Relative thromboembolic risks associated with COX-2 inhibitors
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CRD summary
This review found that celecoxib was the safest cyclooxygenase-2 inhibitor when given in the lowest possible dose. The limited search, inadequate reporting of review methods, lack of a quality assessment of the included studies, and reliance upon data from observational studies to compare drugs mean that any conclusions might not be reliable.

Authors' objectives
To determine if different cyclooxygenase-2 (COX-2) inhibitors are associated with different rates of thromboembolic events.

Searching
MEDLINE was searched from 1996 to March 2005 using the reported search terms. Reference lists were screened. Only articles reported in the English language were included. Although unpublished studies identified from reference lists were included, the author did not seek unpublished data from pharmaceutical companies. For etoricoxib, an abstract was obtained from the American College of Rheumatology and the manufacturers website was searched.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), retrospective and prospective cohort studies, and case-control studies were eligible for inclusion. Reviews of data that were available from published sources were excluded. The duration of the included studies, where stated, ranged from 10 days to 3.1 years.

Specific interventions included in the review
Studied that evaluated COX-2 inhibitors were eligible for inclusion. The included studies evaluated celecoxib (200 or 400 mg twice daily), lumiracoxib (400 mg/day), rofecoxib (12.5 or 50 mg/day), parecoxib, valdecoxib and etoricoxib. Control interventions were other COX-2 inhibitors (or different doses of the same COX-2 inhibitor), non-steroidal anti-inflammatory drugs (NSAIDs: including meloxicam, ibuprofen, diclofenac, naproxen, nabumetone and unspecified NSAIDs) and placebo. Drug doses were reported where available. Some of the included studies controlled for aspirin use.

Participants included in the review
Inclusion criteria were not specified in terms of the participants. The participants in the primary studies were patients with osteoarthritis, rheumatoid arthritis, adenomatous polyps, pain after coronary artery bypass graft and multiple unspecified conditions.

Outcomes assessed in the review
Studies that assessed the efficacy or safety of COX-2 inhibitors were eligible for inclusion. The included studies assessed coronary disease, cardiovascular (CV) events, myocardial infarction (MI), cerebrovascular events, peripheral venous thrombosis and serious events.

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

Assessment of study quality
The author did not state that he had assessed validity.
Data extraction
The author did not state how the data were extracted for the review, or how many reviewers performed the data extraction. For each study, the relative risks (RRs) of cardiovascular events, along with 95% confidence intervals (CIs), or the percentage of treatment groups with the outcome of interest were extracted.

Methods of synthesis
How were the studies combined?
The studies were grouped by specific COX-2 inhibitor and combined in a narrative.

How were differences between studies investigated?
Some differences between the studies were apparent from the tables. The influence of drug exposure period was mentioned in the discussion.

Results of the review
Seventeen studies were included; 8 reports of 9 RCTs (n=43,143), 3 case-control studies (n=102,632) and 6 retrospective cohort studies (n=742,395).

Two RCTs (n=10,003) and one retrospective cohort study (n=36,545) evaluated celecoxib.
One RCT (n=18,325) evaluated lumiracoxib.
Three RCTs (n=12,682) and 2 retrospective cohort studies (n=512,449) evaluated rofecoxib.
Two RCTs (n=2,133) evaluated parecoxib and valdecoxib
Three case-control studies (n=102,632) and 3 retrospective cohort studies (n=193,401) compared celecoxib versus rofecoxib.

Celecoxib.
One RCT (n=7,968) reported no difference in CV events between celecoxib 400 mg and ibuprofen 800 mg thrice daily or diclofenac 75 mg twice daily.

One RCT (n=2,035) reported that high-dose celecoxib (400 mg twice daily) was associated with a significant increase in CV events compared with placebo (RR 3.4, 95% CI: 1.4, 7.8), but reported no significant difference between low-dose celecoxib (200 mg twice daily) and placebo.

One retrospective cohort study (n=36,545) reported no significant difference in CV events between celecoxib and meloxicam.

Rofecoxib. One RCT (n=8,076) reported that naproxen 500 mg twice daily was associated with a significant decrease in the risk of MI compared with rofecoxib 50 mg/day (RR 0.2, 95% CI: 0.1, 0.7).

One report of 2 RCTs (n=2,020) reported mixed results: one RCT (n=1,042) suggested that the risk of CV events was lower with rofecoxib than with nabumetone, but not placebo (0.2% versus 0.4% versus 0%, respectively), while the other RCT (n=978) suggested that CV events were more common with rofecoxib than with nabumetone or placebo (1.5% versus 0.5% versus 0.5%, respectively).

One RCT (n=2,586) reported that rofecoxib was associated with a significant increase in the risk of CV events compared with placebo (RR 1.92, 95% CI: 1.19, 3.11). One retrospective cohort study (n=478,094) reported that users of higher dose rofecoxib (25 mg/day or more) had a non significantly higher risk of developing coronary disease compared with non-users of rofecoxib (RR 1.7, 95% CI: 0.98, 2.95). New users of rofecoxib had a significantly higher risk of a CV event (RR 1.93, 95% CI: 1.09, 3.42). One retrospective cohort study (n=34,355) reported no significant difference in the risk of CV events between rofecoxib and meloxicam.
Parecoxib and valdecoxib.

One RCT (n=462) reported that parecoxib and valdecoxib were associated with an increase in the risk of serious events (including MI, cerebrovascular disease, pulmonary thromboembolism and sternal wound infection) compared with placebo (19% versus 9.9%).

One RCT (n=1,671) reported that parecoxib and valdecoxib were associated with a significant increase in the risk of CV events compared with placebo (RR 1.9, 95% CI: 1.1, 3.2).

Celecoxib versus rofecoxib.

Three case-control studies (n=54,475, n=39,639 and n=8,518) reported that rofecoxib was associated with an increased risk of CV events compared with celecoxib: the OR of acute MI was 1.24 (95% CI: 1.01, 1.46), the RR of MI was 1.59 (95% CI: 1.10, 2.32), and the OR of MI was 2.72 (95% CI: 1.24, 5.95), respectively. Two of the case-control studies reported that higher doses of rofecoxib (25 mg/day or more) were associated with a significantly increased risk of CV events compared with celecoxib.

One retrospective study (n=127,427) reported no significant difference in the risk of MI between celecoxib versus non-NSAID users or between rofecoxib versus non-NSAID users.

One retrospective study (n=59,724) reported that rofecoxib significantly increased the risk of MI compared with no NSAID use (RR 1.24, 95% CI: 1.05, 1.46), but found no significant difference between celecoxib and no NSAID use. One retrospective study (n=6,250) reported no significant difference in the risk of CV events between either rofecoxib or celecoxib and non-naproxen NSAIDs.

Lumiracoxib.

One RCT (n=18,325) reported no significant difference in the risk of CV events between lumiracoxib (400 mg/day) and naproxen (500 mg twice daily).

Etoricoxib.

No published studies that assessed safety were identified.

**Authors’ conclusions**

The risks of CV events differed amongst COX-2 inhibitors. Based on existing data, celecoxib was the safest COX-2 inhibitor when given in the lowest possible dose for the shortest time in the ideal target population.

**CRD commentary**

The review addressed a clear question that was defined in terms of the intervention, outcomes and study design; inclusion criteria for the study design and outcomes were broad. In view of the review’s focus on specified adverse effects, it was not clear why studies that assessed efficacy were eligible. Limiting the main search to one database might have resulted in the omission of other relevant studies. No attempts were made to minimise language bias and no specific attempts were made to locate unpublished studies, thus raising the potential for publication bias. The methods used to select the studies and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer errors and bias. Since the validity of the included studies was not assessed, the results from these studies and any synthesis might not be reliable.

The narrative synthesis seemed appropriate given the diversity of the studies. Higher quality sources of evidence (from RCTs) were not adequately highlighted and potential reasons for reported differences in the results of studies of the same drugs were not discussed. Apart from celecoxib versus rofecoxib, comparisons between different drugs were based on indirect comparisons. Comparisons between celecoxib and rofecoxib were based on case-control studies or retrospective data and not clinical trials; this reliance upon observational studies weakens any conclusions. The limited search, lack of reporting of review methods, lack of a quality assessment of the included studies, and reliance upon data
from observational studies to compare drugs mean that any conclusions may not be reliable.

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

**Practice:** The author stated that clinicians should take account of the CV risk status of patients before prescribing or recommending COX-2 inhibitors. In view of the existing data, it would seem sensible to avoid COX-2 inhibitors in patients with CV risk factors.

**Research:** The author stated that research is required to determine the mechanisms whereby COX-2 inhibitors cause CV disease.

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