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Reviewed: January 28, 2018
Evidence Updated: 2 new large RCTs
Bottom Line: Small change
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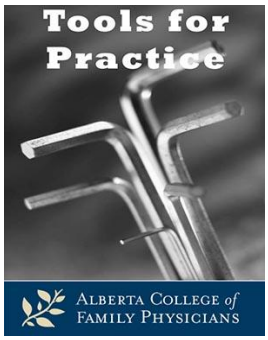

NSAIDs and Cardiovascular Safety: The truth makes my heart hurt

Clinical Question: Do different non-steroidal anti-inflammatory drugs (NSAIDs) have different cardiovascular risks?

Bottom Line: COX-2 inhibitors and traditional NSAIDs, except naproxen, may increase the risk of major vascular events and death. When prescribing NSAIDs, patients' gastrointestinal (GI) and cardiovascular (CV) risk should be assessed, with naproxen or low-dose ibuprofen possibly preferred for patients at risk of CV disease.

Evidence:

- Meta-analysis of 754 randomized controlled trials (RCTs) with ~350,000 patients:[1]
  - Mixed population, primarily arthritis, at low-moderate CV risk (i.e. CV event rate ~1% per year).
  - COX-2 inhibitors, compared to placebo, increased:
    - All-cause mortality, relative risk (RR) 1.22 (95% Confidence Interval 1.04–1.44).
    - Major CV events, RR 1.37 (1.14–1.66).
  - Diclofenac (150 mg/day): Similar risks to COX-2s for mortality [RR 1.02 (0.84–1.24)] and CV events [RR 0.97 (0.84–1.12)].
    - Indirectly, diclofenac significantly increases CV events [RR 1.41 (1.12–1.78)] but not mortality [RR 1.20 (0.94–1.54)] compared to placebo.
  - Naproxen (1,000 mg/day) has less CV events and mortality than COX-2 inhibitors and may be similar to placebo.
  - RR similar between patients with or without prior CV disease.
- Two large RCTs showed similar risk of CV events between celecoxib and NSAIDs:
  - 7,297 patients with arthritis with no prior CV disease followed for three years:[2] 3.4% in both groups.
  - 24,081 patients with arthritis with low-moderate CV risk followed for 2.8 years:[3] Celecoxib 2.3%, ibuprofen 2.7%, naproxen 2.5%.
  - However, several limitations challenge "non-inferiority" of celecoxib: Wide non-inferiority margin (up to 40% higher CV risk),[2,3] different conclusion based on analysis used,[2] enrolled a lower-risk population than planned,[2,3] comparison of

non-equipotent doses with lower efficacy with celecoxib,[2,3] high discontinuation and loss-to-follow-up,[3] and others.[4]
- Meta-analysis of observational trials:[5]
  - All COX-2s and NSAIDs, except naproxen and low-dose ibuprofen (≤1,200 mg/day), increase CV risk.
  - Risk increases with increasing NSAID dose.

Context:
- In Canada, naproxen (28%), celecoxib (21%), and diclofenac (17%) account for the majority of NSAIDs prescribed.[6]
- The magnitude of the CV risk with high-risk NSAIDs is similar to the magnitude of the CV benefit with statin therapy. Choosing high-risk NSAIDs (taken daily) can cause one additional CV event over five years in:[1]
  - ~100 low-risk patients (baseline 5% ten-year CV risk).
  - ~25 high-risk patients (baseline 20% ten-year CV risk).
- Generally, NSAIDs with relatively lower CV risks (naproxen) have relatively higher GI complication risks (ulcers and bleeds) and vice versa (coxibs).[7]
  - Adding a proton pump inhibitor to a non-selective NSAID results in similar GI complication risks as COX-2s.[8]
- All NSAIDs increase risk of heart failure.[1]

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