Cardiovascular Toxicity of Non-Cardiovascular Drugs

By:

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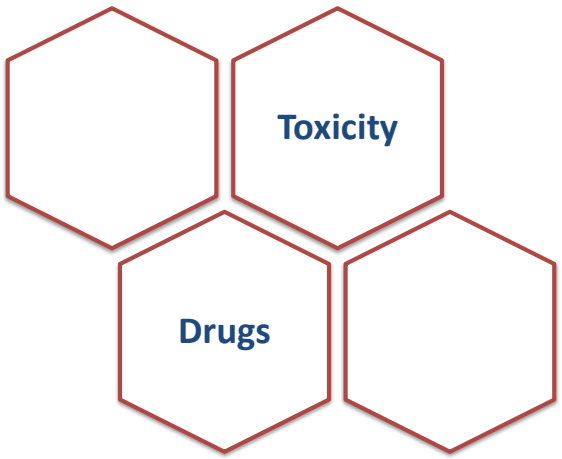

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Cardiovascular Toxicity

- ***Cardiotoxicity of drugs can include a wide array of disorders; which can include:***
  - **Myocardial dysfunction and Heart Failure**
  - **Vascular disorders;**
    - Thromboembolic disease [Coronary artery disease, PVD and Stroke]
    - Arterial Hypertension
    - Pulmonary Hypertension
  - **Arrhythmias**
  - **Valvular Disease**
  - **Other complications** (Eg; Pericardial disease)

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Cardiotoxic Drugs

- ***A wide array of non-cardiovascular medication can have cardiotoxicities.***
- ***Cardiotoxic medications can belong to varying classes; including:***
  - **Analgesics**
  - **Anesthesia medication**
  - **Antidiabetic medication**
  - **Medication for BPH**
  - **Anti-cancer**
  - **Anti-depressants**
  - **Anti-psychotics**
  - **And much more……**

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Today's Session, we will discuss…

- ***One of the most commonly used medications in the elderly (Probably with cardiovascular disease)***
- ***One of the most commonly prescribed medications globally.***
- ***In the United States:***
  - **Over 70,000,000 (70 Million) prescriptions annually**
  - **Over 30,000,000,000 (30 Billion) OTC medication sold annually**

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Today's Session, we will discuss…

Non-Steroidal Anti-Inflamatory Drugs (NSAIDs)

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Agenda

I. Pharmacology and Classification

II. Cardiovascular Toxicities:

– Thrombotic Complications and Myocardial dysfunction

A. Evidence

B. Drug interaction with Aspirin

C. Take Home Messages

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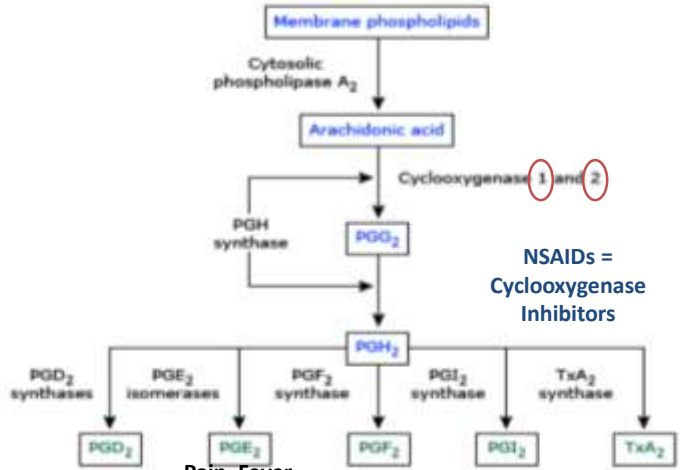
I. Pharmacology of NSAIDs



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I. Pharmacology of NSAIDs

Cyclooxygenases (COX)

COX-1

- Expressed in most tissues
- Described as a "housekeeping" enzyme, regulating normal cellular processes (such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and kidney function).

COX-2

- Mainly expressed in the brain, kidney, bone, and probably in the female reproductive system, but which is undetectable in most other tissues.
- Expression is increased during states of inflammation, or experimentally in response to mitogenic stimuli

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I. Pharmacology of NSAIDs

Cyclooxygenases (COX)

COX-1

- Major (COX) in Gastric and Duodenal Mucosa (Gastric protection)
- Platelets ONLY express (COX-1) to produce Thromboxane A2 (Promoting platelet aggregation)>> Prothrombotic activity

COX-2

- Present in endothelial cells to produce PGI2.
- PGI2 restrains the effect of Thromboxane A2 (Inhibiting platelet aggregation)>> Antithrombotic activity

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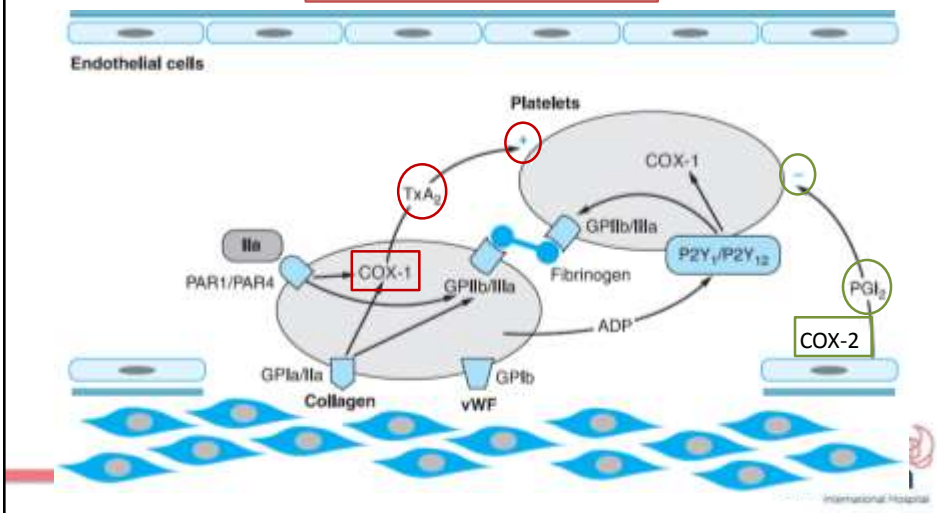
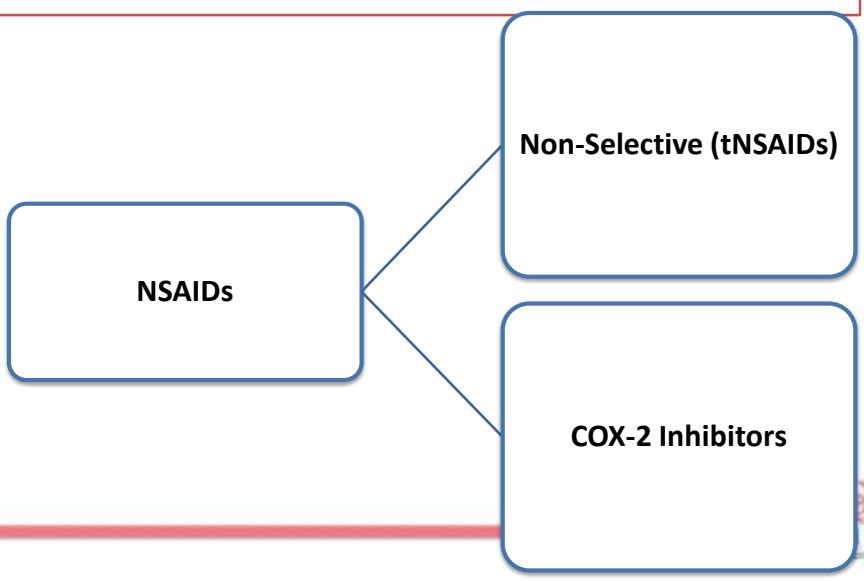
I. Pharmacology of NSAIDs

COX and Platelets

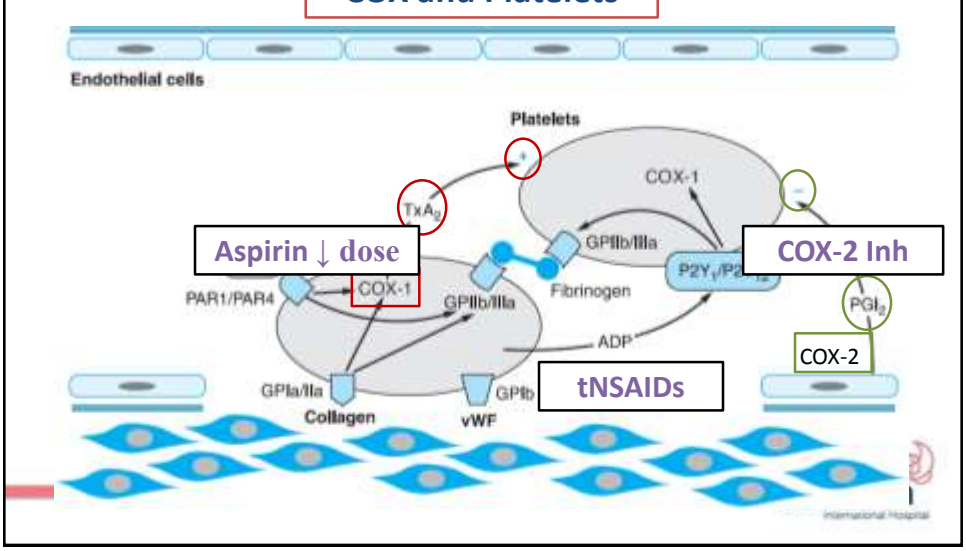


I. Pharmacology of NSAIDs

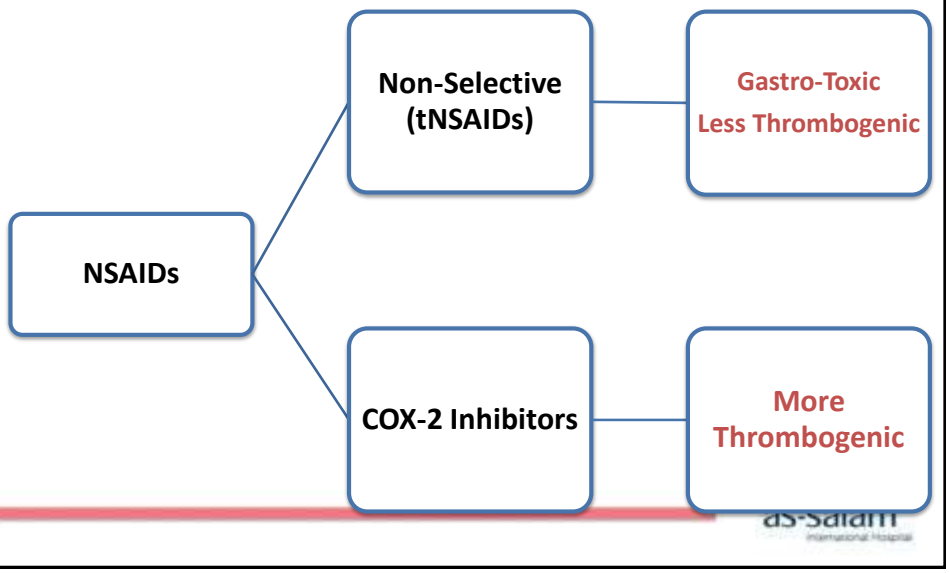


I. Pharmacology of NSAIDs

COX and Platelets



I. Pharmacology of NSAIDs



II. Thrombotic Complications and Myocardial Dysfunction

A. Evidence

2013 ESC guidelines

The Management of Stable Coronary Artery Disease

7.3 Other drugs

7.3.1 Analgesics

The use of selective cyclooxygenase-2 (COX-2) inhibitors and traditional non-selective non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with an increased risk for CV events in recent clinical trials in arthritis and cancer prevention and are not recommended.[361–363] In patients at increased CV risk in need of pain relief, it is therefore recommended to commence with acetaminophen or aspirin at the lowest efficacious dose, especially for short-term needs.

A. Evidence

2016 AHA Scientific Statement

Drugs That May Cause or Exacerbate Heart Failure

Table 1. Prescription Medications That May Cause or Exacerbate HF

Drug or Therapeutic Class	Association With HF		Magnitude of HF Induction or Precipitation	Level of Evidence for HF Induction or Precipitation	Possible Mechanism(s)	Onset
	Causes Direct Myocardial Toxicity	Exacerbates Underlying Myocardial Dysfunction				
Analgesics						
COX, nonselective inhibitors (NSAIDs)		x	Major	B	Prostaglandin inhibition leading to sodium and water retention, increased systemic vascular resistance, and blunted response to diuretics	Immediate
COX, selective inhibitors (COX-2 inhibitors)		x	Major	B		

A. Evidence

So…

Can't we find a way to use NSAIDs rationally in cardiovascular patients?

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A. Evidence

Let's take A Deeper Look into the evidence behind recommendations!

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A. Evidence

A Deeper Look

Retrospective Cohort JAMA, 2009

ORIGINAL INVESTIGATION

Increased Mortality and Cardiovascular Morbidity Associated With Use of Nonsteroidal Anti-inflammatory Drugs in Chronic Heart Failure

CNT Metaanalysis Lancet, 2013

Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials

PRECISION Double-Blinded RT NEJM, 2016

Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis

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A. Evidence

ORIGINAL INVESTIGATION

Increased Mortality and Cardiovascular Morbidity Associated With Use of Nonsteroidal Anti-inflammatory Drugs in Chronic Heart Failure

Type-Journal-Year	Retrospective Cohort-JAMA-2009
Population	107 092 patients surviving their first hospitalization because of HF between January 1, 1995, and December 31, 2004 and their subsequent use of NSAIDs
Comparators	Rofecoxib, Celecoxib, Ibuprofen, Diclofenac, Naproxen, and other NSAIDs
End Points	• Hazard Ratios for Death • Hospitalization Because of HF • Hospitalization Because of AMI

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A. Evidence

ORIGINAL INVESTIGATION

Increased Mortality and Cardiovascular Morbidity Associated With Use of Nonsteroidal Anti-inflammatory Drugs in Chronic Heart Failure

- ***Conclusion:***
  - Treatment with NSAIDs, **both** selective COX-2 inhibitors and nonselective NSAIDs, in patients with chronic HF is associated with **increased mortality and cardiovascular morbidity, with a dose-dependent response**.
  - ***Therefore, patients with HF should, if possible, avoid using any NSAIDs at any dosage for most NSAIDS and at high dosages for ibuprofen and naproxen.***

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A. Evidence

A Deeper Look

Table 3. Hazard Ratios for Death, and Hospitalization Because of HF or AMI

Drug	Death HR (95% CI)	Death P Value[a]	Hospitalization Because of HF HR (95% CI)	Hospitalization Because of HF P Value[a]	Hospitalization Because of AMI HR (95% CI)	Hospitalization Because of AMI P Value[a]
Rofecoxib						
Any use	1.70 (1.58-1.82)	<.001	1.40 (1.29-1.55)	<.001	1.30 (1.07-1.59)	.01
≤25 mg/d	1.42 (1.31-1.54)	<.001	1.33 (1.23-149)	<.001	1.26 (1.01-1.57)	.04
>25 mg/d	3.54 (3.12-4.02)	<.001	1.86 (1.46-2.35)	<.001	1.59 (0.97-2.61)	.07
Celecoxib						
Any use	1.75 (1.63-1.88)	<.001	1.24 (1.12-1.39)	<.001	1.38 (1.13-1.69)	.001
≤200 mg/d	1.34 (1.22-1.48)	<.001	1.24 (1.09-1.41)	.001	1.33 (1.05-1.69)	.02
>200 mg/d	2.72 (2.45-3.02)	<.001	1.26 (1.04-1.53)	.02	1.50 (1.08-2.10)	.02
Ibuprofen						
Any use	1.31 (1.25-1.37)	<.001	1.16 (1.10-1.23)	<.001	1.33 (1.19-1.50)	<.001
≤1200 mg/d	0.99 (0.94-1.04)	.65	1.16 (1.09-1.23)	<.001	1.31 (1.15-1.48)	<.001
>1200 mg/d	2.83 (2.64-3.02)	<.001	1.18 (1.04-1.33)	.01	1.47 (1.15-1.89)	.002
Diclofenac						
Any use	2.08 (1.95-2.21)	<.001	1.35 (1.24-1.48)	<.001	1.38 (1.12-1.64)	.002
≤100 mg/d	1.31 (1.20-1.42)	<.001	1.34 (1.21-1.48)	<.001	1.14 (0.91-1.43)	.28
>100 mg/d	5.54 (5.08-6.03)	<.001	1.42 (1.17-1.73)	.004	2.43 (1.74-3.40)	<.001
Naproxen						
Any use	1.22 (1.07-1.39)	.004	1.18 (1.00-1.40)	.05	1.52 (1.11-2.06)	.01
≤500 mg/d	0.88 (0.73-1.05)	.15	1.18 (0.97-1.44)	.10	1.47 (1.02-2.10)	.04
>500 mg/d	1.97 (1.64-2.36)	<.001	1.18 (0.88-1.57)	.27	1.60 (0.97-2.73)	.07
Other NSAID	1.28 (1.21-1.35)	<.001	1.27 (1.18-1.36)	<.001	1.32 (1.13-1.54)	.004

A. Evidence

ORIGINAL INVESTIGATION

Increased Mortality and Cardiovascular Morbidity Associated With Use of Nonsteroidal Anti-inflammatory Drugs in Chronic Heart Failure

- ***Is Naproxen Safer?***
  - Authors **DO NOT** state this conclusion
  - Authors recommend avoiding "high doses of naproxen and ibuprofen" in patients with heart failure

Results show uncertainty regarding Naproxen's association with mortality or hospitalization for HF or AMI

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A. Evidence

Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials

Type-Journal-Year	"Coxib, Traditional NSAID Trialist (CNT)" Meta-Analysis-Lancet-2013
Population	280 Randomized trials of NSAIDs versus placebo (124 513 participants) and 474 Randomized trials of one NSAID versus another NSAID (229 296 participants)
Comparators	Any Coxib (Celecoxib, Rofecoxib, Lumiracoxib) Individual tNSAIDs (Naproxen, Ibuprofen, Diclofenac)
Relevant End Points	• Major Vascular events (non-fatal myocardial infarction, non-fatal stroke, or death from a vascular Cause) • Major Coronary Events • Vascular Deaths • Hospitalization for Heart Failure

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A. Evidence

Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials

- ***Conclusion:***
  - Major **Cardiovascular events** increased by **Coxibs** and **Diclofenac** (Mainly due to inc. in coronary events)
  - Major **coronary** events only increased by **Ibuprofen**
  - **Vascular Deaths** increased by **Coxibs** or **Diclofenac**.
  - **Vascular Deaths** increased by **ibuprofen** (But **not statistically significant**)
  - **Heart Failure risk was doubled by ALL NSAIDS**

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A. Evidence

Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials

- ***Conclusion:***
  - Naproxen did NOT increase major cardiovascular events, major coronary events or vascular deaths

The vascular risks of high-dose diclofenac, and possibly ibuprofen, are comparable to coxibs, whereas high-dose naproxen is associated with less vascular risk than other NSAIDs.

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A. Evidence

Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials

- ***However:***
  - *Is it fair to compare individual tNSAIDs with ALL Coxibs and make a conclusion to Celecoxib only ;* Given that *Rofecoxib was withdrawn for proven cardiovascular toxicity???*
  - *Possibly Biased results*

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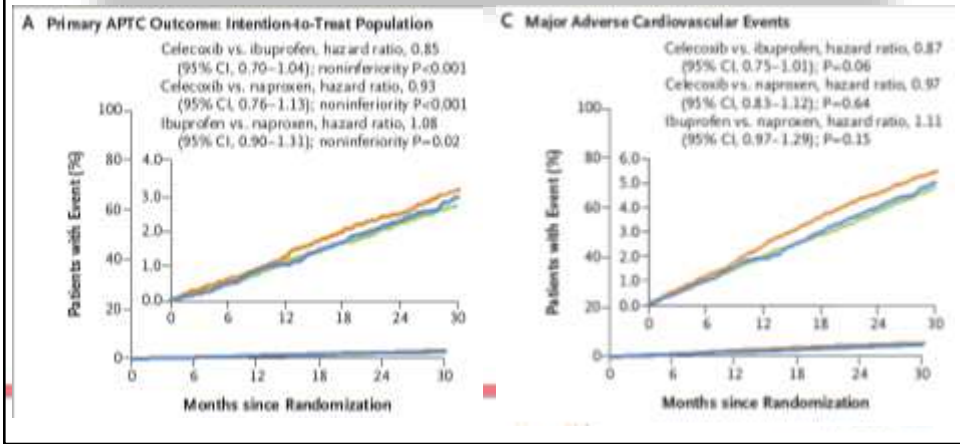
A. Evidence

Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis

Type-Journal-Year	"PRECISION Trial" Blinded Randomized Non-inferiority Trial-NEJM-2016
Population	**24,081 patients with a Primary diagnosis (osteoarthritis or rheumatoid arthritis) randomly assigned, in a 1:1:1 ratio**
Comparators	**Celecoxib** (100 mg twice a day) **Ibuprofen** (600 mg three times a day) **Naproxen** (375 mg twice a day)
Relevant End Points	• **HR of Antiplatelet Trialists Collaboration (APTC) criteria** (i.e., death from cardiovascular causes, including hemorrhagic death; nonfatal myocardial infarction; or nonfatal stroke). • **HR of Major Adverse Cardiovascular Events (MACE):** APTC plus coronary revascularization, hospitalization for unstable angina or transient ischemic attack

A. Evidence

Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis



A. Evidence

Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis

- ***Conclusion:***
  - **At moderate doses, celecoxib was found to be non-inferior to ibuprofen or naproxen with regard to cardiovascular safety.**

However, could the trial funding have influenced the results??? [Funded by Pfizer, the manufacturer of Celecoxib]

Possibly Biased Results

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A. Evidence

- ***To Sum things up:***
  - **All NSAIDs** (Including COX-2 selective inhibitors) **have potential for thrombotic complication, exacerbation of myocardial dysfunction or increase risk of vascular mortality**
  - **The risk is possibly dose related**
  - **COX-2 inhibitors may carry the greatest risk**
  - **Naproxen may carry the least risk**

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B. DDI with Aspirin

- ***Aspirin is the only tNSAID that binds IRREVERSIBLY on COX:***
  - Effect on Platelets' COX-1:
    - **Short Duration (Hours)**

    BUT

    - **Prolonged Antiplatelet effect (Days)**

B. DDI with Aspirin

- ***What will Happen, if another COX-1 inhibitor (tNSAIDs), competes with Aspirin to Binding with platelets COX-1 during this short duration??***
  - **Can also cause a transient increase in antiplatelet activity> Increase the risk of bleeding**
  - **Can diminish Antiplatelet effect of Aspirin > Increase the risk of cardiovascular thrombotic events**

B. DDI with Aspirin

	Ketorolac	Ibuprofen	Other tNSAIDs	Celecoxib
DDI	- Diminish Anti-Plt effect - Increase risk of bleeding	- Diminish Anti-Plt effect - Increase risk of bleeding - ↓ Ibuprofen serum conc	- Diminish Anti-Plt effect - Increase risk of bleeding - ↓ tNSAIDs serum conc	Increase risk of GI bleeding (However, less significant with "Low doses" of Aspirin)
Management	Contraindicated	Avoid regular frequent use of Ibuprofen with Aspirin Give Ibuprofen 30-120 mins after Aspirin, or at least 8 hrs before aspirin	Avoid regular frequent use of tNSAIDs with Aspirin Give tNSAIDs at least 2 hrs after Aspirin	Monitor closely for GI ulceration/ Bleeding

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C. Take Home Messages

We Should:

1. *Council our patients on the hazards of NSAIDs and always ask for detailed medication histories*
2. *Avoid use of NSAIDs in patients with/at risk of cardiovascular disease*
3. *Avoid use of NSAIDs in patients taking Aspirin*
4. *Never combine Aspirin with Ketorolac*
5. *Consider Acetaminophen as an alternative if possible*

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C. Take Home Messages

We Should:

6. *If necessary, Avoid regular/frequent use of NSAIDs and use them at the lowest effective doses*
7. *For CV patients who are NOT ON Aspirin, Consider Naproxen and Avoid Celecoxib*
8. *For CV patients ON Aspirin, consider Celecoxib or Naproxen*
9. *For patients taking tNSAIDs with Aspirin, consider administring the tNSAID dose 2 hours after Aspirin*
10. *Always monitor our patients for increased risk of bleeding*

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Questions?

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References

- [The PRECISION Trial]: Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med 2016
- Gislason GH, Rasmussen JN, Abildstrom SZ, et al. Increased mortality and cardiovascular morbidity associated with use of nonsteroidal anti-inflammatory drugs in chronic heart failure. Arch Intern Med 2009
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