Risk of cardiovascular events and rofecoxib: cumulative meta-analysis

CRD summary
This meta-analysis evaluated the risk of myocardial infarction (MI) in patients with chronic musculoskeletal disorders who were taking rofecoxib or a control treatment. The authors concluded that rofecoxib is associated with a significantly increased risk of MI and that robust evidence of this was available in 2000, although the drug was not withdrawn until September 2004. The authors' conclusions appear reliable.

Authors' objectives
To determine whether robust evidence on the cardiovascular adverse effects of rofecoxib was available before the drug was withdrawn by the manufacturer, Merck, in September 2004. A further objective was to determine whether naproxen, which was used as a control in some trials of rofecoxib, was associated with reduced cardiovascular risk.

Searching
The Cochrane Controlled Trials Register (Issue 3, 2004), and MEDLINE, EMBASE and CINAHL (from inception to September 2004) were searched. The authors also examined citations of key papers in the Science Citation Index, screened reference lists, and sought information from experts and from the proceedings of the relevant Food and Drug Administration (FDA) advisory panels.

Study selection
Study designs of evaluations included in the review
For rofecoxib, only randomised controlled trials (RCTs) were eligible for inclusion. No randomised trials addressing the cardiovascular protective effects of naproxen were available, so cohort and case-control studies were eligible for inclusion.

Specific interventions included in the review
Studies that compared rofecoxib (12.5 to 50 mg/day) with another non-steroidal anti-inflammatory drug (NSAID) or placebo were eligible for inclusion. The included studies compared rofecoxib (12.5, 25 or 50 mg) with placebo, ibuprofen (2,400 mg), naproxen (1,000 mg) diclofenac (150 mg) or nabumetone (1,000 mg) over 4 to 56 weeks. Studies that examined the association between use of naproxen and cardiovascular risk were also eligible.

Participants included in the review
Studies of rofecoxib in adults with chronic musculoskeletal disorders were eligible for inclusion. The participants in the included studies were mainly patients with osteoarthritis or rheumatoid arthritis; one study of patients with chronic low back pain was also included. Inclusion criteria (for participants) were not specified for studies of naproxen. Ten of the 11 included studies used data from large administrative or clinical databases from the USA, UK or Canada, while the remaining study looked at cases of myocardial infarction (MI) from 36 hospitals and community controls from the area around Philadelphia, USA.

Outcomes assessed in the review
For rofecoxib trials, the primary end point was fatal or nonfatal MI. The secondary end points were stroke, cardiovascular death, and a composite outcome of serious cardiovascular events (nonfatal MI, nonfatal stroke, death from a vascular cause or death from an unknown cause) used in a meta-analysis sponsored by the manufacturer. MI was the only outcome assessed in studies of naproxen.

How were decisions on the relevance of primary studies made?
Two authors independently assessed studies for inclusion. The authors did not state how any disagreements were resolved.
Assessment of study quality
The validity of the RCTs was assessed on the basis of concealment of treatment allocation and external review of serious cardiovascular events. Two reviewers assessed validity as part of the data extraction process. The authors did not state how any disagreements were resolved.

Data extraction
Two reviewers extracted the data using a standardised form. Two different reviewers then checked the completed data extraction forms. Data on the number of patients and events in each group were used to calculate the relative risks (RRs) for primary and secondary outcomes. Where there was a discrepancy in the number of cardiovascular events between published reports and FDA files, data from the FDA were used.

Methods of synthesis
How were the studies combined?
The results from the RCTs of rofecoxib were combined using standard and cumulative random-effects meta-analyses. For the cumulative meta-analysis, safety data were assigned to the year they first became available (through submission to the FDA, presentation at a major meeting or publication in a journal). A random-effects meta-regression was used to determine whether the estimates of RR were affected by dose, type of control, trial duration, adequacy of allocation concealment or external review of cardiovascular events. Appropriate weighting was used in trials with more than two arms and for extensions of trials to avoid duplication of the data. Comparisons with no events in either group were excluded; for comparisons with events only in one group, 0.5 was added to all cells.

Risk ratios and odds ratios from observational studies of naproxen were pooled using a random-effects meta-analysis. A meta-regression was used to investigate the effect of study design, funding source and whether or not analyses had been adjusted for aspirin use.

How were differences between studies investigated?
The authors calculated an I-squared statistic for all meta-analyses and performed standard tests for heterogeneity.

Results of the review
Eighteen RCTs of rofecoxib with 25,273 participants were included. Eleven observational studies (8 case-control studies and 3 retrospective cohort studies) of naproxen were included.

The risk of MI was significantly higher in patients taking rofecoxib than controls (combined RR 2.24, 95% confidence interval, CI: 1.24, 4.02, P=0.007). There was no evidence of heterogeneity between the trials. The cumulative meta-analysis showed that data indicating an increased risk of MI with rofecoxib use were available by the end of 2000 (RR 2.30, 95% CI: 1.22, 4.33, P=0.010). The meta-regression indicated that the RR was not significantly affected by the type of control, dose of rofecoxib, trial duration or adequacy of allocation concealment. The estimated RR of MI was higher in trials with external review of cardiovascular events than those without (P=0.011). The RRs for stroke, cardiovascular death and the composite of serious cardiovascular events did not differ significantly between the rofecoxib and control groups.

The combined RR for MI from observational studies of naproxen was 0.86 (95% CI: 0.75, 0.99), indicating that naproxen had a small protective effect. There was significant heterogeneity between the studies. The meta-regression indicated that the heterogeneity was largely explained by funding source: studies funded by Merck showed larger protective effects than those with funding from other sources.

Authors' conclusions
Rofecoxib should have been withdrawn several years earlier on the basis of data available in 2000. The cardioprotective effect of naproxen was small and could not explain the increased risk of MI in the rofecoxib group in trials comparing rofecoxib with naproxen.
CRD commentary
The meta-analysis addressed a clear question and the inclusion and exclusion criteria were clearly defined. The authors searched a range of sources, although the search terms and language restrictions (if any) were not reported. The authors did not report that they attempted to assess publication bias, but publication bias was unlikely given that the meta-analysis investigated RCTs conducted by the drug manufacturer and submitted to the regulatory authorities. Two independent reviewers selected the studies and checked the data extractions, thus reducing the risk of bias and errors during the review process. The validity of the included RCTs was not fully assessed, but some relevant aspects were evaluated and taken into account in the meta-regression analysis.

Relevant details of the included studies were presented, although information about the participants was limited. The authors used standard methods for meta-analysis and to assess and investigate heterogeneity between the studies. Overall, the results of this meta-analysis are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that the FDA and other drug regulatory authorities should ensure that drug safety information is continuously updated and made available to decision-makers and researchers.

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

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