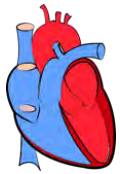
Academic Detailing Service

CAUTION!

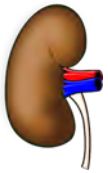
RISKS ASSOCIATED WITH ORAL NSAIDs

Cardiovascular (CV)

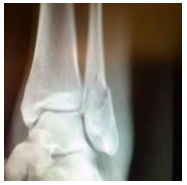


- Both non-selective NSAIDs and COX-2 inhibitors can significantly increase risk for *CV events (MI and stroke)* based on meta-analyses of RCTs.
  - Celecoxib, diclofenac and high-dose ibuprofen (2400mg/day) have increased vascular risk compared to other NSAIDs. Naproxen may have a lower risk for CV events.
  - NSAIDs can increase the risk of MI, even within the first week of use. Risk of MI does not decrease with time elapsed since MI.
- All NSAIDs increase the risk of *heart failure* exacerbations.
  - Individuals with pre-existing or severe uncontrolled heart failure are recommended to use alternative analgesics to NSAIDs.
- Based on their mechanism of action, NSAIDs can increase *blood pressure (BP)* levels and decrease the effectiveness of medications for hypertension.
  - Monitoring of BP is recommended if taking NSAIDs and antihypertensive drugs concomitantly.
- Concomitant use of ASA and NSAIDs may reduce the cardioprotective effects of ASA; a pharmacodynamic interaction.
  - Ibuprofen is recommended to be taken 30 minutes after or 8 hours before immediate-release ASA (81 mg; not enteric-coated).
  - Naproxen is recommended to be taken 2 hours after ASA.

Renal



- The risk of AKI and CKD development with NSAID use is unclear due to a lack of high-quality evidence. Lower doses may be safer than higher doses.
- In those with chronic kidney disease (*CKD*), observational data show a potential association of AKI and NSAID use.
- Risk factors increasing the likelihood of AKI with NSAID use include: CKD, severe hypercalcemia, nephrotic syndrome, cirrhosis and heart failure or volume depletion (from diuretic, vomiting or diarrhea).
- There is no evidence to suggest COX-2 inhibitors are safer than non-selective NSAIDs in AKI risk.
- The concomitant use of an ACE-I or ARB + diuretic + NSAID ("triple whammy") increased the relative risk of AKI by ≈ 30% in a large retrospective nested case-control cohort.
- NSAIDs require dosage adjustments for those with renal impairment and are contraindicated in those with severe renal impairment (CrCL <30 mL/min).



Gastrointestinal (GI)

- All NSAIDs can significantly increase the risk for GI adverse events; celecoxib has a lower risk compared to naproxen and ibuprofen.
- Risks for NSAID related GI adverse events include: Age > 65 years, high dose NSAID, history of peptic ulcer disease and concomitant ASA (including low dose), corticosteroid or anticoagulant use.
- Risk increases with higher doses and longer duration of therapy. GI complications may occur early and an increased risk persists over time. Consider gastroprotection in at-risk patients when starting regularly scheduled NSAID therapy.
- Risk reduction and gastroprotective strategies for higher risk patients:
  - Standard once daily dose proton pump inhibitor (PPI) is considered the most effective gastroprotective strategy. Alternatives include misoprostol 200mcg qid or double dose H2RA (e.g., ranitidine 300 mg bid).
  - All PPIs appear comparable with respect to reducing risk of ulcer complications.
  - Non-selective NSAID + PPI is considered to have a similar rate of GI complication as a COX-2 inhibitor alone.
  - Indomethacin, piroxicam and ketorolac have higher GI adverse effects risk; can occur within the first week of use.

Fracture Healing

- Overall, the evidence surrounding NSAIDs and fracture healing impairment is unclear. There is no high-quality robust evidence on this topic.
- RCTs are small and considered low-quality with risks of bias.
- The majority of other clinical studies are retrospective with many potential biases.
- Systematic reviews and meta-analyses include both RCTs and retrospective studies with different NSAIDs used. Some studies do not provide details on NSAID dose or duration used.
- Based on the current available evidence from human clinical trials, short term, low dose NSAID use may be safe for pain relief in fracture care.

Laminate references are available in the Academic Detailing handout:
https://medicine.dal.ca/departments/core-units/cpd/programs/academic-detailing-service/AC-Service-Resources.html

Academic Detailing Service

CARDIOVASCULAR AND GASTROINTESTINAL RISK ASSESSMENT TOOLS for NSAID use

CARDIOVASCULAR (CV) RISK ASSESSMENT

STEP 1 Assess CV risk factors

- History of CV event (established CV disease)
- Diabetes Mellitus
- Hypertension
- Hyperlipidemia (total cholesterol, HDL-C)
- Obesity
- Smoking
- Age (especially ≥ 70 years)

Canadian Cardiovascular Society Framingham Risk calculator (copy and paste in browser):
https://ccs.ca/images/Guidelines/Tools_and_Calculators_En/FRS_eng_2017_fnl1.pdf
https://ccs.ca/calculators-and-forms/

STEP 2 Determine if NSAID therapy is appropriate

Consider:

- If CV risk is high, the risk of taking any NSAID may outweigh the benefit.
- Contraindications and precautions for all NSAIDs (non-selective and COX-2 inhibitors):
  - Contraindicated in those with severe uncontrolled heart failure.
  - Associated with an increased risk of myocardial infarction and stroke (Increased risk of MI can occur in the first week of therapy).
  - Increase blood pressure and decrease the effectiveness of medications for hypertension.
  - Contraindicated in patients with reduced kidney function (CrCL < 30 ml/min).
  - May reduce the cardioprotective efficacy of low dose ASA.
- Gastroprotection - especially if taking concomitant ASA.
  - Ibuprofen to be taken at least 30 minutes post or 8 hours before immediate release ASA
  - Naproxen is recommended to be taken 2 hours post ASA.

STEP 3 Choose NSAID with lower CV Risk

NSAIDs with Lower CV risk

- Naproxen 500 mg bid
- Low dose ibuprofen (< 2400 mg/day)

NSAIDs with Higher CV risk

- NSAIDs with higher COX-2 selectivity may be associated with higher CV risk (e.g., celecoxib, meloxicam) and are generally avoided in patients who have/are at high risk of CV disease.
- Diclofenac increases the risk of stroke.

GASTROINTESTINAL (GI) RISK ASSESSMENT

STEP 1 Assess GI risk factors

- Age > 65 years
- High dose NSAID
- History of peptic ulcer disease
- Concomitant ASA (including low dose), corticosteroid or anticoagulant use

High GI risk	*Medium GI Risk*	*Low GI Risk*
• **Previous history of peptic ulcer disease, especially if recent, or a complicated ulcer** • **> 2 risk factors**	**1-2 risk factors**	**No risk factors**

H pylori infection is an independent and additive risk factor if considering long term NSAID therapy

STEP 2 Determine if NSAID therapy is appropriate

Consider:

- If the GI risk is high, the risk of taking any NSAID may outweigh the benefit.
- Dose and duration:
  - Risk increases with higher doses and longer duration of therapy.
  - GI complications may occur early and an increased risk persists over time.
  - If NSAID therapy is an option are there differences between NSAIDS?
    - COX-2 inhibitors modestly reduce GI complications vs. non-selective NSAIDs.
    - Indomethacin, piroxicam and ketorolac are considered higher risk for GI events.
- Is gastroprotection required?
  - Standard once daily dose PPI is considered the most effective gastroprotective strategy.
  - Alternatives include misoprostol 200 mcg qid or double dose H2RA (e.g., ranitidine 300 mg bid).

STEP 3 Choose NSAID with lower GI risk +/- appropriate gastroprotective strategy

High GI risk	*Medium GI Risk*	*Low GI Risk*
Avoid NSAIDs if possible. **COX-2 inhibitor + PPI** ***unless also at high cardiovascular risk.***	**COX-2 inhibitor ± PPI** ***OR*** **Low dose NSAID ± PPI** ***Non-selective NSAID + PPI ≈ risk as COX-2 inhibitor.***	**Low dose NSAID and shortest duration possible.** **Gastroprotection is not required.**

OPTIONS FOR LOWERING NSAID CV and GI RISKS

Cardiovascular Risk	Gastrointestinal Risk: Low GI Risk	Medium GI Risk	High GI Risk
Low CV risk	**Any NSAID alone (Lowest dose/shortest duration)**	**COX-2 inhibitor ± PPI *OR* Low dose NSAID + PPI**	**Avoid all NSAIDS/use alternative therapy *OR* COX-2 inhibitor + PPI**
High CV risk	**Naproxen 500 mg bid *OR* Low dose ibuprofen (< 2400 mg/day) (consider adding a PPI if also taking ASA)**	**Naproxen 500 mg bid + PPI *OR* Low dose ibuprofen (< 2400 mg/day) + PPI**	**Avoid all NSAIDS/use alternative therapy**

Use the lowest effective dose of NSAID for the shortest period of time

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