

# Review: Studies on the cardiovascular effects of selective COX-2 inhibitors show mixed results

Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA. 2001 Aug 22/29;286:954-9.

## QUESTION

In patients with arthritis, do rofecoxib or celecoxib increase the risk for cardiovascular events?

## DATA SOURCES

Studies were identified by searching MEDLINE (1998 to February 2001) and the Internet. The Adverse Events Reporting System was searched for U.S. events on 12 October 2000.

## STUDY SELECTION

English-language studies were selected if they were randomized, double-blind, controlled trials reporting the cardiovascular effects of celecoxib or rofecoxib.

## DATA EXTRACTION

Data were extracted on study methods, patient characteristics, drug regimens, aspirin use, and cardiovascular events.

## MAIN RESULTS

4 studies met the selection criteria. The Vioxx Gastrointestinal Outcomes Research study compared rofecoxib, 50 mg/d, with naproxen, 1000 mg/d, in 8076 patients with rheumatoid arthritis. Aspirin use was not permitted. Patients in the rofecoxib group had an increased risk for cardiovascular events {relative risk increase 138%, 95% CI 39 to 300; number needed to harm 146, CI 69 to 517}\*.

The Celecoxib Long-term Arthritis Safety Study (CLASS) compared celecoxib, 400 mg twice daily; ibuprofen, 800 mg 3 times daily; and diclofenac, 75 mg twice daily, in 8059 patients with osteoarthritis or rheumatoid arthritis. Patients were allowed to take aspirin (< 325 mg/d). Celecoxib and nonsteroidal anti-inflammatory drugs did not differ for cardiovascular event rates. 2 studies compared rofecoxib, 12.5 mg/d; nabumetone, 1000 mg/d; and placebo for 6 weeks in 1042 and 978 patients

with osteoarthritis of the knee. Patients were allowed to take low-dose aspirin. In both studies, the groups did not differ for cardiovascular event rates.

## CONCLUSIONS

Compared with other nonsteroidal anti-inflammatory drugs (NSAIDs), highly cyclooxygenase-2-selective NSAIDs seem to increase the risk for cardiovascular thrombotic events in patients who are not taking aspirin.

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\*Numbers calculated from data in article.

## COMMENTARY

Platelet cyclooxygenase (COX)-1 is a main source of the potent vasoconstrictor and platelet aggregator  $\text{TxA}_2$ . Macrovascular endothelial COX-2 is a main source of the potent vasodilator and platelet inhibitor  $\text{PGI}_2$  (1). Thus, one might well have predicted that the highly COX-2-selective inhibitor rofecoxib would increase the risk for thrombosis. In an ex vivo assay in human whole blood, celecoxib was less COX-2-selective than rofecoxib, etodolac, or meloxicam and only slightly more selective than nimesulide (2).

The clinical research to date confirms the available basic research. Compared with nonselective NSAIDs, rofecoxib slightly decreases the risk for gastrointestinal (GI) hemorrhage but increases the risk for thrombosis. The most important celecoxib study (CLASS) (3) is now mired in controversy because of the publication of the more favorable 6-month data instead of the less favorable 12-month outcomes. Celecoxib's failure to decrease GI events and failure to increase vascular events relative to ibuprofen or diclofenac could be explained by either the co-administration of aspirin allowed in CLASS or by its relatively modest COX-2 selectivity.

The concomitant use of aspirin, even at low doses, may largely negate the GI safety advantage of COX-2-selective NSAIDs. Additionally, some NSAIDs (e.g., ibuprofen) seem to inhibit the protective effects of aspirin, whereas others (e.g., diclofenac and rofecoxib) do not (4). The current well-supported and widespread use of aspirin

may increase depending on the results of the Aspirin in Asymptomatic Atherosclerosis Trial and other studies currently being done.

Physicians should continue to prescribe aspirin for secondary prevention of vascular events, with the understanding that patients who need aspirin will probably derive no safety advantage from COX-2-selective NSAIDs. Until additional pharmacodynamic studies and large clinical trials determine the clinical importance of its prothrombotic effects, rofecoxib should be avoided.

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## References

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