Cardiovascular risk of celecoxib in 6 randomized placebo-controlled trials: the Cross Trial Safety Analysis


CRD summary
This review concluded that the risk of experiencing a cardiovascular event was greater with higher doses of celecoxib and with a greater underlying risk of such events. Despite some limitations in the review, the conclusion seems reliable for the populations evaluated in the trials, but might not be generalisable to populations treated with celecoxib on a long-term basis.

Authors' objectives
To assess the cardiovascular risk associated with long-term celecoxib treatment and the relationship between the cardiovascular risk before treatment and the effect of celecoxib on cardiovascular events.

Searching
The authors searched public literature (details not provided), and contacted the National Institutes of Health and Pfizer to identify unpublished trials.

Study selection
Randomised controlled trials (RCTs) of celecoxib, compared with placebo, were eligible for inclusion if they planned to follow-up each patient for at least three years. The primary outcome was the composite of cardiovascular death, myocardial infarction, stroke, heart failure, and a thromboembolic event. Analyses were conducted on cardiovascular deaths and other composites of two or more of the outcomes.

The trials used celecoxib for the prevention of colorectal adenoma or colonic polyp recurrence, to treat postmenopausal women with breast cancer, or to attenuate age-related cognitive decline and prevent Alzheimer's disease. None of the trials evaluated celecoxib for patients with arthritis and all the doses evaluated were higher than those used for patients with osteoarthritis. The mean age ranged from 59 to 75 years, and the percentage of patients who were male ranged from zero to 68. One trial was restricted to patients with diabetes, while the other trials had 10% or fewer patients with diabetes. Hypertension was present in 34% to 62% of patients, and 27% to 100% were at a high risk of cardiovascular events (Framingham Heart Study risk factors). The dose of celecoxib was 200mg twice daily or 400mg once or twice daily. The comparators were exemestane, anastrozole, naproxen sodium, and selenium, as well as placebo. Most trials stratified randomisation by low-dose aspirin use. The planned follow-up ranged from three to seven years.

The authors did not state the number of reviewers involved in selecting trials.

Assessment of study quality
Only trials reported as being double blind were included. The research teams, who had undertaken the trials, produced summaries of all the possible cardiovascular or cerebrovascular events; two clinicians with relevant experience judged these according to set end-point definitions. They were masked to treatment allocation and categorised events as definite, probable, or possible. Research trialists were not involved in the verification or checking of data.

Data extraction
Patient-level data was obtained. The incidences of cardiovascular death, non-fatal myocardial infarction, stroke, heart failure, and thromboembolic events were extracted. Hazard ratios, odds ratios, and their 95% confidence intervals were calculated.

Methods of synthesis
The hazard ratio and 95% confidence interval were calculated for each composite risk, with all doses of celecoxib, and for each dose separately, from Kaplan-Meier curves constructed using Cox models; these were stratified by study-specific variables. The pooled odds ratio and 95% confidence interval were calculated, using the Mantel-Haenszel
method and a Cox model stratified by study and baseline aspirin dose. The primary analysis included those events that were judged to be definite and used an intention-to-treat population. A cardiovascular risk score was used to determine the baseline risk, and a Cox model stratified by study was used to investigate the relationship between cardiovascular risk and celecoxib use.

**Results of the review**

Six trials met the inclusion criteria (n=7,950 patients, with 16,070 years of patient follow-up, range 101 to 6,234) and individual patient data were retrieved for all six trials. The median follow-up ranged from 5 to 37 months.

For the composite of cardiovascular death, myocardial infarction, stroke, heart failure, and thromboembolic events, the overall pooled hazard ratio was 1.6 (95% CI 1.1 to 2.3). For celecoxib 400mg once daily the hazard ratio was 1.1 (95% CI 0.6 to 2.0), for 200mg twice daily the hazard ratio was 1.8 (95% CI 1.1 to 3.1), and for 400mg twice daily the hazard ratio was 3.1 (95% CI 1.5 to 6.1).

For cardiovascular death, the pooled hazard ratio was 0.5 (95% CI 0.2 to 1.7) for 400mg daily, 1.7 (95% CI 0.6 to 4.9) for 200mg twice daily, and 2.7 (95% CI 0.7 to 10.2) for 400mg twice daily. For any cardiovascular event (including angina, etc), the pooled hazard ratio was 1.3 (95% CI 0.9 to 2.0) for 400mg daily, 1.3 (95% CI 1.0 to 1.7) for 200mg twice daily, and 1.6 (95% CI 1.1 to 2.3) for 400mg twice daily. The event rates increased with increasing baseline cardiovascular risk.

**Authors’ conclusions**

Evidence of differential cardiovascular risk as a function of celecoxib dose and baseline cardiovascular risk was found.

**CRD commentary**

The authors addressed a clear review question with appropriate inclusion criteria. The full search strategy was not reported, which makes it unclear whether all eligible trials were identified. It was unclear whether trial selection was conducted in duplicate, and reviewer error and bias cannot be ruled out. The data were verified independently and appropriate methods of synthesis were used.

Despite some limitations, the conclusion seems reliable for the populations evaluated in the trials, but it might not be generalisable to populations treated with celecoxib on a long-term basis.

Research support received from Pfizer, manufacturer of celecoxib, and three of the trials received support from Pfizer.

**Implications of the review for practice and research**

**Practice:** The authors stated that the findings will guide rational clinical decisions on celecoxib use.

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

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