Non-steroidal anti-inflammatory drugs and cardiac failure: meta-analyses of observational studies and randomised controlled trials

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CRD summary
This review concluded that non-steroidal anti-inflammatory agents (NSAIDS) increased the risk of cardiac failure, but that the overall risk was low. The risks were similar for conventional NSAIDs and Cox-2 specific non-steroidal anti-inflammatory drugs (COXIBs). There were some methodological problems with the review and these conclusions should be treated with some caution.

Authors' objectives
To assess the risk of cardiac failure in people taking non-steroidal anti-inflammatory drugs, including the risk with Cox-2 specific non-steroidal anti-inflammatory drugs.

Searching
MEDLINE, EMBASE, CINAHL and the Cochrane Library were searched from January 1997 to March 2008. Search terms were reported. Reviews and published bibliographies were checked. Only peer reviewed papers published in English were eligible for inclusion.

Study selection
Randomised controlled trials (RCTs) or observational studies that reported on the effects of non-steroidal anti-inflammatory drugs (NSAIDS) or Cox-2 specific non-steroidal anti-inflammatory drugs (COXIBs) in people with arthritis or non-rheumatic diseases were eligible for inclusion. Included studies were required to contain sufficient information to evaluate the presence of frequency of cardiac failure.

Three types of studies were included: RCTs that compared NSAIDs (including COXIBs) (celecoxib, rofecoxib, naproxen) with placebo in people with colonic adenomas, Alzheimer's disease or raised prostate specific antigen (PSA); RCTs that compared COXIBs (rofecoxib, celecoxib, etoricoxib, lumiracoxib, etoricoxib) with traditional NSAIDs (diclofenac, ibuprofen, naproxen) or placebo in people with arthritis; case control or retrospective cohort studies that included control groups or cohorts where differences between conventional NSAIDs or COXIBs were assessed.

In the included studies, lowest ages of participants ranged from 18 to 70 years. Some studies excluded people with pre-existing cardiac failure. The measures of heart failure appeared to vary between studies and included in-patient and out-patient occurrences, first or any admission.

Two reviewers independently assessed studies for inclusion, disagreements were resolved by consensus.

Assessment of study quality
The quality of RCTs was assessed using the Jadad 5 point quality assessment scale.

The authors did not state how the validity assessment was performed.

Data extraction
In RCTs and case control studies odds ratios were calculated. In cohort studies relative risks were calculated.

Two reviewers extracted data independently. Disagreements were resolved by consensus.

Methods of synthesis
For RCTs pooled Peto odds ratios were calculated; for observational studies pooled odds ratios (case control studies) or relative risks (cohort studies) were calculated using DerSimonian and Laird's random-effects model.
Heterogeneity was assessed using I\(^2\) test and Cochran's X\(^2\) test. Significance value of P was set at less than 0.05. Possible causes of heterogeneity were discussed.

### Results of the review

Twenty one studies (343,280 participants) were included. Six RCTs were placebo controlled randomised controlled trials (RCTs) and six RCTs compared Cox-2 specific non-steroidal anti-inflammatory drugs (COXIBs) to conventional non-steroidal anti-inflammatory drugs (NSAIDs). No RCTs directly compared COXIBs and non-steroidal anti-inflammatory drugs in non-rheumatic diseases. All RCTs scored 4 or 5 (out of 5) for quality. Nine observational studies were included, of which five were case control studies and four were cohort studies. All of the included studies were funded (or partly funded) by pharmaceutical companies.

**RCTs for non-rheumatic diseases** (6 RCTs, 15,778 participants): People taking non-steroidal anti-inflammatory drugs (NSAIDs) for non-rheumatic diseases were more likely to develop cardiac failure compared to placebo, 40 events with NSAIDs and 13 with controls (odds ratio 2.31, 95% Confidence Interval (CI): 1.34 to 4.00). There was no evidence of heterogeneity.

**RCTs for rheumatic diseases** (six RCTs, 62,954 participants): There was no difference between Cox-2 specific non-steroidal anti-inflammatory drugs (COXIBs) and conventional NSAIDs in people with arthritis (odds ratio 1.14, 95% CI: 0.85 to 1.53). There was evidence of heterogeneity, which the authors suggested may in part have been caused by one study with differing methodology. The numbers of events was low; 95 in COXIBs group and 82 in NSAIDs group (this included only six events in three of the trials). The largest of the trials (34,701 participants) showed an increased risk with etoricoxib compared to diclofenac (odds ratio 1.65, 95% CI: 1.11 to 2.44).

**Case control studies** (five studies, 61,574 participants): The studies showed an association between non-steroidal anti-inflammatory drugs (NSAIDs) compared to controls and cardiac failure although this did not reach statistical significance (odds ratio 1.36, 95% CI: 0.99 to 1.85). There was significant heterogeneity. The authors stated that this was caused by one study which excluded people with existing heart failure, and that the four other studies all showed a significant association. There was no association of cardiac failure with use of conventional NSAIDs or celecoxib, but there was an association with use of rofecoxib (see paper for details).

**Cohort studies** (four studies, 202,974 participants): The use of non-steroidal anti-inflammatory drugs (NSAIDs) compared to unexposed controls increased the risk of cardiac failure (relative risk 1.97, 95% CI: 1.73 to 2.25; two studies). There was no evidence of heterogeneity. There was no difference in risk with use of rofecoxib (one study) and celecoxib (one study), compared to conventional NSAIDs (see paper for data).

### Authors' conclusions

Non-steroidal anti-inflammatory drugs increased the risk of heart failure. However, the overall risk was relatively small and was similar with conventional non-steroidal anti-inflammatory drugs and Cox-2 specific non-steroidal anti-inflammatory drugs.

### CRD commentary

The inclusion criteria for this review were only partly stated. In particular, the outcome measures for heart failure were not defined. A number of relevant databases were searched, but unpublished studies or those published in languages other than English were not eligible for inclusion (although the authors say that no study was excluded because of language). It is possible that studies were missed and this could affect the results of the review. Although the process of quality assessment of RCTs was not described study selection, data extraction was conducted in a way likely to reduce the introduction of reviewer bias.

The quality of observational studies did not appear to have been assessed, so it is not possible to comment on the validity of data from these studies. Also, it should be noted that data from observational studies is not considered to be as reliable as that from RCTs. When pooling data, studies were grouped according to study design. This was appropriate, as were the methods of pooling data. Heterogeneity was assessed. Where heterogeneity was identified, the authors, whilst suggesting that particular studies were responsible, did not formally investigate this.
Little information was included about the participants in the included studies. This could affect the generalisability of the results. All of the included studies were funded (or partly funded) by pharmaceutical companies. Overall, the authors conclusions should be treated with some caution, in particular the evidence relating to the comparison of Cox-2 specific non-steroidal anti-inflammatory drugs to conventional non-steroidal anti-inflammatory drugs was not convincing.

Implications of the review for practice and research

Practice: The authors stated that non-steroidal anti-inflammatory drugs should be used with caution in those with, or at high risk of developing, cardiac failure.

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

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