# Upper gastrointestinal event risk with COX-2 inhibitors depended on known risk factors

Laine L, Bombardier C, Hawkey CJ, et al. **Stratifying the risk of NSAID-related upper gastrointestinal clinical events: results of a double-blind outcomes study in patients with rheumatoid arthritis.** Gastroenterology. 2002;123:1006-12.

### QUESTION

Which groups of patients with rheumatoid arthritis (RA), have gastrointestinal (GI) events while taking rofecoxib or naproxen?

### DESIGN

Randomized {allocation concealed*}†, blinded {clinicians, patients, data collectors, outcome assessors, and data analysts}†,* placebo-controlled trial with median 9-month follow-up.

### SETTING

301 centers in 22 countries.

### PATIENTS

8076 patients who were ≥ 50 years of age or ≥ 40 years and receiving corticosteroids, had RA, and were expected to require nonsteroidal antiinflammatory drugs (NSAIDs) for ≥ 1 year. Exclusion criteria included use of aspirin or other antiplatelets, anticoagulants, misoprostol, sucralfate, proton pump inhibitors, and prescription-strength histamine-2–receptor antagonists. All patients were included in the analysis.

### INTERVENTION

Patients were allocated to rofecoxib, 50 mg daily ($n$ = 4047), or naproxen, 500 mg twice daily ($n$ = 4029). Patients received matching placebos for each study medication.

### MAIN OUTCOME MEASURES

Clinical upper GI events (bleeding, perforation, obstruction, and symptomatic ulcers). The secondary endpoint was complicated upper GI events (perforation, obstruction, and major bleeding).

### MAIN RESULTS

Analysis was by intention to treat. Fewer patients who received rofecoxib than naproxen had clinical upper GI events (relative risk reduction [RRR] 54%, 95% CI 36 to 66; number needed to treat [NNT] 41) and complicated upper GI events (RRR 57%, CI 22 to 76; NNT 128). The strongest risk factors for clinical upper GI events were previous upper GI complications (630 patients [7.8%]) (RR 3.73, CI 2.25 to 6.17), age ≥ 75 years (410 patients [5%]) (RR 3.87, CI 2.41 to 6.22), and severe RA (146 patients [1.8%]) (RR 2.27, CI 1.10 to 4.79). The effect of rofecoxib did not change across risk factor subgroups (RR range 0.30 to 0.68 compared with naproxen) but the absolute risk reductions were higher in patients with risk factors than in those without. The NNT was most favorable among high-risk subgroups of patients (Table).

### CONCLUSION

Patients with rheumatoid arthritis taking rofecoxib still had frequent upper gastrointestinal events, but more events were avoided in high-risk patients taking rofecoxib than in those taking naproxen.

*Source of funding: Merck and Co.*

*For correspondence: Dr. L. Laine, University of Southern California School of Medicine, Los Angeles, CA, USA. E-mail llaine@usc.edu.* ■

*See Glossary.

†Information provided by author.

**Rofecoxib vs naproxen to prevent clinical upper gastrointestinal (GI) events in rheumatoid arthritis at median 9 months‡**

| Risk factors | Rate per 100 patient-y | | RRR (95% CI) | NNT in 1 y |
|---|---|---|---|---|
| | Rofecoxib | Naproxen | | |
| Previous upper GI events | 5.24 | 13.54 | 61% (5 to 84) | 12 |
| No previous upper GI events | 1.72 | 3.67 | 53% (33 to 67) | 51 |
| Age ≥ 75 y | 4.51 | 14.46 | 69% (15 to 88) | 10 |
| Age < 65 y | 1.64 | 3.15 | 48% (21 to 66) | 66 |
| Baseline steroid use | 2.11 | 5.67 | 63% (44 to 75) | 28 |
| No baseline steroid use | 2.03 | 2.97 | 32% (–15 to 59) | 106§ |

‡Abbreviations defined in Glossary.

§Not significant.

## COMMENTARY

The risk for serious GI complications from NSAIDs is known to be greater in certain at-risk groups, such as elderly persons and those with serious chronic diseases. This is because their background risk is high, so the additional effect of NSAIDs results in a greater excess risk. Until now, the belief that the relative safety of cyclooxygenase 2 (COX-2) selective inhibitors compared with nonselective NSAIDs is greatest in such high-risk groups has been based on assumptions rather than evidence. This reanalysis by Laine and colleagues of the VIOXX Gastrointestinal Outcomes Research (VIGOR) trial comparing rofecoxib with naproxen confirms the advantage of the more selective drug in high-risk patients.

These new data are reassuring, but questions remain. The excess risk for coronary events found in the VIGOR study has recently been confirmed in a controlled observational study (1). The overall benefit-to-harm ratio of COX-2 inhibitors (compared with NSAIDs) is uncertain. It is possible that the excess coronary risk associated with rofecoxib is concentrated in the same groups that have the most to gain from the drug's relative GI safety. It is also unclear whether all COX-2 inhibitors are the same. A large observational study has found a lower risk for GI complications with celecoxib than with rofecoxib (2). Finally, even if the overall benefit-to-harm ratio with COX-2 inhibitors is superior to nonselective NSAIDs, it comes at a high price in most countries. Clinician efforts should concentrate on channeling treatment to those patients who will benefit the most. At a policy level, the COX-2 NSAIDs are often restricted to high-risk groups, but an alternative approach would be to request companies to lower their prices to a point where they represent value for money for typical users.

*David Henry, MB, ChB, FRCP*
*University of Newcastle*
*Patricia McGettigan, MD, FRACP*
*Newcastle Mater Hospital*
*Newcastle, New South Wales, Australia*

***References***

1. **Ray W, Stein MC, Daugherty JR, et al.** Lancet. 2002;360:1071-3.
2. **Mamdani M, Rochon PA, Juurlink DN, et al.** BMJ. 2002;325:624-9.

  