Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies

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CRD summary
The authors' reasonably cautious conclusion that naproxen and ibuprofen have the most favourable cardiovascular risk profiles is likely to be reliable, but should be weighted against other risks when making clinical decisions.

Authors' objectives
To assess comparative estimates of risk for individual non-steroidal anti-inflammatory drugs (NSAIDs) and to investigate effects of non-prescription use through examination of risk at low-doses, over short time periods and in low risk populations. This is an update of a previous review (see Other Publications of Related Interest).

Searching
PubMed, EMBASE, The Cochrane Library, Google Scholar, epidemiological research websites and abstracts of scientific meetings were searched from January 1985 to end of November 2010. Reference lists of relevant studies were also checked. Searches using authors names known to have conducted relevant research in the area were undertaken. Search terms were reported. There were no language restrictions.

Study selection
Eligible for inclusion were non-randomised controlled studies that reported on cardiovascular risk associated with the current use of an individual NSAID (including selective coxibs, Cox-2 inhibitors), compared to non-use or remote use as the reference exposure. Trials had to be population-based observational studies. Studies of paediatric populations, patients with cancer, studies of NSAID use not current at time of cardiovascular event and channelling/usage pattern studies were excluded.

Most studies assessed both NSAIDs and coxibs, but some studies assessed only NSAIDs or only coxibs. Included studies were published from 1987 up to 2007 so included the now withdrawn NSAIDs rofecoxib and valdecoxib. Populations varied, and included healthy, community and hospitalised participants. The length of the observational period varied across studies, ranging from 10 months to nine years. Where reported, mean age ranged from 62 years to 80 years, percentage of male participants ranged from 15% to 97%, percentage of smokers ranged from 25% and 33% and percentage of diabetics ranged from 4% to 31%. The most commonly reported outcome was acute myocardial infarction, but others reported coronary heart disease related death, a composite of myocardial infarction and coronary heart disease death, or stroke.

Study selection was performed by more than one reviewer, but it was not clear whether this was carried out independently.

Assessment of study quality
Study quality was assessed using the Newcastle-Ottawa Scale; the maximum score for case control studies was 9, and for cohort studies the maximum score was 10.

Quality of included trials was assessed by two reviewers; any disagreements were resolved by consensus.

Data extraction
Adjusted risk estimates for individual drugs and doses and 95% confidence intervals (CIs) were extracted. Where reported, risk estimates by population (high or low background risk of cardiovascular events) and duration of exposure were also extracted. Authors were contacted where additional information was required.

Two reviewers extracted data and any disagreements were resolved by discussion.

Methods of synthesis
Studies were pooled using a random-effects model and summary odds ratios (ORs), risk ratios (RRs) or hazard ratios (HRs) were calculated. Statistical heterogeneity was assessed using the Cochran Q and I². Paired risk ratios with high and low doses of drugs and in high and low risk populations were also compared. A series of pair-wise comparisons of individual drugs that had been included in the same studies were carried out, as direct comparisons were potentially confounded at study level. The authors calculated 99% rather than 95% confidence intervals around the pooled ratio of relative risk (RRR) values, and the threshold p-value was based on the Bonferroni adjustment for multiple comparisons. Sensitivity analyses were performed using a method proposed by Schneerweiss (2006); this was limited to the pair-wise comparisons of the drugs.

Results of the review
Fifty-one studies (of 43 unique data sets) were included in the review; 30 case-control studies (26 unique data sets; 184,946 cases and 1,18,6354 controls) and 21 cohort studies (17 unique data sets; 2,711,084 users and 2,366,480 non-users). With regard to the validity assessment, fully-reported case-control studies scores ranged from 7 to 8 out of a possible 9 points, and cohort studies scores ranged from 7 to 8 out of a possible 10 points.

A significantly greater risk of a cardiovascular event compared to control was found for naproxen (OR 1.09, 95% CI 1.02 to 1.16; \(I^2=71\% \); 41 studies), celecoxib (OR 1.17, 95% CI 1.08 to 1.27; \(I^2=84\% \); 35 studies), ibuprofen (OR 1.18, 95% CI 1.11 to 1.25; \(I^2=83\% \); 38 studies), meloxicam (OR 1.20, 95% CI 1.07 to 1.33; \(I^2=0\% \); seven studies), indomethacin (OR 1.30, 95% CI 1.19 to 1.41; \(I^2=33\% \); 14 studies), diclofenac (OR 1.40, 95% CI 1.27 to 1.55; \(I^2=87\% \); 29 studies), rofecoxib (OR 1.45, 95% CI 1.33 to 1.59; \(I^2=84\% \); 34 studies), etodolac (OR 1.55, 95% CI 1.45 to 2.88; \(I^2=0\% \); four studies). No significant between group differences were found for piroxicam and valdecoxib.

Dose response relationships in the most widely used NSAIDs demonstrated no significant difference in risk of cardiovascular disease for low daily dose ibuprofen, and both low and high dose naproxen when compared with control. Risk of cardiovascular disease was significantly elevated with low doses of rofecoxib, celecoxib and diclofenac, and increased with higher daily doses. No significant difference between risk ratio estimates for risk of cardiovascular disease was found between low and high risk populations for rofecoxib, celecoxib, ibuprofen, naproxen and diclofenac.

In the most widely used NSAIDs, pair-wise comparisons demonstrated that etoricoxib had a significantly higher relative risk than ibuprofen or naproxen, etodolac was not significantly different from diclofenac, naproxen and ibuprofen. Naproxen had a small but significant advantage over ibuprofen. Diclofenac was found to have a similar risk to rofecoxib (but significantly higher risk than celecoxib, naproxen or ibuprofen), and indomethacin had a significantly higher increase (23%) in risk than naproxen.

Results on less widely used drugs were also reported, as were results from sensitivity analyses.

Authors’ conclusions
Results suggested that among widely used NSAIDs, naproxen and low dose ibuprofen had the most favourable cardiovascular risk profiles. Diclofenac in low doses elevated this risk. Pair-wise comparisons, although based on limited data, suggested that eritoricoxib has a significantly higher risk of cardiovascular disease than naproxen or ibuprofen.

CRD commentary
The review was supported by defined inclusion and exclusion criteria, and several sources were searched without language restriction for relevant studies. More than one reviewer was involved in the study selection, data extraction and quality assessment, but it was not clear whether this was performed independently in the selection of studies. The quality of the included studies was assessed with a standardised tool but individual results were not presented in the paper. Patient characteristics were available in an online supplement. The authors reported odds ratios as risk ratios in the text. This could have been problematic where event rates were high as the different measures may lead to over or under-estimation of the treatment effect.

Significant statistical heterogeneity was found in many of the analyses, which suggested that pooling was not appropriate. However, investigation of potential sources of heterogeneity was undertaken. The authors highlighted a number of limitations, including that the evidence was based on observational studies. It should also be noted that data for non-prescription drug use came solely from prescription drug administration databases and might not be an accurate
reflection of use. All direct comparisons were versus placebo, and all NSAIDs considered demonstrated significantly higher cardiovascular risk. While the authors are reasonably cautious in their conclusion that naproxen and ibuprofen are the least likely to increase risk, their implications for practice should be taken into consideration as they reflect the risks more accurately.

No comparison between the NSAIDs least likely to increase risk (naproxen and ibuprofen) with rofecoxib was made.

**Implications of the review for practice and research**

**Practice:** The authors indicate that naproxen and low-dose ibuprofen had the most favourable cardiovascular risk profiles, but these should be weighted against the drugs gastrointestinal risks, and avoidance of antagonism of aspirin’s beneficial effect with ibuprofen, when making clinical decisions. Data for etoricoxib was limited but raised serious concerns about its safety, and results supported calls for regulatory action with regard to diclofenac. Labelling warnings (in the case of ibuprofen) should be strengthened to stop patients at high background risk of cardiovascular disease exceeding the maximum dose for non-prescription use. The authors also state that the risk of cardiovascular disease with indomethacin, an older and rather toxic drug, cast doubt on its continued clinical use and that meloxicam should be avoided in patients at high risk of cardiovascular events.

**Research:** The authors did not explicitly state any implications for research.

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