NSAID use selectively increases the risk of non-fatal myocardial infarction: a systematic review of randomised trials and observational studies

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CRD summary
This review concluded that use of non-steroidal anti-inflammatory drugs increased the risk of non-fatal myocardial infarction with no substantial effect on fatal events. The authors’ conclusions appeared reliable, but a cautious interpretation is advised given the limitations of the study data and some potential limitations of the review methods.

Authors’ objectives
To assess the effect of non-steroidal anti-inflammatory drugs (NSAIDs) on myocardial infarction (MI), differentiating fatal from non-fatal events.

Searching
PubMed was searched from January 1990 to March 2010 for studies in any language. Search terms were not reported. Reference lists of previously published systematic reviews were used to identify further studies (especially unpublished studies).

Study selection
Randomised controlled trials (RCTs) of more than 1,500 participants and six months duration and observational studies that evaluated traditional NSAIDs and selective cyclooxygenase-2 inhibitors (coxibs) were included in the review if they reported separate data for risks of non-fatal and fatal myocardial infarction.

The included observational studies used various definitions for NSAID exposure (zero days since last use to more than 22 days in any month). Two of the included observational studies reported that all participants had prior coronary heart disease. One study included no participants with coronary heart disease. Other studies included between 17% and 22% of participants with coronary heart disease. The age of included participants in the studies ranged from 40 to 89 years. Study periods spanned 1987 to 2007. The included RCTs compared celecoxib versus placebo, rofecoxib versus placebo, rofecoxib versus naproxen, lumiracoxib versus naproxen versus ibuprofen, celecoxib versus diclofenac versus ibuprofen and etoricoxib versus diclofenac. Drug dosages were reported in the review. Included participants had colon adenomas removed, colorectal carcinoma, rheumatoid arthritis, osteoarthritis or a family history of Alzheimer's disease. Mean age of participants ranged from over 18 years to over 70 years. Aspirin use ranged from 4% to 56%.

The authors did not state how many reviewers performed the selection.

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

Data extraction
Endpoint specific adjusted estimates for numbers of fatal and non-fatal events were extracted, as well as numbers of exposed and unexposed person time. Relative risks (RRs) with 95% confidence intervals (CIs) were calculated. Where these data were unavailable crude incidence rates and relative risks were used.

Two reviewers extracted study data. Any discrepancies were resolved through consensus.

Methods of synthesis
Studies were grouped by design and outcome. Pooled relative risks with 95% CIs were calculated using random-effects models. Additional analyses were performed according to use of prior history of cardiovascular disease as a trial entry criterion (observational studies) and type of comparator (RCTs). Meta-regression was used to explore further sources of heterogeneity between non-fatal and fatal endpoints.
Results of the review
Nine RCTs, four cohort studies and two nested case-control studies were included in the review. RCT sample sizes ranged from 1,561 to 34,701 and follow-up ranged from six months to three years. No sample sizes and study durations were reported for observational studies.

Six observational studies reported that NSAID therapy in comparison with control was associated with a statistically significant increase in non-fatal myocardial infarction (RR 1.30, 95% CI 1.20 to 1.41), but no significant difference in fatal myocardial infarction (RR 1.02, 95% CI 0.89 to 1.17).

The nine RCTs reported that coxibs (selective NSAIDs), compared with either traditional NSAIDs (four trials) or placebo (five trials), were associated with an increase in non-fatal myocardial infarction (RR 1.61, 95% CI 1.04 to 2.50), but no significant difference in fatal myocardial infarction (RR 0.86, 95% CI 0.51 to 1.47).

Overall risk increase for non-fatal myocardial infarction was 25% higher (95% CI 11% to 42%) than for fatal myocardial infarction. The two cohort studies that included only individuals with prior cardiovascular disease presented risk estimates for nonfatal myocardial infarction on average 58% greater (95% CI 26% to 98%) than those for fatal myocardial infarction.

Authors' conclusions
NSAID usage increased the risk of non-fatal myocardial infarction with no substantial effect on fatal events.

CRD commentary
This review answered a clearly defined research question. Some attempts were made to reduce risks of publication and language biases; however, the limited number of resources searched meant that the risk of bias could not be ruled out. Without further details of the search terms used to retrieve studies it would be difficult to reproduce the search strategy. Some attempt was made to reduce the risk of reviewer error and bias when extracting study data; it was unclear whether similar precautions were taken when selecting studies for inclusion. The methodological quality of the studies was not assessed and so data reliability was unclear. Inherent methodological problems associated with observational studies meant that data from these studies were likely to be less reliable.

Differences in study design made use of separate analyses to pool different study designs appear appropriate. There was evidence of variation across all of the included studies, especially for characteristics of the study populations. Some attempts were made to investigate potential sources of heterogeneity, although there were insufficient data to carry out all of the planned analyses.

The authors’ conclusions appeared reliable, but a cautious interpretation is advised given the limitations of the study data and some potential limitations of the review methods.

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

Research: The authors stated that further studies were required to investigate the coronary risk associated with NSAID use and the specific mechanisms involved. Studies should include genetic and epigenetic markers and to identify specific patient groups at highest risk.

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Bibliographic details
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.