Do selective COX-2 inhibitors increase the risk of cerebrovascular events: a meta-analysis of randomized controlled trials

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CRD summary
The review concluded that there was no evidence of a significantly increased risk of cerebrovascular events associated with selective cyclooxygenase-2 inhibitors compared with placebo or other active treatment such as non-steroidal anti-inflammatory drugs. The authors' conclusions are appropriate, given the evidence presented, and are likely to be reliable.

Authors' objectives
To evaluate the risk of cerebrovascular events (CVEs) associated with selective cyclooxygenase-2 inhibitors (coxibs).

Searching
MEDLINE (1966), EMBASE (1980), the Cochrane Database of Systematic Reviews and the Cochrane CENTRAL Register were searched to April 2006; the search terms were reported. Reference lists of retrieved studies, review articles, conference reports, proceedings of the Food and Drug Administration advisory panels and the online Clinical Study Results Database were also screened for relevant articles. No language restrictions were applied.

Study selection
Double-blind, randomised controlled trials (RCTs) comparing any individual coxib against placebo or other active treatment, and reporting the proportion of patients experiencing CVEs, were eligible for inclusion. The duration of treatment had to be at least 4 weeks. The included trials assessed varying doses of the following coxibs: celecoxib, etoricoxib, lumiracoxib, rofecoxib and valdecoxib. Active treatment included non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac, naproxen and ibuprofen. Treatment duration ranged from 6 weeks to 4 years. Studies included in the review assessed participants with rheumatoid arthritis, osteoarthritis, chronic lower back pain, colorectal adenomas, mild cognitive impairment or early Alzheimer's disease.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Methodological quality was assessed using the Jadad scale. Studies had to score a minimum of 2 points (for randomisation and double-blinding) to be included.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Data were extracted on the number of participants experiencing fatal and nonfatal CVEs (including ischaemic or haemorrhagic stroke or transient ischaemic attacks) and the total number randomised to each study arm. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for the proportion of participants experiencing CVEs. Data on the condition treated, treatment regimen and duration were also extracted.

Two reviewers independently extracted the data.

Methods of synthesis
The results from individual studies were pooled using a fixed-effect meta-analysis. Where no CVEs were reported in one of the treatment groups a continuity correction was used, this being inversely proportional to the relative size of the opposite group in the study. Fixed-effect meta-regression models were used to examine the effect of dose of coxibs, trial duration and the disease state of treated participants. Subgroup analyses were conducted to explore differences in
Results of the review
Forty RCTs (n=88,116) were included in the review.

Pooled results from 17 RCTs (n=16,464) comparing all coxibs with placebo found no evidence of increased risk of CVEs (OR 1.03, 95% CI: 0.71, 1.50, p=0.88). There was no evidence of statistical heterogeneity (p=0.93; I²=0%). Other outcomes were reported.

Pooled results from 29 RCTs (n=76,620) comparing coxibs with non-selective NSAIDS also found no evidence of increase risk of CVEs (OR 0.86, 95% CI: 0.64, 1.16, p=0.33). There was no evidence of statistical heterogeneity (p=0.815; I²=0%). Other outcomes were reported.

Analyses of trials making direct comparisons between different coxibs found no statistically significant differences between celecoxib and rofecoxib (2 RCTs, n=1,474), celecoxib and lumiracoxib (2 RCTs, n=2,577), or rofecoxib and lumiracoxib. There was no evidence of statistical heterogeneity for the pooled comparisons.

The meta-regression found no statistically significant effects of treatment duration, disease type or dose of coxibs. Subgroup analyses comparing coxibs with naproxen (12 RCTs, n=42,990) also found no evidence of an increased risk of CVEs (OR 0.94, 95% CI: 0.60, 1.46, p=0.49).

Authors' conclusions
The results found no evidence of a significantly increased risk of CVEs associated with coxibs compared with placebo or non-selective NSAIDs. There is a likelihood that an increase in the risk of thrombotic vascular events associated with coxibs may largely be attributable to an increased risk of myocardial infarction, but not CVEs.

CRD commentary
The inclusion criteria were clearly defined. Several relevant sources were searched and attempts were made to minimise language and publication bias. The methods used to select studies and assess validity were not described, so it is not known whether any efforts were made to reduce reviewer error and bias. Although the results of the validity assessment were not reported, only studies which were randomised and double-blind were eligible for inclusion. The methods used to combine the studies appear appropriate and statistical heterogeneity was assessed. The authors' conclusions are appropriate, given the evidence presented, and are likely to be reliable.

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

Research: The authors stated that further meta-analyses based on individual patient data (IPD) should be conducted and include covariates such as treatment dose, treatment duration, use of concomitant drugs and individual patient's risk profiles. Further evaluation using IPD meta-analyses is also required in relation to adverse events and safety concerns.

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