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## CLINICAL UPDATE

# COX-2 inhibitors and gastrointestinal toxicity

**Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al, for the VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis.** ***N Engl J Med*** **2000;343:1520-8.**

***Background:*** Although selective cyclooxygenase-2 (COX-2) inhibitors are not superior to equivalent doses of nonselective NSAIDs for treating arthritis, they are popular as a first-line therapy because of a lower incidence of gastrointestinal mucosal injury.[1,2]

***Question:*** Is rofecoxib therapy associated with fewer episodes of symptomatic gastrointestinal toxicity than naproxen in patients with rheumatoid arthritis?

***Design:*** This double-blind, multicentre, randomized trial compared the gastrointestinal toxicity of rofecoxib and naproxen in 8076 patients with rheumatoid arthritis who were expected to require treatment with NSAIDs for at least 1 year. Eligible patients were at least 50 years of age (or at least 40 if receiving long-term glucocorticoid therapy) and did not have a history of significant comorbid medical conditions such as renal failure, cancer (within the past 5 years), recent coronary artery bypass surgery or myocardial infarction. Patients taking anticoagulants, antiplatelet agents, proton-pump inhibitors, misoprostol or prescription-dose histamine $H_2$-receptor antagonists were also excluded. After stratification for prior history of gastroduodenal ulcer and its complications, patients were randomly assigned to receive either 50 mg of rofecoxib once daily or 500 mg of naproxen twice daily. The primary outcome measure was the incidence of confirmed upper gastrointestinal events, including symptomatic gastric and duodenal ulcers and their complications (bleeding, perforation and obstruction). An independent committee, blinded to the treatment status of the patients, used prespecified criteria to determine whether a study end point had occurred. Functional status and the Global Assessment of Disease Activity scale were used to assess the efficacy of the regimens in treating underlying rheumatoid arthritis. The study was supported by a grant from Merck, which manufactures Vioxx (rofecoxib).

***Results:*** Most of the subjects were late middle-aged white women (mean age 58 years) who had had rheumatoid arthritis for at least 2 years. Most of the patients had used NSAIDs, and about half were taking either glucocorticoid medication or methotrexate at baseline. Few (7.8%) had a prior history of upper gastrointestinal events. Rofecoxib and naproxen were equally efficacious in the treatment of rheumatoid arthritis. About 30% of the patients in each group stopped the study medication because of adverse effects or lack of efficacy.

Of the 177 patients with confirmed upper gastrointestinal events over a median follow-up of 9 months, 56 were in the rofecoxib group and 121 in the naproxen group (relative risk 0.5, 95% confidence interval [CI] 0.3–0.6, $p < 0.001$). Only 16 of the 53 patients with confirmed complicated events (perforation, obstruction and severe bleeding) were in the rofecoxib group (relative risk 0.4; 95% CI 0.2–0.8, $p = 0.005$). Significant reductions in the incidence of gastrointestinal events occurred in subgroups with and without a prior history of gastrointestinal events. Patients positive for *Helicobacter pylori* at baseline were more likely than those who were *H. pylori* negative to have gastrointestinal events. The incidence of myocardial infarction was significantly lower in the naproxen group than in the rofecoxib group (relative risk 0.2, 95% CI 0.1–0.7).

***Commentary:*** This study demonstrated a significantly lower incidence of symptomatic gastrointestinal events among patients treated with rofecoxib than among those given naproxen. As the authors suggest, the antiplatelet effects of naproxen and the fact that several patients with clear cardiovascular indications for ASA were not taking this medication probably contributed to the higher incidence of myocardial infarction in the rofecoxib group. When patients with an indication for ASA were excluded from the analysis, the incidence of myocardial infarction was not significantly different between the 2 groups.

***Practice implications:*** This study's finding of a lower incidence of symptomatic gastrointestinal events among patients taking rofecoxib than among those given naproxen is consistent with the results of another recently published randomized trial comparing celecoxib with 2 nonselective NSAIDs.[3] The absolute risk reduction is such that only 41 patients would need to be treated with rofecoxib (as opposed to naproxen) for 1 year to prevent 1 symptomatic upper gastrointestinal event. To date, no published studies have compared COX-2 inhibitors with standard practice using NSAIDs in combination with misoprostol or proton-pump inhibitors for the prevention of gastrointestinal toxicity. Given the costs involved, a pharmacoeconomic analysis comparing such strategies is needed. — *Kathryn A. Myers*

The Clinical Update section is edited by Dr. Donald Farquhar, head of the Division of Internal Medicine, Queen's University, Kingston, Ont. The updates are written by members of the division.

### References

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