Systematic review and meta-analysis of the risk of major cardiovascular events with etoricoxib therapy
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CRD summary
This review concluded that limited available data provided weak evidence for an increased risk of cardiovascular thromboembolic events in patients treated with etoricoxib (consistent with a class effect of cyclooxygenase-2 enzyme inhibitors); these conclusions are appropriately cautious.

Authors' objectives
To assess the risk of thromboembolic cardiovascular events associated with the use of etoricoxib, a cyclooxygenase-2 inhibitor.

Searching
MEDLINE, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials (CENTRAL), DARE and EMBASE were searched to January 2005; Search terms were reported. American College of Physicians Journal Club was also searched. Bibliographies of relevant articles were screened for additional studies. Merck (the manufacturer of etoricoxib) was approached for details of any relevant studies.

Study selection
Randomised double-blind controlled clinical trials of etoricoxib were eligible for inclusion. Trials had to be a minimum of six weeks duration and report major cardiovascular thromboembolic events.

Included trials used etoricoxib to treat rheumatoid arthritis, osteoarthritis, and chronic lower back pain; etoricoxib doses were 30mg, 60mg and 90mg. All trials were placebo-controlled; some also included the non-steroidal anti-inflammatory drug naproxen as an active comparator.

Two reviewers independently assessed studies for inclusion.

Assessment of study quality
The authors did not state that they assessed methodological quality.

Data extraction
Data were extracted on the numbers of subjects, in the etoricoxib, naproxen and placebo groups, who had experienced a major cardiovascular thromboembolic event. These data were used to calculate the probability difference, with 95% confidence intervals (CIs), of a major cardiovascular thromboembolic event (etoricoxib versus placebo).

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
A fixed-effect model was used to generate a pooled odds ratio (OR) for the risk or cardiovascular event with active treatment versus placebo; trials were weighted by inverse variance.

A fixed-effect model was also used to generate an estimate of the absolute probability difference in cardiovascular events between treatments and a point estimate of the number needed to harm.

An adjustment of 0.5 was added to all cell counts in the analyses to deal with zero cell counts.

The I² statistic was used to assess between study heterogeneity.
Results of the review
Five trials were included in the review (n=2,919 patients).

There were seven major cardiovascular thromboembolic events in the 1,441 patients treated with etoricoxib, one major cardiovascular thromboembolic event in the 906 patients treated with placebo, and none in 572 patients treated with naproxen.

The odds ratio for the risk of cardiovascular events in patients treated with etoricoxib compared with placebo was 1.49 (95% CI 0.42 to 5.31; I²=0%).

For the four trials with at least one event in one of the arms, the pooled estimate of the absolute probability difference for a cardiovascular event between patients treated with etoricoxib and placebo was 0.5% (95% CI 0.1 to 1.0). This was equivalent to a point estimate of numbers needed to harm of 197 (95% CI 105 to 1,553).

Authors' conclusions
The clinical trials of etoricoxib provided limited data on major cardiovascular thromboembolic events as they were neither designed nor powered to assess the potential cardiovascular risks with etoricoxib therapy. However, the limited data that were available provided weak evidence of an increased cardiovascular risk with etoricoxib (consistent with a class effect for cyclooxygenase-2 inhibitors).

CRD commentary
The review reported a clear research question and defined inclusion criteria. A range of sources were searched for relevant studies, although it was unclear whether any language or publication status restrictions were applied. Measures were taken to minimise error and/or bias in the study selection process, but it was unclear whether similar measures were applied to data extraction.

No assessment of the methodological quality of included trials was reported. Overall, there was insufficient information to judge the extent to which reported results may have been subject to bias. The analysis methods applied were reasonable.

The authors highlighted the inherent weakness of the evidence due to the small number of trials and low event rates; their conclusions were appropriately cautious.

Implications of the review for practice and research
The authors made no specific recommendations for clinical practice or further research.

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