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

CRD summary
This generally well-conducted review found little evidence to suggest that any of the non-steroidal anti-inflammatory drugs investigated were safe in terms of cardiovascular risk, and that cardiovascular risk needs to be taken into consideration when prescribing. There were limitations with the included trials and limitations inherent with network analysis, but the authors' conclusions seem appropriately cautious.

Authors' objectives
To assess the cardiovascular safety of non-steroidal anti-inflammatory drugs (NSAIDs) using direct and indirect evidence.

Searching
An updated search of MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) was undertaken up to July 2009. Some search strategies were reported in a supplementary web appendix (see URL for Additional Data). Proceedings from the major rheumatological and oncological conferences were searched, as were registries of ongoing studies and the Food and Drug Administration website. In addition, reference lists of relevant articles and reports were searched using Science Citation Index. Google was also searched to identify further relevant information.

Study selection
Large randomised controlled trials (RCTs) that compared any non-steroidal anti-inflammatory drug (NSAID) with other non-steroidal drugs, paracetamol (acetaminophen), or placebo, in patients with any medical condition other than cancer, were eligible for inclusion. Eligible trials had to include at least two study arms with at least 100 patient years of follow-up. Interventions were only included if at least 10 patients receiving the same intervention had experienced a myocardial infarction.

The primary outcome of interest was fatal or non-fatal myocardial infarction. Secondary outcomes were haemorrhagic or ischaemic fatal or non-fatal stroke; cardiovascular death and death from unknown causes; death from any cause; and the Antiplatelet Trialists’ Collaboration composite score for non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death.

Included trials were of patients with Alzheimer's disease, rheumatoid arthritis, adenomatous polyps (colon), adjuvant colon cancer, osteoarthritis, and patients at risk for prostate cancer. The main NSAID assessed was celecoxib, but diclofenac, etoricoxib, ibuprofen, lumiracoxib, naproxen and rofecoxib were also assessed. Treatment doses varied between trials. Twenty-five trials allowed low dose aspirin.

Two reviewers independently screened studies for inclusion.

Assessment of study quality
Trial quality was assessed based on allocation concealment, blinding, independent event adjudication, and intention-to-treat analysis.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Two reviewers independently extracted the number of outcome events at the last follow-up for each treatment group to calculate rate ratios (RRs) and their 95% credible intervals (Crl). Analyses were based on intention-to-treat data, where possible. Trials reporting zero events in all treatment arms were excluded from the analysis.

Primary authors and pharmaceutical companies were contacted for missing data.
Methods of synthesis
Rate ratios and 95% credible intervals for direct comparisons were combined using a Bayesian random-effects model. A Bayesian random-effects model using Markov chain Monte Carlo methods was used to combine direct and indirect comparisons. Results from the network analysis were compared with those from the direct-comparison analysis.

Statistical heterogeneity was assessed using $T^2$. The consistency of the network analyses was also assessed using six inconsistency factors. Sensitivity analyses were undertaken by including only: trials of patients with musculoskeletal conditions; trials with external adjudication of events; trials using low dose aspirin; trials with at least 500 patient-years per trial arm and trials with at least 50 myocardial infarctions; high-dose trials; and by excluding outliers.

Confidence levels were calculated for each treatment and each outcome; rate ratios less than the pre-specified threshold of 1.3 indicated greater confidence in the treatment estimates. Linear regression was used to assess whether there was an association with cyclo-oxygenase-2 selectivity (data available in a supplementary web appendix).

The goodness of fit of the model was assessed by calculating the residual deviance.

Results of the review
Thirty-one RCTs were included in the review (n=116,429 participants). Twenty-nine trials had adequate concealment. All trials were blinded. Sixteen trials were externally adjudicated for myocardial infarction. Thirteen trials use intention-to-treat analyses. Follow-up ranged from 12 weeks to over four years.

Myocardial infarction (29 RCTs): Rofecoxib was associated with statistically significant increased risk of myocardial infarction compared with placebo (RR 2.12, 95% CrI 1.26 to 3.56).

Stroke (26 RCTs): Diclofenac (RR 2.86, 95% CrI 1.09 to 8.36) and lumiracoxib (RR 2.81, 95% CrI 1.05 to 7.48) were associated with a statistically significant increased risk of stroke compared with placebo.

Cardiovascular death (26 RCTs): Risk of cardiovascular death was statistically significantly higher with diclofenac (RR 3.98, 95% CrI 1.48 to 12.70) and etoricoxib (RR 4.07, 95% CrI 1.23 to 15.70) compared with placebo.

All-cause death (28 RCTs): Rofecoxib was associated with a statistically significant increased risk of death from any cause compared with placebo (RR 1.56, 95% CI 1.04 to 2.23).

Antiplatelet Trialists' Collaboration composite score (30 RCTs): Ibuprofen (RR 2.26, 95% CrI 1.11 to 4.89) and lumiracoxib (RR 2.04, 95% CrI 1.13 to 4.24) showed statistically increased risk of the composite of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death compared with placebo.

No other comparisons for any outcome were statistically significant. However, with the exception of naproxen, other treatments had rate ratios above the 1.3 threshold for most outcomes (as reported in the review).

The goodness of fit of the model was adequate for all outcomes. Statistical heterogeneity among trials was low or moderate for all outcomes (range: $T^2$ 0.03 to 0.12). Inconsistency was shown to be less than 50% for all outcomes; there was no association between risk for any outcome and cyclo-oxygenase-2 selectivity.

Sensitivity analyses significantly altered some results, but most remained similar to the main analyses. Statistical heterogeneity remained low to moderate for most analyses.

Results from the network analysis were similar to the direct comparison analysis (further results were reported in the review and in supplementary web appendices).

Authors' conclusions
Little evidence was found to suggest that any of the treatments investigated were safe in terms of cardiovascular risk. Cardiovascular risk needs to be taken into consideration when prescribing any non-steroidal anti-inflammatory drug. Naproxen seemed to be the least harmful treatment.

CRD commentary
The review question and supporting inclusion criteria were clearly defined. A comprehensive search of the literature was undertaken, including attempts to locate unpublished data, although it was unclear whether any language restrictions were applied. The authors acknowledged that they were unable to obtain some unpublished data from one manufacturer, so some data may have been missing.

Appropriate criteria were used to assess trial quality, and this was generally adequate. However, the authors stated that the reporting in the trials was poor. The authors completed study selection and data extraction in duplicate, although it was unclear whether this was true for quality assessment. Few patient characteristics were reported, and there was some heterogeneity among patients in terms of their health conditions. Therefore, it was unclear whether pooling of the data was appropriate. There was evidence of low to moderate heterogeneity among the trials. The authors acknowledged that the low number of outcome events resulted in imprecise estimates, preventing any meaningful conclusions to be made. Credible intervals were also high, further reducing the robustness of the findings.

This was a generally well-conducted review and, although the limitations with the included trials and the limitations inherent with network analysis need to be taken into consideration, the authors' cautious conclusions seem appropriate.

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

**Practice:** The authors stated that treatment options for chronic musculoskeletal pain were limited and that other NSAIDs not covered in the review should be reconsidered in terms of cardiovascular risk, as should over the counter NSAIDs such as diclofenac and ibuprofen.

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

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