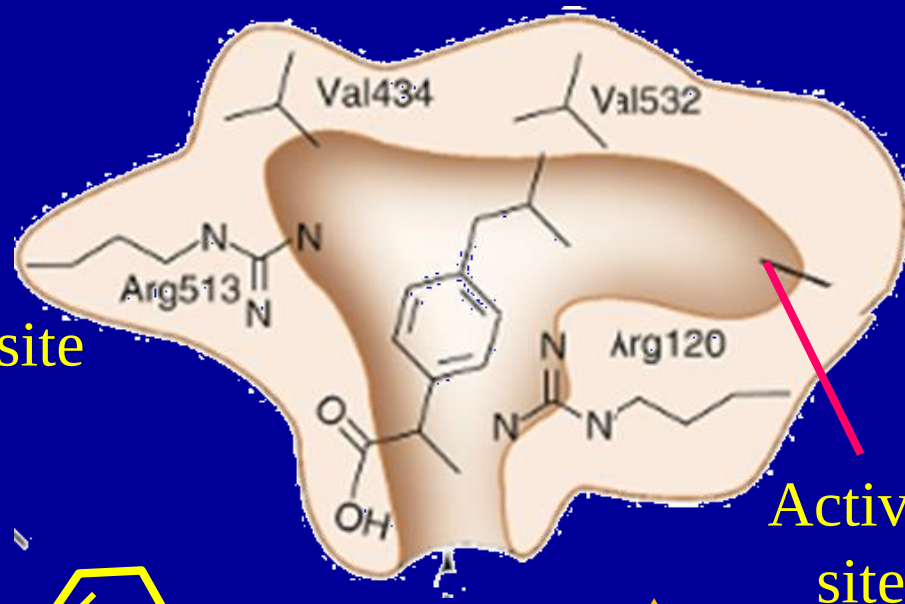
**Non selective
Cox Inhibitor**

COX Structure

Cox-1



Cox-2



Chemical Classification of NSAIDs

Chemical Classification	Drug
Salicylates	Aspirin
Indole derivatives	Indomethacin, Tolmentin
Phenylacetic acid	Diclofenac
Propionic acids	Naproxen, Ibuprofen
Enolic acids	Piroxicam, Meloxicam
Sulfonylurea	Celecoxib

Classification According to COX-1 vs. Cox-2 Inhibition

Type	NSIADs
COX-1 selective	Low-dose ASA
COX non selective	Ibuprofen, Naproxen, Indomethacin
COX-2 Selective	Diclofenac, Meloxicam
COX-2 highly selective	Celecoxib

Adverse Effects

Gastrointestinal

- Abdominal Pain
- Nausea
- Anorexia
- Diarrhea
- Erosions/Ulcers
- Hemorrhage/Perforation

GI Ulcer & Bleeding

- 30-50% of NSAIDs users

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• ↑ 4-fold

Ulcer Complication

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Ulcer Complication

- GI risk is evident within the first 6 months.

Adelowo et al, Lancet 2013

GI Ulcer & Bleeding

- 30-50% of NSAIDs users

• ↑ 4-fold

Ulcer Complication

- GI risk is evident within the first 6 months.

Adelowo et al, Lancet 2013

- No correlation between symptoms and lesion

GI Ulcer & Bleeding

- Risk Factors

- H. Pylori infection
- Alcohol
- ASA
- Clopidogrol
- Warfarin
- Glucocorticoids
- Age
- Smoking

In Daily Practice

- Lowest dose and Frequency

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 - Consider COX-2 selective inhibitors
- Or
- A nonselective NSAID and gastric protective agent (PPI or PGE2)

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- Cox-2 selective +ASA needs protection.

In Daily Practice

- Lowest dose and Frequency
- Consider COX-2 selective inhibitors
- Or
- A nonselective NSAID and gastric protective agent (PPI or PGE2)
- COX-2 selective ~ PPI+ non-selective
- Cox-2 selective +ASA needs protection.
- Naproxen has the highest risk.

In Daily Practice

- Nonselective COX inhibitors
- COX-2 selective inhibitors
- ASA

Linear dose–response relationship with
GI side effects

Hepatotoxicity

Hepatotoxicity

- Transaminitis

All NSAIDs

(15% have Mild↑)

Hepatotoxicity

- Transaminitis

All NSAIDs

- Diclofenac

More commonly

Hepatotoxicity

- Transaminitis

All NSAIDs

- Diclofenac

More commonly

- Severe hepatitis

Indomethacin

Diclofenac

Sulindac

Hepatotoxicity

- Transaminitis

All NSAIDs

- Diclofenac

More commonly

- Severe hepatitis

Indomethacin

Diclofenac

Sulindac

- Fatal hepatotoxicity

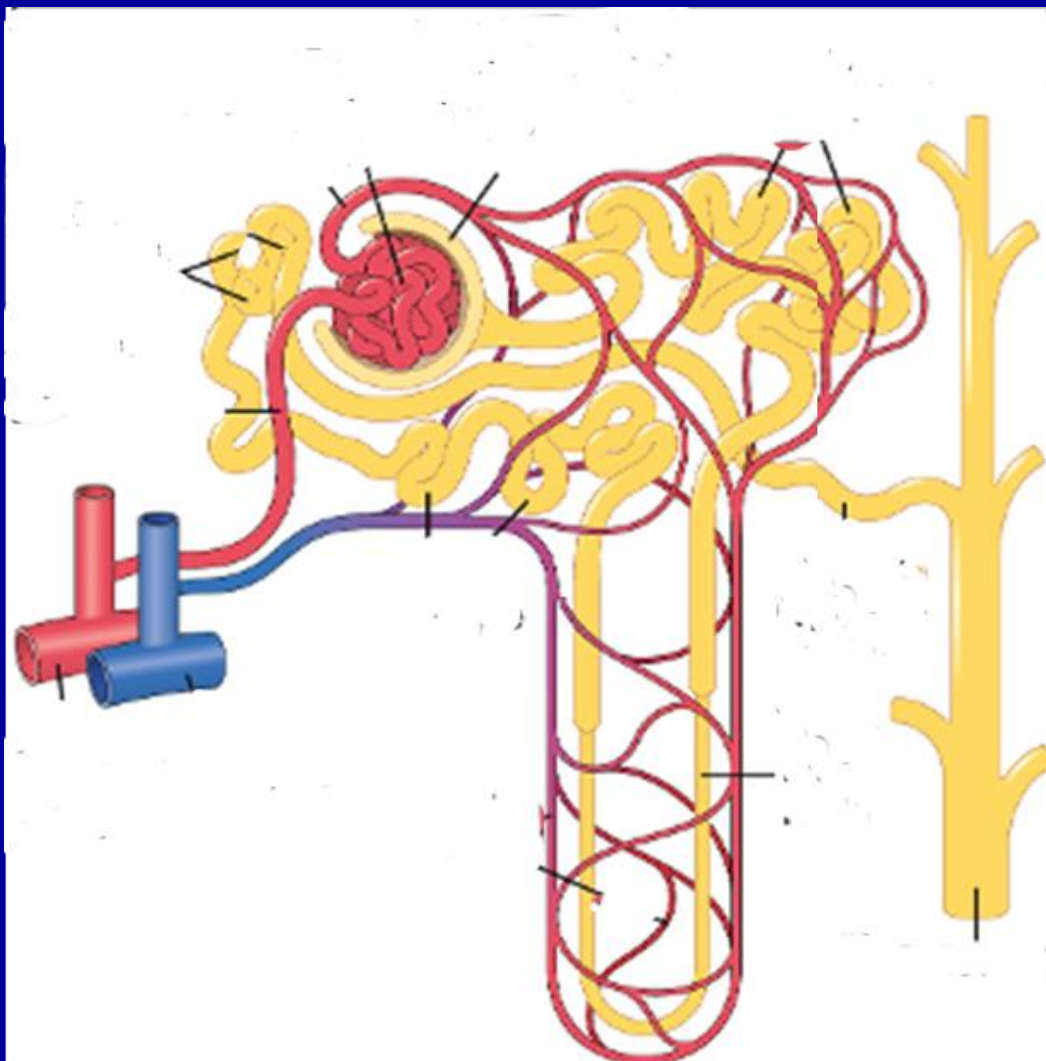
Indomethacin in
children

In Daily Practice

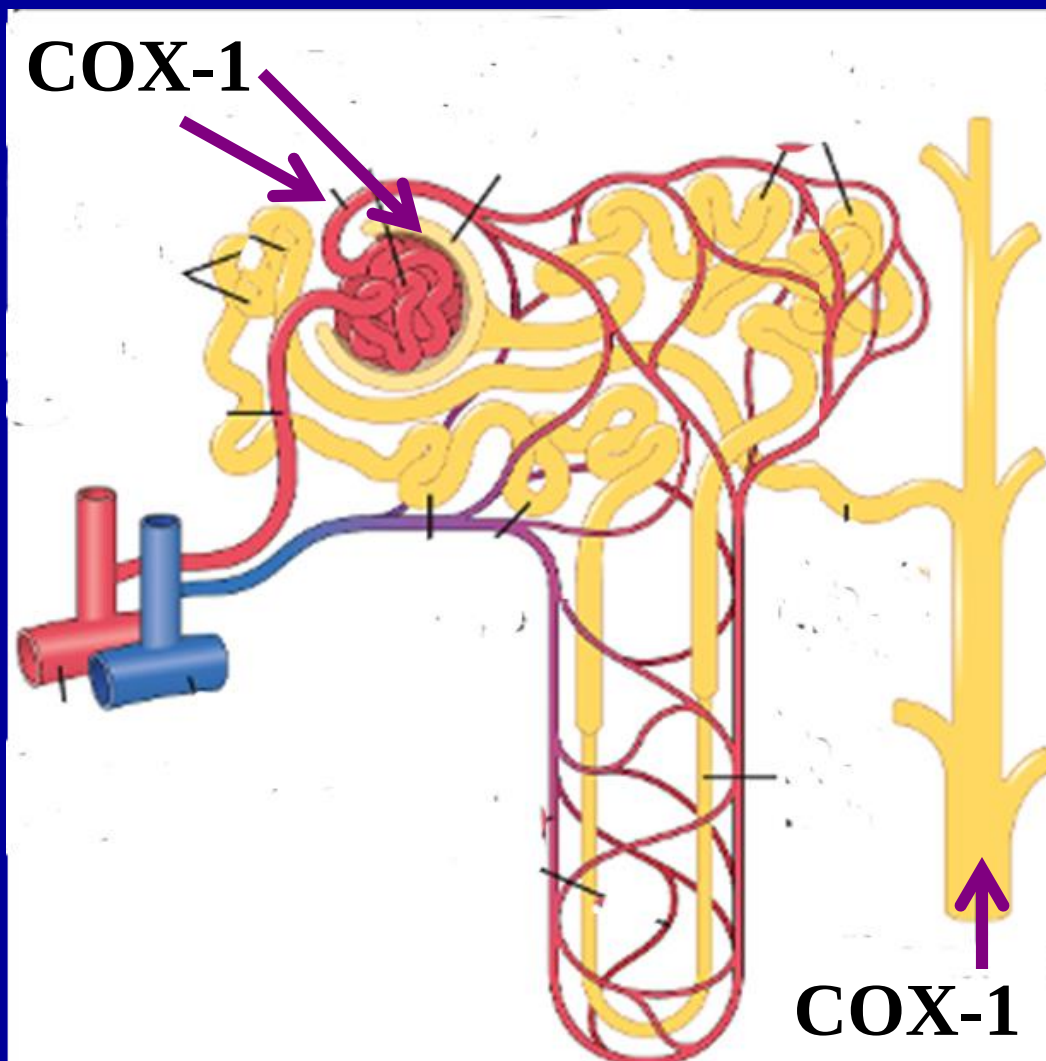
- Check LFT every 8-12 weeks

Adverse Effects Renal

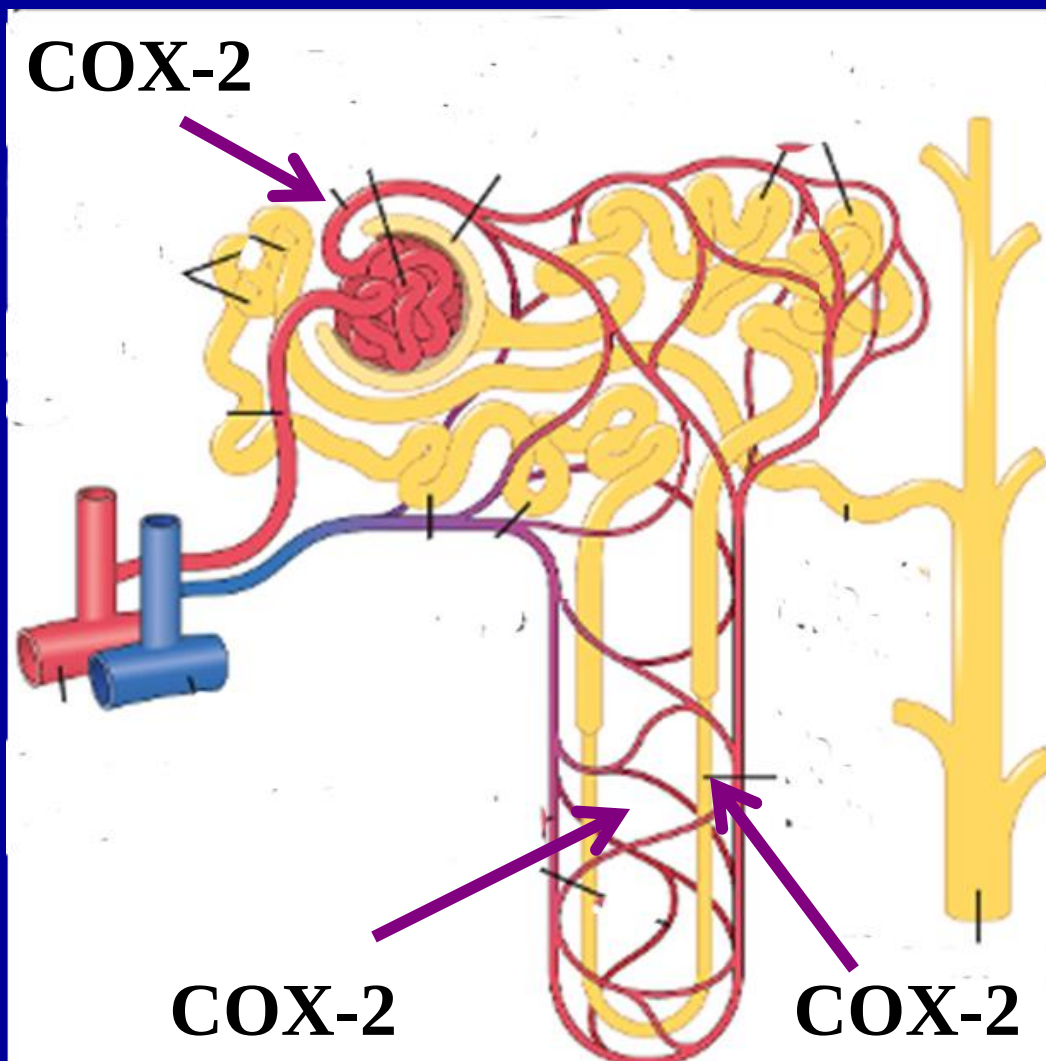
COX in Kidney



COX in Kidney



COX in Kidney



Renal

- Sodium Retention
- Hypertension
- Acute Renal Failure
- Papillary necrosis
- Interstitial Nephritis
- Chronic kidney disease

Adverse Effects Cardiovascular

Cardiovascular

- COX-1



TX-A2

- COX-2



PG-I2

Cardiovascular

- COX-1



TX-A2

- COX-2



PG-I2

**Non selective COX
Coxib**

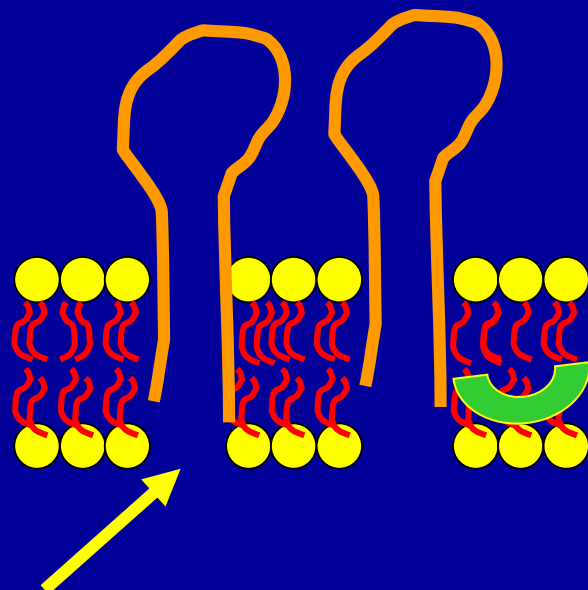


Cardiovascular

- Interfere with the irreversible inhibition of platelet COX-1 by Aspirin

ASA + NSAIDs

COX-1

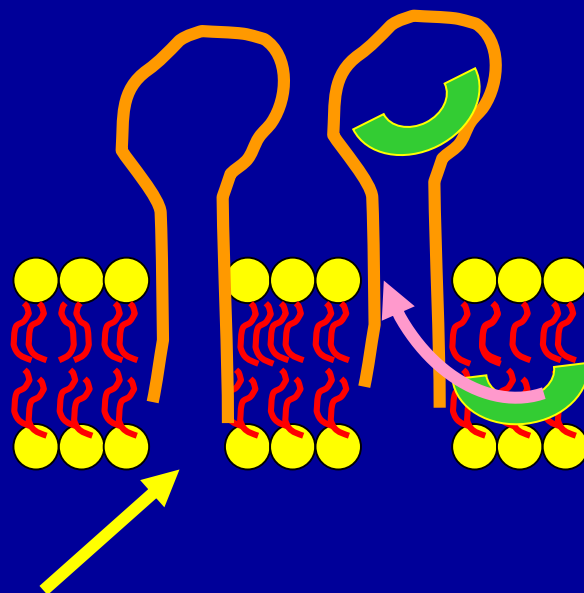


Arachidonic acid

Channel of Access

ASA + NSAIDs

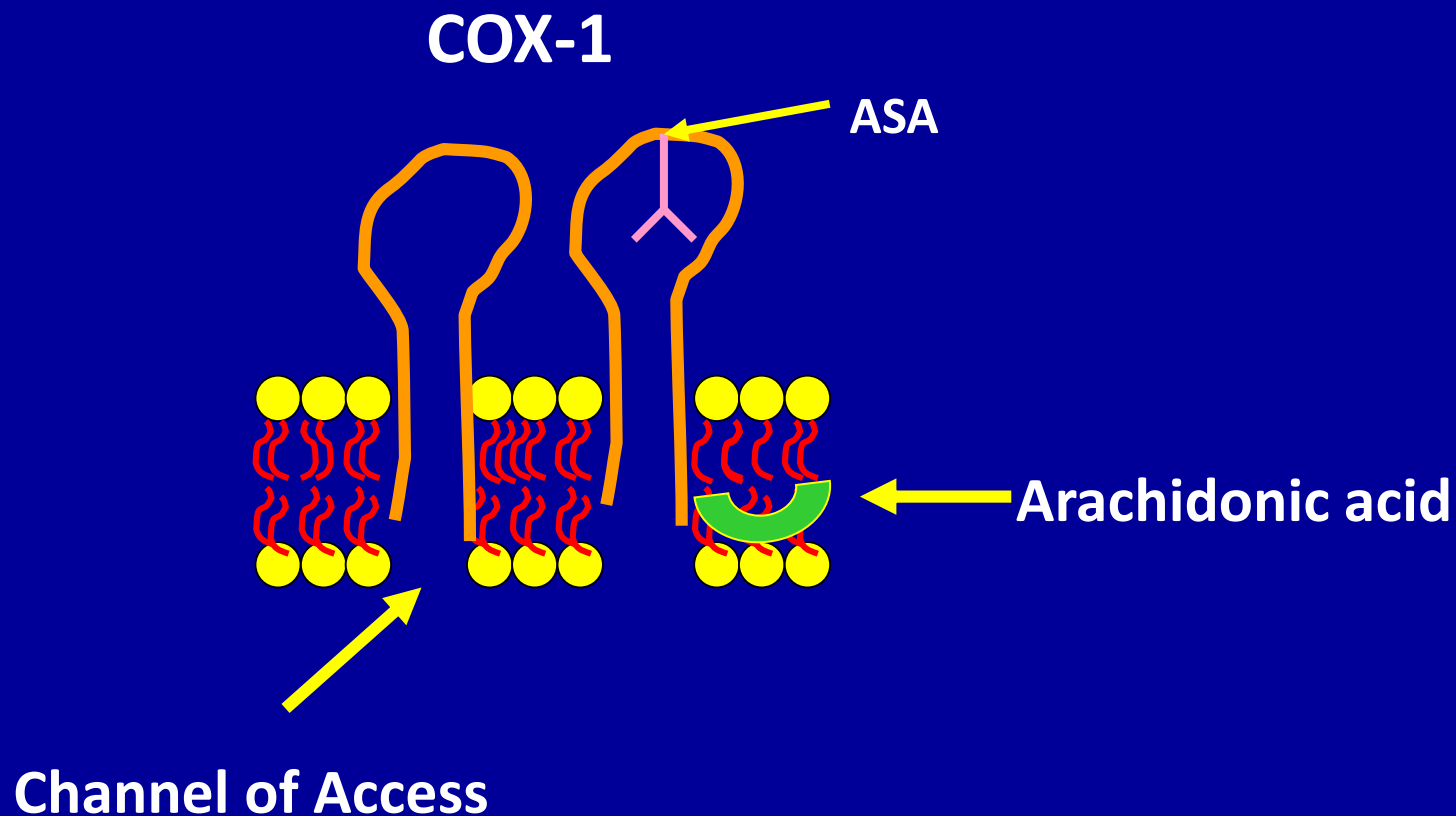
COX-1



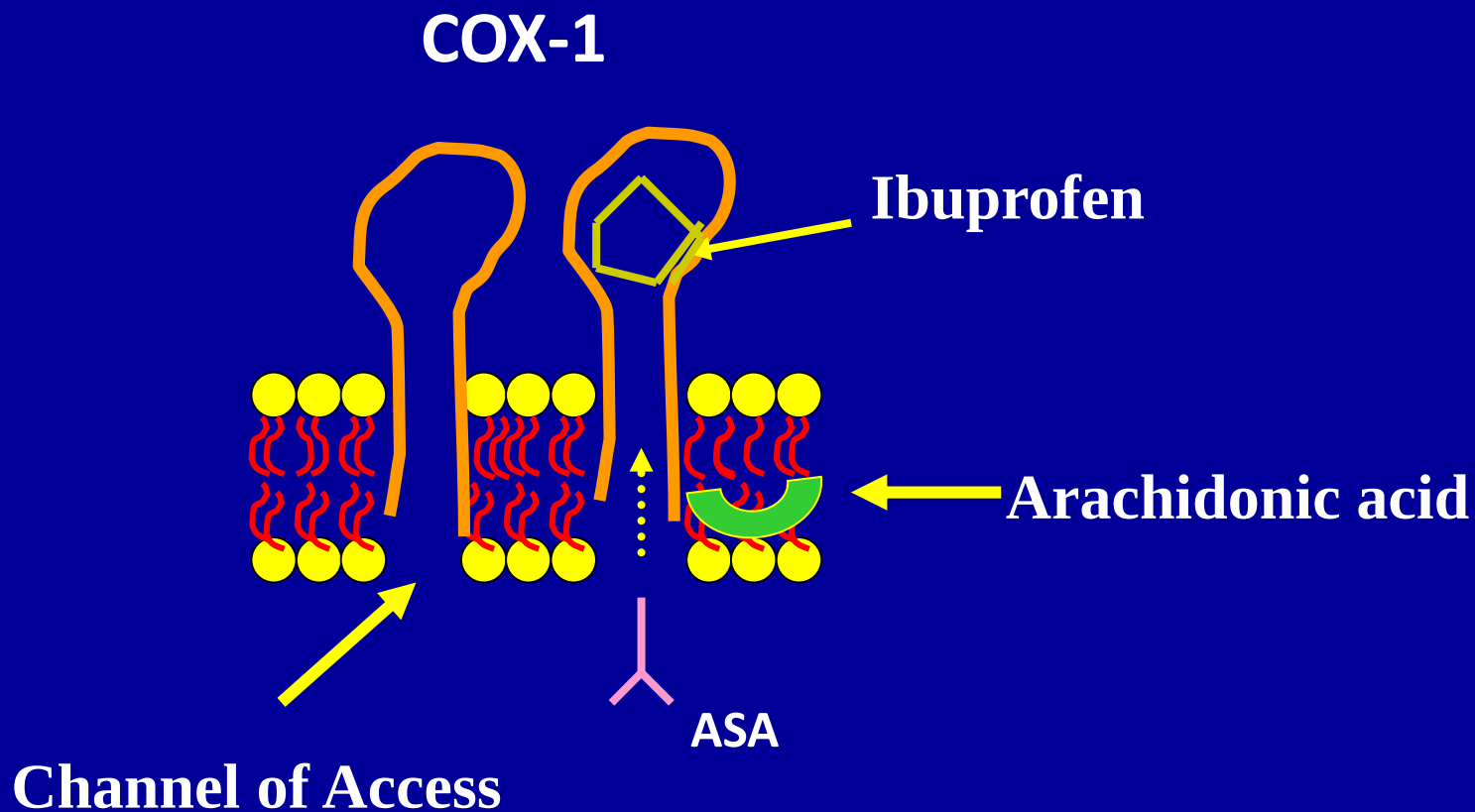
Arachidonic acid

Channel of Access

ASA + NSAIDs



ASA + NSAIDs





Cardiovascular



1397

- Vascular Events
- Heart Failure
- Closure of the Ductus Arteriosus



In Daily Practice

- No NSAID is safe.
- High-dose Diclofenac/ Ibuprofen ~ Coxibs
- Naproxen is the safest.

Adelowo et al, Lancet 2013

- In patients with CHF, celecoxib may be safer.

In Daily Practice

- Take aspirin dose ≥ 2 hr before NSAID dose.
- No NSAIDs within 3-6 mo of an acute cardiovascular event.
- Blood pressure Control
- No extended-release formulations

Preoperative Care

Preoperative Care

- Increase risk of bleeding

Preoperative Care

- Stop ASA 7-10 days

Preoperative Care

- Stop ASA 7-10 days
- NSAIDs 3-5 half-life
 - Ibuprofen, Diclofenac, Indomethacin 1day
 - Celecoxib, Naproxen 4 days
 - Piroxicam 7 days

Pregnancy

- With Caution in the 1th Trimester of Pregnancy

Flint et al, Rheumatology. 2016

- Probable Cryptorchidism in the 2the Trimester

Bloor et al, Anesth.Analg. 2013

- Don't use beyond 32 weeks

Flint et al, Rheumatology. 2016

Breastfeeding

- Safe

Drug Interactions

Drug Interactions

Drug	Effect
Anti-Hypertensive	Decreased
Anticoagulant	Increased
Methotrexate	Increased (Not Celecoxib)
Phenytoin	Decreased
Valproate	Increased
Digoxin	Increased

Glucocorticoids

Preoperative Care

Preoperative Care

- Adrenal Suppression
 - Even 5mg/day prednisolone

Kirwan, J. R. *et al.* (2006)

- Risk of Infection
 - Higher than other DMARDs

Smitten, A. L. *et al.* (2008)

Preoperative Care

Most patients receive high dose of Steroids

True or Not?

Preoperative Care

- Supraphysiologic doses are not usually necessary

Lloyd EL. (1981)

Glowniak *et al*, (1997)

Marik *et al*, (2008)

Zaghiyan *et al*, (2012)

Kelly *et al*. (2013)

Preoperative Care

- ACTH test is a reasonable approach

Preoperative Care

- ACTH test is a reasonable approach
- But, when cannot be obtained

Preoperative Care

Follow need-based approach

Coursin, D. B. *et al.* JAMA (2002)

Preoperative Care

- Minor
 - Inguinal hernia repair
 - Colonoscopy
 - Mild febrile illness
 - Mild–moderate
nausea/vomiting
 - Gastroenteritis

Preoperative Care

- **Minor**

- Inguinal hernia repair
- Colonoscopy
- Mild febrile illness
- Mild–moderate
nausea/vomiting
- Gastroenteritis

- 25 mg hydrocortisone

Or

- 5 mg methylprednisolone

IV on day of procedure
only

Preoperative Care

- Moderate
 - Open cholecystectomy
 - Hemicolectomy
 - Significant febrile illness
 - Pneumonia
 - Severe gastroenteritis

Preoperative Care

- **Moderate**
 - Open cholecystectomy
 - Hemicolectomy
 - Significant febrile illness
 - Pneumonia
 - Severe gastroenteritis
- 50–75 mg hydrocortisone
Or
- 10–15 mg methylprednisolone IV on day of procedure;
- taper quickly over 1–2 days to usual dose

Preoperative Care

- Severe
 - Major cardiothoracic surgery
 - Whipple procedure
 - Liver resection
 - Pancreatitis

Preoperative Care

- **Severe**
 - Major cardiothoracic surgery
 - Whipple procedure
 - Liver resection
 - Pancreatitis
- 100–150 mg hydrocortisone
Or
- 20–30 mg methylprednisolone IV on day of procedure
- taper quickly over 1–2 days to usual dose

Preoperative Care

- Critically ill
 - Sepsis-induced hypotension or shock

Preoperative Care

- Critically ill
 - Sepsis-induced hypotension or shock
- 50–100 mg hydrocortisone IV every 6–8 h
- Or
- 0.18 mg/kg/h as a continuous infusion plus 50 µg per day fludrocortisone until shock resolved
- may take several days to a week or more, then gradually taper, following vital signs and serum sodium

12th Annual Iranian Congress of Rheumatology