Risk of cardiovascular events and celecoxib: a systematic review and meta-analysis
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CRD summary
This review assessed the evidence for an increased risk of cardiovascular events associated with the cyclooxygenase-2 inhibitor celecoxib. The review included a number of large trials addressing diverse conditions and found that celecoxib was associated with a higher risk of myocardial infarction than placebo or any other treatment. Despite some poorly reported methodology, this conclusion is likely to be reliable.

Authors' objectives
To assess the risk of cardiovascular events with administration of the cyclooxygenase-2 (COX-2) specific inhibitor celecoxib.

Searching
MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, the Cochrane CENTRAL Register, DARE and ACP Journal Club were searched up to April 2005; the search terms were not reported. The U.S. Food and Drug Administration (FDA) website was checked, as were other relevant websites including those of the manufacturer, who was also contacted.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Trials in which celecoxib was administered for a period of at least 6 weeks were eligible for inclusion. The included trials used doses of 200, 400 and 800 mg/day. Trials included in the review had comparison groups treated with placebo, paracetamol, or a non-steroidal anti-inflammatory drug (NSAID). The duration of treatment in the included trials ranged from 6 to 161 weeks.

Participants included in the review
Inclusion criteria for the participants were not explicitly stated, but participants included in the review were treated for a range of medical conditions including rheumatoid arthritis, osteoarthritis, Alzheimer's disease, and the prevention of colorectal adenoma in high-risk individuals.

Outcomes assessed in the review
Studies that reported serious cardiovascular thromboembolic events were eligible for inclusion. The primary outcome was fatal and nonfatal myocardial infarction (MI). The secondary outcomes were fatal or nonfatal cerebrovascular events (thrombotic or haemorrhagic), cardiovascular mortality, and the composite outcome of serious cardiovascular thromboembolic events.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies for inclusion in the review.

Assessment of study quality
Validity was assessed on the basis of the following criteria: cardiovascular risk assessment stated as a study objective; individuals with cardiovascular disease included; criteria defined for diagnosing a cardiovascular event; electrocardiogram routinely undertaken before and after treatment; review of cardiovascular events by a blinded external board; and sufficient sample size for 80% power to detect a 0.4% difference in the occurrence of MI.
The authors did not state how the validity assessment was performed.

**Data extraction**
Two reviewers extracted data on cardiovascular events using a standardised form. A third reviewer checked the data extraction. For each study, the number of events of interest was extracted for each treatment arm and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each outcome for each comparison. A power calculation was performed to assess the ability of individual studies to identify an increased risk of MI.

**Methods of synthesis**

*How were the studies combined?*
The studies were combined in fixed-effect meta-analyses for each outcome based upon the comparisons reported, and pooled ORs with 95% CIs were calculated. The primary meta-analysis compared celecoxib with placebo, while secondary meta-analyses compared celecoxib with placebo, paracetamol and NSAIDs.

*How were differences between studies investigated?*
Placebo comparisons were pooled separately. Statistical heterogeneity between trials was assessed using the I-squared statistic. A sensitivity analysis, calculating the pooled absolute difference in risk for each outcome, was also conducted; this included only studies reporting at least one event.

**Results of the review**
Six RCTs with a total of 12,780 patients were included in the review.

**Quality.**
None of the studies was either adequately powered or specifically designed to assess the risk of cardiovascular thromboembolic events with celecoxib treatment. None of the studies reported systematic monitoring for cardiovascular events, and few studies reported that cardiovascular data were examined by a blinded external reviewer. The authors also stated that they found discrepancies in the reporting of the cardiovascular events in various publications of one of the included studies.

**MI.**
Four studies (n=4,422) compared celecoxib with placebo and assessed MI. The risk of MI was higher in the celecoxib groups, although of borderline statistical significance (pooled OR 2.26, 95% CI: 1.0, 5.1). Five studies (n=12,180) compared celecoxib with any other treatment and assessed MI. The risk of MI was significantly higher in the celecoxib groups (pooled OR 1.88, 95% CI: 1.15, 3.08).

**Cerebrovascular events.**
Four studies (n=4,422) compared celecoxib with placebo and assessed cerebrovascular events. There was no difference in the occurrence of cerebrovascular events between the groups (pooled OR 1.0, 95% CI: 0.51, 1.84). Six studies (n=12,780) compared celecoxib with any other treatment and assessed cerebrovascular events. Again there was no difference between the groups (pooled OR 0.73, 95% CI: 0.42, 1.26).

**Cardiovascular mortality.**
Three studies (n=4,021) compared celecoxib with placebo and assessed cardiovascular mortality. There was no difference in deaths from cardiovascular events between the groups (pooled OR 1.06, 95% CI: 0.38, 2.95). Five studies (n=11,989) compared celecoxib with any other treatment and assessed cardiovascular mortality. Again there was no difference between the groups (pooled OR 1.02, 95% CI: 0.52, 1.99).

**Composite cardiovascular events.**
Four studies (n=4,422) compared celecoxib with placebo and assessed composite cardiovascular events. These occurred more often in the celecoxib groups, but there was no significant difference between the groups (pooled OR 1.38, 95% CI: 0.91, 2.10). Six studies (n=12,780) compared celecoxib with any other treatment and assessed composite cardiovascular events. These occurred more often in the celecoxib groups, but again there was no significant difference between the groups (pooled OR 1.22, 95% CI: 0.92, 1.62).

**Authors' conclusions**

There is an increased risk of MI associated with celecoxib therapy. This is consistent with a class effect for COX-2 specific inhibitors.

**CRD commentary**

The review question and the inclusion criteria were clear, with the exception of the lack of a definition for eligible participants. The search was thorough and included attempts to locate unpublished papers, making the introduction of publication bias into the review less likely. Only double-blind RCTs were included in the review. An additional validity assessment included some standard criteria and also criteria specific to the objective of the review. However, the results of the validity assessment were not utilised in the analysis of the study data. The authors reported using appropriate methods to minimise bias and error when extracting data for the review, but not when selecting studies or assessing their validity.

The decision to combine the studies in meta-analyses was appropriate, but there was little exploration of sources of heterogeneity, which would have been useful in light of the diverse range of conditions treated in the included trials. The authors’ conclusion is supported by the evidence presented, which includes data from a number of large trials. Overall, the conclusion is likely to be reliable, although the rigour of the review methodology is not clear.

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

Practice: The authors stated that the current FDA preferential risk/benefit assessment for celecoxib over other COX-2 inhibitors may not be supported by the available evidence.

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

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