Cardiovascular safety of NSAIDs

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Clinical question

Do different nonsteroidal anti-inflammatory drugs (NSAIDs) have different cardiovascular (CV) risks?

Bottom line

Cyclooxygenase-2 (COX-2) inhibitors and traditional NSAIDs except naproxen increase the risk of serious CV events and death. When prescribing NSAIDs, patients' gastrointestinal (GI) and CV risks should be assessed, with naproxen or low-dose ibuprofen preferentially chosen for patients at risk of CV disease.

Evidence

- Meta-analysis of 754 RCTs (about 350 000 patients)[1]:
  - -Mixed population, primarily patients with arthritis at low to moderate CV risk (ie, CV event rate about 1% per year).
  - -Use of COX-2 inhibitors compared with placebo increased
    - —all-cause mortality, rate ratio (RR) = 1.22 (95% CI 1.04 to 1.44); and
    - —serious CV events, RR = 1.37 (95% CI 1.14 to 1.66).
  - -Diclofenac (150 mg daily): similar risks to COX-2 inhibitors for mortality (RR = 1.02 [95% CI 0.84 to 1.24]) and CV events (RR = 0.97 [95% CI 0.84 to 1.12]).
    - —Indirectly, diclofenac significantly increases CV events (RR = 1.41 [95% CI 1.12 to 1.78; *P* = .0036]) but not mortality (RR = 1.20 [95% CI 0.94 to 1.54]) compared with placebo.
  - -Naproxen (1000 mg daily) is associated with fewer CV events and lower mortality than COX-2 inhibitors and might be similar to placebo.
  - -Relative risk similar between patients with and without existing CV disease.
- Meta-analysis of observational trials[2]:
  - -All COX-2 inhibitors and NSAIDs except naproxen and low-dose ibuprofen (≤ 1200 mg daily) increase CV risk.
  - -Risk increases with increasing NSAID dose.
- Results are consistent with previous meta-analysis.[3]

Context

- In Canada, naproxen (28%), celecoxib (21%), and diclofenac (17%) account for most of the NSAIDs prescribed.[4]
- The magnitude of CV risk with high-risk NSAIDs is similar to the magnitude of the CV benefit with statin therapy. Taking high-risk NSAIDs daily can cause 1 additional CV event in 5 years in[1]
  - -about 100 low-risk patients (baseline 5% 10-year CV risk); and
  - -about 25 high-risk patients (baseline 20% 10-year CV risk).
- Generally, NSAIDs with low CV risks (naproxen) have high GI risks (ulcers and bleeding) and vice versa.[5]
  - -Adding a proton pump inhibitor to a non-selective NSAID has similar GI complication risks to a COX-2 inhibitor.[6]
- All NSAIDs increase the risk of heart failure.[1]

Implementation

Long-term CV and GI risks of NSAIDs drive the need for safer options. In patients with hand or knee osteoarthritis in whom acetaminophen results in suboptimal pain relief,[7] topical NSAIDs are an option. Compared with placebo, more patients using topical diclofenac achieved a 50% reduction in pain (number needed to treat 5 to 10).[8] Topical diclofenac also had similar pain reduction as oral NSAIDs but fewer GI side effects (RR = 0.66 [95% CI 0.56 to 0.77]). With negligible systemic absorption,[9] topical NSAIDs are expected to have minimal CV effects versus oral agents, although actual clinical evidence is limited.[8,10] Topical NSAIDs should be considered before oral NSAIDs in patients with hand or knee osteoarthritis who have the manual dexterity to apply these products.

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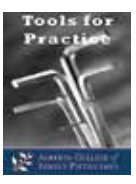

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