Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2

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CRD summary
This review concluded that there is an increased risk of cardiovascular events with rofecoxib that are not seen with commonly used doses of celecoxib, and that there is no protective effect of naproxen. The authors also raised concerns over the safety of diclofenac. Given the limitations of this review, the conclusions should be regarded with some caution.

Authors' objectives
To evaluate the risk of serious cardiovascular events with non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase 2 (COX-2) inhibitor use.

Searching
MEDLINE, EMBASE, the Cochrane Library, Google Scholar, and epidemiological websites were searched from 1985 to January 2006; a search on authors' names was also performed. Abstracts of scientific meetings and bibliographies of relevant studies were also searched.

Study selection
Study designs of evaluations included in the review
Controlled studies, of case-control or cohort design, were eligible for inclusion.

Specific interventions included in the review
Studies of selective COX-2 inhibitors and NSAIDs, either alone or in combination, compared with non-use or remote use, were eligible for inclusion. The drugs evaluated in the included studies were classified as COX-2 inhibitors (celecoxib, meloxicam and rofecoxib) or NSAIDs (naproxen, diclofenac, ibuprofen, indomethacin and piroxicam). The data mainly came from electronic databases or electronic medical records which use prescribing or dispensing as a proxy for drug consumption.

Participants included in the review
Inclusion criteria relating to the participants were not specified. Where reported, the age ranged from 18 to 100 years, the proportion of men ranged from 20 to 65%, and participants were registered with insurance companies, were part of general practice databases, or were listed on population registries.

Outcomes assessed in the review
Studies reporting on cardiovascular risks were eligible for inclusion. The outcomes reported in the included studies were primarily myocardial infarction (MI) and cardiovascular death.

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

Assessment of study quality
Studies were assessed in relation to the methods used to select participants, the comparability of the two groups, and ascertainment of exposure to COX-2 inhibitors and/or NSAIDs. Two reviewers independently performed the validity assessment, with any discrepancies being resolved by consensus.
Data extraction
Two reviewers independently extracted the data, with any discrepancies being resolved by consensus. Odds ratios were extracted from each case-control study, and hazard or risk ratios from each cohort study, along with their 95% confidence intervals (CIs). All individual studies adjusted the outcomes for cardiovascular risk factors; some used further adjustments. As the outcome was rare, all extracted outcomes were deemed comparable to relative risks and were all treated as such.

Methods of synthesis
How were the studies combined?
Pooled relative risks (RRs) and 95% CIs were calculated using a random-effects meta-analysis (DerSimonian and Laird). The results of case-control and cohort studies were combined separately, and an overall summary estimate was calculated by pooling the results from case-control and cohort studies together. The results were pooled separately for celecoxib, rofecoxib meloxicam, naproxen, diclofenac, ibuprofen, indomethacin, piroxicam and any/other NSAIDs.

How were differences between studies investigated?
Heterogeneity was evaluated statistically using the chi-squared test and I-squared statistic. Forest plots were supplied to allow visual inspection of heterogeneity, and study details were tabulated. Two different dose regimens of rofecoxib were compared. Attempts were made to investigate the impact of concomitant aspirin use. Sensitivity analyses were conducted to investigate possible double counting of the participants. The risk of early use of selective COX-2 inhibitors (first 30 days of treatment) was discussed separately.

Results of the review
Seventeen case-control studies (86,193 cases; at least 528,000 controls) and 6 cohort studies (75,520 COX-2; 375,619 NSAIDs; 594,720 unexposed) were included.

Fifteen of the case-control studies scored 7 or 8 out of a possible 9 for quality; two were available only as abstracts and scored 4 and 5. All 6 cohort studies scored 7 or 8 out of a possible 9.

COX-2 inhibitors.
The RR of a cardiovascular event was significantly higher with rofecoxib when evaluated using a case-control design (RR 1.31, 95% CI: 1.18, 1.46; 9 studies), or when data from case-control and cohort studies were combined (RR 1.35, 95% CI: 1.15, 1.59; 11 studies), but not from cohort studies alone (RR 1.53, 95% CI: 0.68, 3.44; 2 studies). There was evidence of significant heterogeneity for the combined analyses (p<0.001; I-squared 86.8%). The RR of cardiovascular events was greater with the higher doses of rofecoxib. There was no significant increase in the RR of a cardiovascular event with celecoxib or meloxicam.

NSAIDs.
The RR of a cardiovascular event was significantly higher with diclofenac when evaluated using a case-control design (RR 1.36, 95% CI: 1.21, 1.54; 7 studies), or when data from case-control and cohort studies were combined (RR 1.40, 95% CI: 1.16, 1.70; 9 studies), but not from cohort studies alone (RR 1.36, 95% CI: 0.51, 3.65; 2 studies). There was evidence of significant heterogeneity for the overall result (p<0.001; I-squared 84.9%). Indomethacin was only evaluated in case-control studies; it resulted in a significantly higher RR of a cardiovascular event (RR 1.30, 95% CI: 1.07, 1.60; 6 studies). There was no significant increase in cardiovascular risks with naproxen, ibuprofen or piroxicam, regardless of study design.

Authors' conclusions
There is an increased risk of cardiovascular events with rofecoxib that is not seen with commonly used doses of celecoxib. There is no protective effect of naproxen. There are concerns about the safety of diclofenac.
CRD commentary
The review question was clear in terms of the intervention, outcomes and study design; no criteria relating to the participants were stated. The author searched several relevant sources, however, it was unclear whether any language restrictions were applied. Both the data extraction and validity assessment were conducted in duplicate, but it was unclear whether the same precautions were taken to prevent error and bias at the study selection stage. The level of evidence of the included studies was low; e.g. case-control studies are inherently prone to bias, particularly selection bias, and it should be noted that the significant differences seen in the risk of cardiovascular events are seen when the results of studies with this design are combined, either alone or with the cohort studies. In addition, drug use was based only on a proxy estimate.

The authors provided updated estimates to include a recently published study; this did not change their conclusions. The conclusions reflect the presented data but, given the limitations of the review, the conclusions have to be regarded with some caution.

Implications of the review for practice and research
Practice: The authors stated that the results of the review give grounds for reviewing the regulatory status of diclofenac.

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

Funding
National Health and Medical Research Council of Australia, grant number 252469; the National Heart Foundation Australia, grant number G 05S 1980.

Bibliographic details

PubMedID
16968831

DOI
10.1001/jama.296.13.jrv60011

Original Paper URL
http://jama.ama-assn.org/

Indexing Status
Subject indexing assigned by NLM

MeSH
Anti-Inflammatory Agents, Non-Steroidal /adverse effects; Cardiovascular Diseases /chemically induced; Celecoxib; Cyclooxygenase 2 Inhibitors /adverse effects; Diclofenac /adverse effects; Humans; Lactones /adverse effects; Naproxen /adverse effects; Pyrazoles /adverse effects; Risk; Sulfonamides /adverse effects; Sulphones /adverse effects

AccessionNumber
12006008388

Date bibliographic record published
31/05/2007

Date abstract record published
31/05/2007
Record Status
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