

RAPID APPRAISAL

Name of Trial: Cardiovascular Risk and Inhibition of Cyclo-oxygenase: A Systematic Review of the Observational Studies of Selective and Non-selective Inhibitors of Cyclo-oxygenase 2

Reference: JAMA 2006; 296 (doi:10.1001/jama.296.13.jrv60011)¹

Question: What are the serious cardiovascular risks with individual non steroidal anti inflammatory drugs and cyclo-oxygenase 2 inhibitors?

Summary: This meta-analysis of 23 studies found that the risk of cardiovascular events was higher with rofecoxib than celecoxib. There is no information given on the relative safety of the newer Cox-II inhibitors such as etoricoxib and lumiracoxib, or etodolac. When compared with other non-selective NSAIDs, naproxen was associated with a lower cardiovascular risk. Diclofenac was shown to have the highest risk of the non-selective NSAIDs, with a relative risk similar to that of rofecoxib, but there is not enough evidence based on this analysis alone to change practice. It is also important when prescribing an NSAID, that the gastrointestinal (GI) risk is considered, with ibuprofen having the lowest risk of GI toxicity. All anti-inflammatory medicines should be used where there is a clear indication at the lowest possible dose and for the shortest possible period necessary to control symptoms.

Did the study ask a clearly focussed question?

Yes - The main objective of this study was to ascertain the risks of serious cardiovascular events (acute myocardial infarction [MI] or sudden cardiovascular death) with both Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and Cyclo-oxygenase-II (Cox-II) inhibitors.

Did the authors look for the appropriate sort of papers?

Yes – Studies were deemed as being eligible for inclusion if they were controlled (either case control or cohort) and they reported cardiovascular risks associated with selective Cox-II inhibitors or conventional NSAIDs in population settings. Non-use or remote exposure was the reference source for calculating relative risk (RR).

Were the important relevant studies included?

Yes - A systematic review and meta-analysis returned 7,086 potentially relevant articles. After application of inclusion and exclusion criteria; 17 case control and 6 cohort studies were included in the review. Of these 23 studies, all included NSAIDs and 13 included Cox-II inhibitors. Eligible studies reported on cardiovascular events (mainly MI) with Cox-II inhibitor, NSAID use or both with non-use/remote use of the drugs as the reference exposure. Most studies were excluded because information was not provided on study outcomes or the drugs of interest.

Many of the studies included did not take account of purchased aspirin or other NSAIDs which may have confounded the results; information on smoking, hypertension and raised cholesterol was

also not included, which may also have confounded the results.

Since this systematic review was submitted, a further trial has been published of the risks of hospitalization with MI and the use of NSAIDs.² This study was not included in this systematic review, but it was reviewed post publication to determine if the new data would change the results or conclusions of this study. Analyses were re-run including the new data, giving revised summary RR estimates, which were stated by the authors as not affecting the original conclusions of the systematic review.

Was the quality of the studies assessed?

Yes – Methodological quality was assessed using an established instrument which assessed case control studies in terms of methods of selection of cases and controls, comparability of cases and controls and ascertainment of exposure to the respective drug. The cohort studies were assessed in terms of selection of the exposed and non-exposed cohorts, comparability of the cohorts and outcomes ascertainment. A scoring system was devised, and studies scored consistently well across the categories, apart from those reported only as abstracts. The data was independently extracted and assessed by two reviewers with any disagreements resolved by consensus.

Was it reasonable to combine the results of the review?

Yes – Details of the structures of each of the cohort and case control studies are clearly shown, and relative risks and point estimates are shown for each of the 23 trials.

The main outcome in all of the studies was either MI or sudden cardiovascular death.

Studies that reported on selective Cox-II inhibitors included celecoxib, rofecoxib or meloxicam. Studies that reported on NSAIDs included mainly ibuprofen, diclofenac, naproxen, indomethacin and piroxicam. All studies reported adjusted estimates of risk for cardiovascular events. Factors that were adjusted for included age, sex, cardiovascular risk factors and use of cardiac medications. Many also adjusted for co-morbidity.

The summary RR estimates from the case-control and cohort analyses were similar. Chi-squared tests for heterogeneity were completed - between-study heterogeneity in the RR estimates was statistically significant, but in quantitative terms, were modest. Possible causes of between-study heterogeneity included the different ages and levels of baseline risks of the study populations, and the variety in the ingested doses of drugs. The range of individual study estimates of RRs was not massive, and the large size of the individual studies led to precise RR estimates. This meant that any small differences between them were statistically highly significant.

What is the overall result of the review?

The data contained in this systematic review confirm that there is a higher risk of cardiovascular events with rofecoxib, and this is even more apparent at higher doses $\geq 25\text{mg/day}$. Celecoxib does not appear to present an increased risk of cardiovascular events for doses around 200mg/day but an increased risk could not be excluded at higher doses. Naproxen is also not associated with an increased risk of cardiovascular events, but neither is it associated with a risk reduction, as reported previously in the VIGOR trial.³ Of the non-selective NSAIDs, the highest risk of cardiovascular events was seen with diclofenac followed by indomethacin; with a similar RR to rofecoxib in this review. An increased risk was not seen with ibuprofen or piroxicam.

How precise are the results?

COX-2 Inhibitors

Rofecoxib was included in a total of 11 trials, and the summary RR for cardiovascular events was 1.35 (95% Confidence Interval [CI]; 1.15 to 1.59). A difference in RR was seen in dosages below and above 25mg/day . The RR for $\leq 25\text{mg/day}$ was 1.33 (1.00-1.79) but for $\geq 25\text{mg/day}$ was 2.19 (1.64 to 2.91). Celecoxib, was included in 11 trials, however did not lead to a higher risk of cardiovascular events, with an overall RR of 1.06 (95% CI; 0.91 to 1.23). Meloxicam was included in 3 studies, of which 1 reported a raised vascular risk. The summary RR was 1.25 (95% CI; 1.00 to 1.55).

NSAIDs

Ibuprofen and / or naproxen were included in 16 studies, diclofenac in 9, and indomethacin in 6 and

piroxicam in 4. The summary RR for naproxen was 0.97 (95% CI; 0.87 to 1.07), and ibuprofen RR was 1.07 (95% CI; 0.97 to 1.18) and piroxicam RR was 1.06 (95% CI; 0.70 to 1.59). There was an increased risk of cardiovascular events with both diclofenac RR 1.40 (95%CI; 1.16 to 1.70) and indomethacin RR 1.30 (95% CI; 1.07 to 1.60).

There were a number of other analyses reported, e.g. risk with early use of selective Cox-II inhibitors, and effects of aspirin use. These were not the overall aims of the systematic review and as such the review was not powered to accurately assess these questions.

Can the results be applied to the local population?

The trial populations originated from Great Britain, USA, Australia, The Netherlands, Denmark and Canada, therefore in geographical terms, the data is applicable to a British population. It is likely, that the results could be applied to Great Britain; however the result might not be as applicable to different ethnic populations, for example people of Asian origin. As many of the studies failed to take account of the consumption of over the counter aspirin and NSAIDs, it is unclear how applicable the results would be to patients who purchase these medications. It is also unclear how applicable the results are to patients who smoke, have hypertension or raised cholesterol, as information on these conditions was not included.

Were all important outcomes considered?

Yes – The discussion surrounding cardiovascular safety of both Cox-II inhibitors and NSAIDs is ongoing, and advice has been variable. A full evaluation of the cardiovascular safety of these drugs is important from both the perspectives of the patients and clinicians.

Should policy or practice change as a result of the evidence contained in this review?

Following the withdrawal of rofecoxib in 2004, celecoxib is the Cox-II inhibitor with the largest spend. Whilst doses at or below 200mg per day appear to have no increased risk, there is uncertainty for higher doses. Given the dose related incidence of cardiovascular events in both Cox-II inhibitors included in this systematic review, it may be wise to use the minimum dose possible of other Cox-II inhibitors until this relationship can be studied further. Cox-II inhibitors studied only included rofecoxib, celecoxib and meloxicam, therefore no information is available on the relative safety of the newer coxibs or etodolac.

Although there does appear to be some evidence in this review that suggests a possible increased cardiovascular risk with diclofenac, there is not sufficient evidence to change practice based on the results from this review alone.

The evidence is insufficient to change the balance of risks and benefits of non-selective NSAIDs and no changes to current practice have yet been recommended.

The situation regarding high risk patients who are stable and controlled on diclofenac, and whether they should have their treatment amended, is still unclear. Whilst it is important to be aware of the increased cardiovascular risks highlighted by this trial with diclofenac, stability of the patient and their long term pain control must be taken into account. Gastrointestinal risk is still an important consideration when selecting a suitable NSAID, and ibuprofen has a low risk of GI toxicity and should usually be the agent of first choice.

Simple analgesia (e.g. paracetamol, codeine) and non-drug interventions may also be appropriate for patients requiring pain relief.⁴

The European Medicines Agency is to update its previous review of the cardiovascular safety of non-selective NSAIDs (October 2005). The agency is expected to give a scientific opinion on the cardiovascular safety of non-selective NSAIDs during its next meeting in October 2006. They currently recommend that all anti-inflammatory medicines (including NSAIDs and 'coxibs) should be used at the lowest possible dose and for the shortest possible period necessary to control symptoms.⁵

REFERENCES

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