Do COX-2 inhibitors raise blood pressure more than nonselective NSAIDs and placebo? An updated meta-analysis

Chan CC, Reid CM, Aw TJ, Liew D, Haas SJ, Krum H

CRD summary
This review found higher risks of hypertension associated with use of cyclo-oxygenase (COX-2) inhibitors compared with placebo and non-steroidal anti-inflammatory drugs (NSAID). Methodological flaws and a lack of information about the quality of the included studies mean that the results should be interpreted with a substantial degree of caution.

Authors' objectives
To evaluate the effect on blood pressure of cyclo-oxygenase (COX-2) inhibitors compared to non-selective non-steroidal anti-inflammatory drugs (NSAID) and placebo medications in patients with comorbidities other than arthritis.

Searching
MEDLINE and Cochrane Database of Systematic Reviews were searched from inception to April 2008 for published English-language studies; search terms were reported. Reference lists from retrieved studies were checked for additional studies.

Study selection
Randomised controlled trials (RCTs) that evaluated the effects of COX-2 inhibitors on systolic and diastolic blood pressure in patients with comorbidities other than arthritis were eligible for inclusion. Studies with treatment durations of less than four weeks or that enrolled fewer than 50 patients were excluded.

Most of the included studies comprised patients with arthritis; other studies enrolled patients with colorectal adenoma, Alzheimer's Disease, hypertension, lower back pain, elevated prostate-specific antigen, ankylosing spondylitis, haemophilic arthropathy and an elderly population on controlled salt diets. COX-2 inhibitors used in the trials were celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib. Placebo was the most commonly used comparator. The most commonly used NSAID was naproxen; other NSAIDs used were diclofenac and ibuprofen. Principal endpoints evaluated were mean changes from baseline to the end of the study period and incidence of hypertensive events.

The authors did not state how the study selection was performed.

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

Data extraction
Data were extracted by one author to calculate risk ratio (RR) estimates with corresponding 95% confidence intervals (CI) for the development of hypertension. Weighted mean differences in systolic and diastolic blood pressure were calculated.

Methods of synthesis
Pooled risk ratios and 95% CIs were calculated using a DerSimonian and Laird random-effects model. Subgroup analyses were conducted by type of COX-2 inhibitor type and the presenting condition of the patients.

Results of the review
Fifty-one trials (n=130,405) were included in the review. Most of the patients had arthritis. Trials ranged in size from 67 to 23,498 patients. Mean age of patients ranged from 35 to 75. Study duration ranged between four and 208 weeks.

There were significantly higher risks of patients developing hypertension after administration of COX-2 inhibitors compared to placebo (RR 1.49, 95% CI 1.18 to 1.88). In a subgroup analysis by type of COX-2 inhibitor, increased risks of hypertension were observed with use of rofecoxib (RR 1.87, 95% CI 1.63 to 2.14) and etoricoxib (RR 1.1, 95%
CI 0.7 to 1.75) compared to placebo. There were no significant differences in risk between the remaining COX-2 inhibitors and placebo for hypertension.

For the comparison between COX-2 inhibitors and NSAIDs, there were no significant differences in the risk of hypertension (RR 1.12, 95% CI 0.93 to 1.35). In a subgroup analysis by type of COX-2 inhibitor, there were higher risks of hypertension with rofecoxib (RR 1.53, 95% CI 1.34 to 1.75) and etoricoxib (RR 1.52, 95% CI 1.39 to 1.66). There was also a significant increased risk associated with use of COX-2 inhibitors compared to the NSAID naproxen (RR 1.31, 95% CI 1.08 to 1.60). There were no significant differences in risk between the remaining COX-2 inhibitors and NSAIDs for hypertension.

**Authors' conclusions**
Use of COX-2 inhibitors was associated with more hypertension than use of NSAIDs and placebo medications. In particular, marked increases in blood pressure was observed with use of rofecoxib and etoricoxib; other COX-2 inhibitors had little effect on blood pressure.

**CRD commentary**
The review addressed a clear question. Inclusion criteria were outlined. Appropriate electronic databases were searched, but the restriction to English-language studies meant there were risks of language biases. Only peer-reviewed published studies were included, which meant there was a risk of publication bias. No reported steps to minimise errors and bias were taken at any stage of the review process. There was no formal assessment of methodological quality of the included trials. No evaluation of statistical heterogeneity was undertaken, although in anticipation of heterogeneity the authors used a random-effects model to pool results from the trials. The appropriateness or otherwise of pooling results across clinically heterogeneous populations was unclear.

Although the conclusions reflected the evidence presented, flaws in the conduct of the review made the authors' conclusions unlikely to be reliable and the results of the review should be interpreted with a substantial degree of caution.

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

**Research**: The authors stated that further research was required to establish whether increases in blood pressure due to the use of COX-2 inhibitors and NSAIDs were linked to increases in myocardial infarction and strokes observed in populations that received these medications.

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