Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis: meta-analysis of randomised trials


CRD summary
This review determined the effect of selective cyclo-oxygenase-2 (COX-2) inhibitors and traditional non-steroidal anti-inflammatory drugs on the risk of vascular events. The authors concluded that selective COX-2 inhibitors are associated with a moderate increase in the risk of vascular events. The lack of detail makes it difficult to judge the extent to which variation between the studies impacted upon the results.

Authors' objectives
To determine the effect of selective cyclo-oxygenase-2 (COX-2) inhibitors and traditional non-steroidal anti-inflammatory drugs (NSAIDs) on the risk of vascular events.

Searching
MEDLINE and EMBASE were searched from January 1966 to April 2005; the search terms were reported. To identify further relevant studies, the authors contacted the manufacturers of each of the selective COX-2 inhibitors and searched the Food and Drug Administration website for data presented at the Cardiorenal Advisory Committee meeting in February 2005.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that compared a selective COX-2 inhibitor with a placebo or traditional NSAID for at least 4 weeks were eligible for inclusion. The selective COX-2 inhibitors assessed in the review were rofecoxib, celecoxib, etoricoxib, lumiracoxib and valdecoxib, all at varying doses. The mean duration of follow-up ranged from 4 to 208 weeks.

Participants included in the review
No a priori criteria were reported. The review included a broad range of participants, including those with arthritis (rheumatoid and osteoarthritis), Alzheimer's disease, back pain, functional abdominal pain, polyps, migraine, prostatitis, ankylosing spondylitis, temperomandibular joint pain and cancer pain.

Outcomes assessed in the review
The primary outcomes were serious vascular events (which included nonfatal myocardial infarction (MI), nonfatal stroke, or vascular death), fatal or nonfatal MI, fatal or nonfatal stroke, and vascular death (including death from MI or stroke).

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
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data
extraction. The number of events per person-years for the outcomes of interest were extracted.

**Methods of synthesis**

**How were the studies combined?**

Rate ratios (RRs) and their confidence intervals (CIs) were calculated for each of the pre-specified comparisons using the Peto ‘one step’ approximation. The 99% CIs were calculated for the individual comparisons of the different COX-2 inhibitors, while 95% CIs were calculated for the pooling of all the drugs.

**How were differences between studies investigated?**

Studies comparing COX-2 inhibitors with placebo and with NSAIDs were pooled separately. In addition to pooling all the COX-2 inhibitors for each of the outcomes, the pooled RR was also reported for the individual drugs. A chi-squared test was used to investigate statistical heterogeneity. For the placebo-controlled trials, subgroup analyses were conducted to investigate the influence of treatment duration, dose and concomitant aspirin use on the event rate. For the trials using NSAIDs as a comparator, naproxen and non-naproxen NSAID trials were pooled separately and subgroup analyses of diclofenac and ibuprofen were conducted.

**Results of the review**

One hundred and thirty-eight RCTs (n=145,373) were included in the review.

**Selective COX-2 inhibitors versus placebo.**

Of the 121 trials, 216 vascular events occurred during 18,490 person-years of exposure to COX-2 inhibitors. COX-2 inhibitors were associated with a 42% relative increase in the incidence of a serious vascular event (RR 1.42, 95% CI: 1.13, 1.78); this was largely due to an increased risk of MI (RR 1.86, 95% CI: 1.33, 2.59). No significant heterogeneity was found between the different selective COX-2 inhibitors. No statistically significant differences between the groups were demonstrated for the incidence of stroke or vascular death.

When only long-term trials (1 year or more) were analysed (9 trials), little difference in the point estimate was shown (RR 1.45, 95% CI: 1.12, 1.89). There was a trend towards an increased incidence of serious vascular events with celecoxib. There were insufficient data to investigate the effect of dose on event rate for the other COX-2 inhibitors. No significant difference between RRs was shown when concomitant use of aspirin was considered.

**Selective COX-2 inhibitor versus traditional NSAIDs.**

There was no statistically significant difference in the rate of a serious vascular event between participants receiving COX-2 inhibitors and any NSAID (RR 1.16, 95% CI: 0.97, 1.38), based on 91 trials; significant heterogeneity was shown.

When compared with naproxen, selective COX-2 inhibitors were associated with an increase in the incidence of a serious vascular event (RR 1.57, 95% CI: 1.21, 2.03) and MI (RR 2.04, 95% CI: 1.41, 2.96). No significant difference in the incidence of stroke or vascular death was found. No statistically significant difference was found between any selective COX-2 inhibitor and non-naproxen NSAID on the incidence of a serious vascular event (RR 0.88, 95% CI: 0.69, 1.12), MI (RR 1.20, 95% CI 0.85, 1.68) or vascular death (RR 0.67, 95% CI: 0.43, 1.06). Selective COX-2 inhibitors were shown to significantly reduce the incidence of stroke in comparison with other non-naproxen NSAIDs (RR 0.62, 95% CI: 0.41, 0.95).

Traditional NSAIDs versus placebo.

Indirect comparisons demonstrated a non statistically significant increased risk of vascular events for ibuprofen, and a statistically significant increase in risk for diclofenac. A reduction in the incidence of vascular events was found for naproxen. No information on how many trials these comparisons were based was provided.

**Authors' conclusions**
Selective COX-2 inhibitors were associated with a moderate increase in the risk of vascular events, as were high-dose regimens of ibuprofen and diclofenac, but high-dose naproxen was not.

CRD commentary
The review question was supported by clear inclusion criteria in terms of the study design, intervention and outcomes. Appropriate databases were searched and attempts were made to locate unpublished articles. However, the lack of a reported review process means that the likelihood of error or bias being introduced could not be assessed. In addition, the quality of the trials did not appear to have been assessed. Details of the trial participants and the results for each of each treatment group in the individual trials were not provided, nor were the results of any test of statistical heterogeneity for the meta-analyses of each drug. The authors discussed limitations of their research and pointed out that further large-scale research is needed to identify which anti-inflammatory drug regimens minimise the risk of adverse gastrointestinal and cardiovascular outcomes. The lack of reported detail makes it too difficult to judge the extent to which heterogeneity impacted upon the results.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further large-scale research is needed to identify which anti-inflammatory drug regimens minimise the risk of adverse gastrointestinal and cardiovascular outcomes.

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Other publications of related interest
This additional published commentary may also be of interest. Laupacis A. Review: Selective COX-2 inhibitors increase vascular events more than placebo and naproxen, but not more than other NSAIDs. ACP J Club 2006;145:66.

Indexing Status
Subject indexing assigned by NLM

MeSH
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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.