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


**Question**

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

**Design**

Randomized [allocation concealed]†, blind- ed [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 non-steroidal antinfiammatory drugs (NSAIDs) for ≥ 1 year. Exclusion criteria included use of aspirin or other antiplatelets, anticoagu- lants, misoprostol, sulcrate, proton pump inhib- itors, 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 sub- groups 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.

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*See Glossary.
†Information provided by author.
‡Abbreviations defined in Glossary.
§Not significant.

**Table**

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Rate per 100 patient-y</th>
<th>RRR (95% CI)</th>
<th>NNT in 1 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous upper GI events</td>
<td>5.24</td>
<td>13.54</td>
<td>61% (5 to 84)</td>
</tr>
<tr>
<td>No previous upper GI events</td>
<td>1.72</td>
<td>3.67</td>
<td>53% (33 to 67)</td>
</tr>
<tr>
<td>Age ≥ 75 y</td>
<td>4.51</td>
<td>14.46</td>
<td>69% (15 to 88)</td>
</tr>
<tr>
<td>Age &lt; 65 y</td>
<td>1.64</td>
<td>3.15</td>
<td>48% (21 to 66)</td>
</tr>
<tr>
<td>Baseline steroid use</td>
<td>2.11</td>
<td>5.67</td>
<td>63% (44 to 75)</td>
</tr>
<tr>
<td>No baseline steroid use</td>
<td>2.03</td>
<td>2.97</td>
<td>32% (15 to 59)</td>
</tr>
</tbody>
</table>

*Observations 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 re- analysis 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.

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**References**