Risk of myocardial infarction associated with selective COX-2 inhibitors: meta-analysis of randomised controlled trials

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CRD summary
The authors concluded that selective cyclooxygenase-2 inhibitors (coxibs) were associated with a significantly increased risk of myocardial infarction compared with placebo and non-selective non-steroidal anti-inflammatory drugs (NSAIDs); the risk of myocardial infarction differed between coxibs and individual NSAIDs. The data appear to support the conclusions, but it is difficult to assess their reliability given the limitations in reporting of review methodology.

Authors' objectives
To evaluate the risk of myocardial infarction (MI) associated with selective cyclooxygenase-2 (COX-2) inhibitors (coxibs).

Searching
MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews and the Cochrane CENTRAL Register were searched from inception to June 2006; some search terms were reported. In addition, the reference lists of retrieved studies and reviews were screened, and conference reports and proceedings of the relevant Food and Drug Administration (FDA) advisory panels and the online Clinical Study Results Database (Pharmaceutical Research and Manufacturers of America) were searched. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) of at least 4 weeks' duration and that scored a minimum of 2 points for randomisation and blinding on the Jadad quality scale were eligible for inclusion. The included studies had follow-ups ranging from 4 weeks to 1 year; most of the studies lasted more than 6 months.

Specific interventions included in the review
Studies that compared any individual coxib that had been licensed in the UK or USA with placebo or another active treatment were eligible for inclusion. The review compared coxibs versus placebo, coxibs versus non-selective non-steroidal anti-inflammatory drugs (NSAIDs), coxibs versus individual NSAIDs and individual coxibs versus each other. The coxibs used were celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib. The most commonly used NSAIDs were naproxen, ibuprofen and diclofenac. Treatment duration ranged from 4 weeks to 1 year.

Participants included in the review
Inclusion criteria were not specified in terms of the participants. Most of the included studies were in patients with osteo- or rheumatoid arthritis; other studies were in patients with ankylosing spondylitis, chronic low back pain, colorectal adenomas, and mild cognitive impairment or early Alzheimer's disease.

Outcomes assessed in the review
Studies that reported the proportion of patients with MI (fatal and nonfatal) were eligible for inclusion in the review. Studies with zero events in both treatment groups were excluded from the meta-analysis.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Only studies with a specified minimum quality score on the Jadad scale were included. The authors did not state how the validity assessment was performed.
Data extraction
Two reviewers independently extracted the number of patients with MI in each treatment arm and the total number randomised to each arm from each study. A value of 0.5 was added to cells with zero events in one treatment group. Where published numbers differed from those presented in the FDA files, the reviewers used the data in the FDA files.

Methods of synthesis
How were the studies combined?
Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using the fixed-effect Mantel-Haenszel method.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the I-squared statistic. Further analyses (including meta-regression and subgroup analyses) were used to examine the influence of coxib dose, trial duration (less than 26 weeks, 27 to 52 weeks, and more than 52 weeks) and disease of patient and to compare individual coxibs with each other and versus individual NSAIDs.

Results of the review
Fifty-five RCTs (n=99,087) were included.

Coxibs versus placebo (28 RCTs; n=26,082): coxibs were associated with a significantly increased risk of MI compared with placebo (OR 1.46, 95% CI: 1.02, 2.09). Individual coxibs (celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) were associated with a non statistically significant increased risk of MI compared with placebo (p>0.05). Higher than recommended daily doses of coxibs were associated with an increased risk of MI compared with placebo; this was only significant for one of the drugs investigated (celecoxib).

Coxibs versus traditional NSAIDs (37 RCTs; n=81,105): coxibs were associated with a significantly increased risk of MI compared with non-selective NSAIDs (OR 1.45, 95% CI: 1.09, 1.93).

Coxibs versus naproxen and diclofenac: coxibs were associated with a significantly increased risk of MI compared with naproxen (OR 1.93, 95% CI: 1.22, 3.05; 18 RCTs, n=48,322). Rofecoxib was associated with a significantly increased risk of MI compared with naproxen (OR 5.39, 95% CI: 2.08, 14.02; 2 RCTs), but there were no significant differences in the risk of MI between other individual coxibs and naproxen. Valdecoxib was associated with a significantly decreased risk of MI compared with diclofenac (OR 0.14, 95% CI: 0.03, 0.73; 3 RCTs, n=2,558), but there were no significant differences in the risk of MI between other individual coxibs (celecoxib, rofecoxib and etoricoxib) and diclofenac.

Coxibs versus each other: there were no significant differences in the risk of MI between celecoxib and rofecoxib (2 RCTs, n=1,902) or between celecoxib and lumiracoxib (5 RCTs, n=5,456).

No evidence of heterogeneity was found for any of the above analyses (I-squared ranged from 0 to 39.9%; p-values ranged from 0.16 to 1.00).

Authors' conclusions
Coxibs were associated with a significantly increased risk of MI compared with placebo and non-selective NSAIDs; the risk of MI differed between coxibs and individual NSAIDs.

CRD commentary
The review addressed a clear question that was defined in terms of the intervention, outcomes and study design. Several relevant sources were searched and attempts were made to minimise language and publication bias. Methods were used to minimise reviewer errors and bias in the extraction of data, but it is unclear whether similar steps were taken at the study selection stage. Only studies meeting minimum quality criteria were included; other aspects of validity were not reported, which makes it difficult to comment on the reliability of the evidence presented. Statistical heterogeneity was assessed, studies were appropriately pooled using meta-analysis, and the influence of relevant variables was examined in...
further analyses. The conclusions appear supported by the data presented, but limitations in the reporting of review methods and the assessment of study validity make it difficult to assess their reliability.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that an analysis of individual patient data should be used to evaluate emerging safety concerns and to examine the influence of potential risk factors on adverse events. In future, the reporting of adverse events in RCTs should be improved so that the safety of new drugs can be monitored after they are licensed.

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