

Cardiovascular safety of non-steroidal anti-inflammatory drugs: Network meta-analysis

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FROM ABSTRACT

Objective : To analyse the available evidence on cardiovascular safety of non-steroidal anti-inflammatory drugs.

Design: Network meta-analysis. "Network meta-analysis allows a unified, coherent analysis of all randomised controlled trials that compare non-steroidal anti-inflammatory drugs head to head or with placebo while fully respecting randomisation." "We analysed the cardiovascular safety of non-steroidal anti-inflammatory drugs by integrating all available direct and indirect evidence in network meta-analyses."

Data sources: Bibliographic databases, conference proceedings, study registers, the Food and Drug Administration website, reference lists of relevant articles, and reports citing relevant articles through the Science Citation Index.

Study selection: All large scale randomised controlled trials comparing any non-steroidal anti-inflammatory drug with other non-steroidal anti-inflammatory drugs or placebo.

Data extraction:

The primary outcome was myocardial infarction.

Secondary outcomes included stroke, death from cardiovascular disease, and death from any cause.

Data synthesis: 31 trials in 116,429 patients with more than 115,000 patient years of follow-up were included.

Patients were allocated to naproxen [Aleve], ibuprofen [Motrin, Advil], diclofenac [Voltaren], celecoxib [Celebrex], etoricoxib [Arcoxia], rofecoxib [Vioxx], lumiracoxib [Prexige], or placebo.

Compared with placebo, rofecoxib [Vioxx] was associated with the highest risk of myocardial infarction (increased risk by 112%), followed by lumiracoxib [Prexige] (increased risk by 100%).

Ibuprofen was associated with the highest risk of stroke (increase risk by 236%), followed by diclofenac [Voltaren] (increased risk by 186%).

Etoricoxib [Arcoxia] (increased risk by 307%) and diclofenac [Voltaren] (increased risk by 298%) were associated with the highest risk of cardiovascular death.

Conclusions

Little evidence exists to suggest that any of the investigated drugs are safe in cardiovascular terms.

Cardiovascular risk needs to be taken into account when prescribing any non-steroidal anti-inflammatory drug.

KEY POINTS FROM THIS STUDY:

- 1) This study is unique. It is the largest network meta-analysis looking at all randomized controlled trials that assess the risk of myocardial infarction, stroke, death from cardiovascular disease, and death from any cause, as a consequence of taking non-steroidal anti-inflammatory drugs (NSAIDs).
- 2) "Non-steroidal anti-inflammatory drugs (NSAIDs) have been the cornerstone of pain management in patients with osteoarthritis and other painful conditions."
- 3) "In the United States an estimated 5% of all visits to a doctor are related to prescriptions of non-steroidal anti-inflammatory drugs and they are among the most commonly used drugs."

Increased Risk Compared to Placebo

Drug	Myocardial Infarction	Stroke	Cardiovascular Death	Death From Any Cause
Naproxen [Aleve]		76%		
Ibuprofen [Motrin, Advil]	61%	236%	139%	77%
Diclofenac [Voltaren]		186%	298%	131%
Celecoxib [Celebrex]	35%		107%	50%
Etoricoxib [Arcoxia]		167%	307%	129%
Rofecoxib [Vioxx]	112%		58%	56%
Lumiracoxib [Prexige]	100%	181%	89%	75%

4) **Cardiovascular death**

A)) The analysis showed that cardiovascular death accounted for 46% of all deaths in those evaluated in this study.

B)) "All drugs except naproxen showed some evidence for an increased risk of cardiovascular death compared with placebo."

5) **Death from any cause**

A)) "All the drugs seemed to be associated with increased risks of death from any cause compared with placebo."

B)) "All drugs seemed to be associated with increased risks of the composite of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death compared with placebo."

6) **Discussion**

A)) "Non-steroidal anti-inflammatory drugs are mainly used for symptomatic treatment of musculoskeletal conditions. Clearly, as for any symptomatic treatment, doing more harm than good with this class of drugs should be avoided."

B)) "Our study confirms previous notions of regulatory bodies, mainly based on observational evidence, that all non-steroidal anti-inflammatory drugs are associated with an increased risk of cardiovascular adverse effects."

C)) "Our results are based on randomised evidence and we therefore believe that our study provides the best available evidence on the safety of this class of drugs."

D)) "Naproxen seems to be the safest analgesic for patients with osteoarthritis in cardiovascular terms but this advantage has to be weighed against gastrointestinal toxicity and the need for concomitant prescription of a proton pump inhibitor in many patients."

E)) Paracetamol [acetaminophen] results in only a small reduction in pain and is associated with clinically relevant hepatotoxicity, even in dosages recommended for musculoskeletal pain.

F)) The analgesic effects of opioids are better than acetaminophen, "but outweighed by large increases in the risk of adverse events."

G)) "In conclusion, the options for the treatment of chronic musculoskeletal pain are limited and patients and clinicians need to be aware that cardiovascular risk needs to be taken into account when prescribing."

H)) In 2004, Vioxx, a COX 2 selective inhibitor, was withdrawn from the market because it increased the risk of cardiovascular events.

Cardiovascular safety of NSAIDs
Editorial
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SOME POINTS FROM THIS EDITORIAL:

- 1) The cardiovascular risks from NSAIDs should prompt evaluation of a broader range of alternatives.
- 2) Millions of patients with chronic musculoskeletal symptoms are long-term users of non-steroidal anti-inflammatory drugs (NSAIDs). Unfortunately, these drugs have common and potentially severe adverse effects, including renal impairment, gastrointestinal complications, and cardiotoxicity.
- 3) The cardiotoxicity from NSAIDs is particularly worrying because many patients with musculoskeletal disease also have cardiovascular disease.
- 4) "All cyclo-oxygenase-2 [COX-2] inhibitors studied in large placebo controlled trials have been found to confer an increased risk of serious cardiovascular disease."
- 5) What does this all mean when prescribing NSAIDs for patients at high risk of cardiovascular disease? Current data suggest that selective cyclo-oxygenase-2 inhibitors, particularly in higher doses, should be avoided.

COMMENTS FROM DAN MURPHY:

Apparently all pain drugs have serious side effects. The drugs include NSAIDs, acetaminophen, and opiates. The side effects I have reviewed in studies include gastrointestinal bleeding, kidney disease, liver disease, heart attack, stroke, increase in all cause mortality, dementia, Alzheimer's dementia, hearing loss, and erectile dysfunction.

As noted above, this wake-up information "should prompt evaluation of a broader range of alternatives." A list of such non-toxic alternatives for pain management was presented by Dr. Joseph Maroon, the neurosurgeon for the Pittsburgh Steelers, in the journal *Surgical Neurology International*, December 2010. I reviewed Dr. Maroon's article, it's Article Review #8-12.

As chiropractors, we should recall that in 2003, *Spine* published a study comparing chiropractic adjustments to the NSAIDs Celebrex and Vioxx in patients with chronic neck and back pain. Chiropractic was better then 5 times more effective than these drugs, caused no side effects, and had a stable therapeutic benefit a year later (Article Reviews 12-03 and 34-04).