

## Upper Gastrointestinal Complications: The Causes, Consequences, and Clinical Outcomes

### Summary

Studies reveal that cyclooxygenase (COX-2) inhibitors seem to markedly lessen the risk of ulcers and upper gastrointestinal complications. Discussion, however, continues whether COX-2 inhibitors reduce the risk of clinical events to the same degree as nonsteroidal anti-inflammatory drugs.

Many questions remain unanswered about the relationship between nonsteroidal anti-inflammatory drug (NSAID) use and gastrointestinal (GI) tract complications. Ulcer deaths increase with the age of the patient, and these deaths include an unknown number that are the result of NSAID use. Overall, NSAID-induced toxicity is associated with approximately 16,500 deaths and 107,000 hospitalizations per year in the United States.<sup>1</sup> One of the cyclooxygenase-2 (COX-2) inhibitors has been proven to reduce the risk of ulcers and GI complications.<sup>2-4</sup> It is unclear whether the reduction in risk is a class effect; this is still subject to interpretation and debate among researchers and clinicians.

### Who Is at Risk?

Several important risk factors for adverse GI events have been identified in multiple studies. These include a history of ulcer or other GI complications, increasing age, concomitant anticoagulant therapy, and concomitant corticosteroid and NSAID use. A history of ulcers or other GI adverse events may be the most

predictive for future events.<sup>5</sup> It is postulated that the baseline risk of GI complications comes from 3 main factors: platelet dysfunction in the presence of underlying GI lesions; pre-existing ulcer disease caused to recur, exacerbate, or complicate by NSAIDs; and clinical ulcers caused de novo by NSAIDs.<sup>6</sup>

### Comparison of Trials and Conclusions

Two double-blind randomized prospective outcome studies, the Vioxx GI Outcomes Research (VIGOR) trial<sup>2</sup> and the Celecoxib Long-term Arthritis Safety Study (CLASS) trial,<sup>7</sup> have addressed the question: "Do COX-2 specific inhibitors significantly decrease GI complications?" In the VIGOR trial, the answer was yes ( $P=0.005$ ); in the CLASS trial, the answer was no ( $P=0.09$ ). (This may be because of limitations in the study design or excessive dropouts. A post-hoc analysis did identify a subgroup in which risk reduction was significant.) The VIGOR trial compared the rate of GI complications in patients randomly assigned rofecoxib (50 mg qd) or naproxen (500 mg bid). Although some clinical thought is that the relative risk reductions (RRRs) for rofecoxib were comparable in both high-risk and low-risk subgroups, because only 8% of trial patients were in high-risk categories, no firm conclusions of the safety of these drugs in high-risk patients can be reached.

### Study Design, Results

Because they are COX-1 sparing drugs, COX-2 selective inhibitors do not cause decreases in platelet function, gastric

mucus production, or mucosal blood flow. The endpoints used to evaluate GI safety and tolerability in recent safety studies are either perforations, obstructions, and bleeds (POBs) or perforations, obstructions, or symptomatic ulcers and bleeds (PUBs). Death is a less instructive endpoint because there are usually many factors contributing to it, including advanced age, comorbid conditions, multiple drugs, and other risk factors.

The CLASS study consisted of 70% osteoarthritis and 30% rheumatoid arthritis patients. Patients exhibiting GI problems in the first 2 days of the trial were excluded from analysis, as were most patients with concomitant risk factors. All data beyond 6 months were also excluded from the analysis. The primary endpoint (ie, the rate of occurrence of complicated ulcers) was not significantly lower in the celecoxib group compared with the NSAID group ( $P=0.09$ ). The design limita-

tions and early closure of the CLASS study may explain why this study did not show a significant decrease in the primary endpoint. The study was powered for detecting a 75% reduction. The study permitted the use of low-dose aspirin, which affected the risk rate, especially as a higher percentage of patients used aspirin than expected (21%). Dropouts were also higher than the investigators had assumed at baseline; 57% of patients completed 6 months of therapy. And finally, the study was terminated prematurely: less than the 40 required complicated ulcer events had occurred.<sup>4,8</sup>

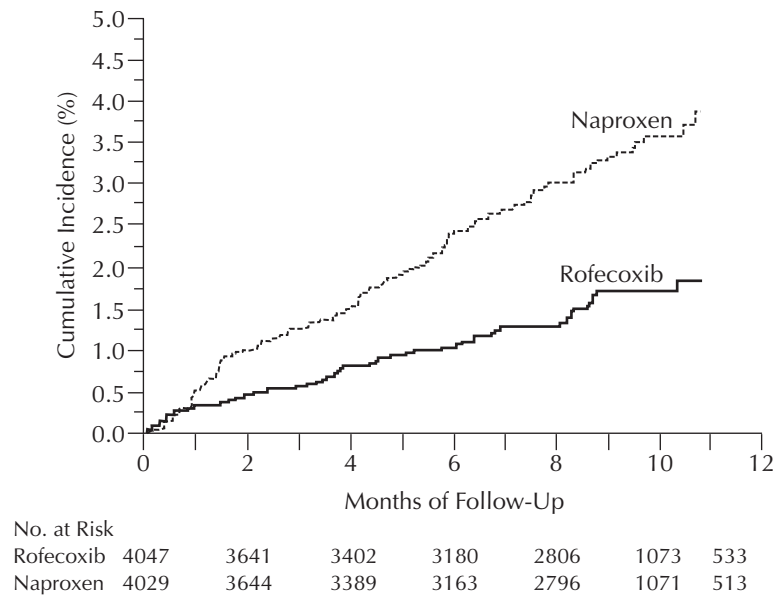
In a nonprespecified, nonaspirin taking subgroup, patients taking nonselective NSAIDs had a significantly higher rate of symptomatic ulcers or ulcer complications than did the patients taking celecoxib ( $P=0.04$ ).<sup>4,7</sup>

In contrast, the VIGOR trial consisted of 100% rheumatoid arthritis patients. No patients were excluded in the statistics because it was an intention-to-treat analysis of the entire study (median follow up of 9 months). This study monitored all serious GI side effects, regardless of the presence or absence of an ulcer. Findings from the VIGOR trial demonstrated an early reduction of risk in those on rofecoxib and significant reductions in PUBs (Figure). This reduction in PUBs is predominantly the result of a reduction in the most common component, GI bleeding. For example, there were 31 GI bleeding episodes among patients in the rofecoxib group, but endoscopy confirmed upper GI lesions in only 12 (ie, 5 gastric ulcers (GUs), 5 duodenal ulcers (DUs), and 2 other sources). There were no differences in perforations or obstructions between the 2 treatment groups. Although clinical ulcers were reduced in the rofecoxib group, it is not known whether this reduction was as a result of less exacerbation of prior peptic ulcer disease or fewer NSAID-induced ulcers.

**GI Toxicity Mechanisms**

Clinically significant GI toxicity of NSAIDs is manifested primarily by bleeding. Lanas et al<sup>9</sup> have shown that only

**Figure.** Cumulative Incidence of the Primary End Point of a Confirmed Upper Gastrointestinal Event Among All Randomized Patients



Source: Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;343:1520-1528. Reprinted with permission.

about 40% of GI bleeding events occur at ulcers (ie, 21% DUs, 19% GUs, and 60% nonulcer sources). Ulcers may precede therapy, may be asymptomatic, or may become symptomatic with NSAID treatment. All nonselective NSAIDs cause platelet dysfunction by inhibiting COX-1 and preventing the synthesis of thromboxane, which activates platelets. The combination of ulcers and decreased platelet function means that even minor GI bleeding may result in anemia; in fact, this is the most common indication for endoscopy in patients older than 60 years of age.<sup>10</sup> The most serious clinical bleeding occurs when platelet dysfunction is superimposed on an active GU or DU. Clinically important upper GI events occur in 3% to 4.5% of patients taking NSAIDs, and serious complications develop in approximately 1.5%.<sup>5</sup> Bleeding from ulcers is about 5 times more common than perforation. However, all bleeding from the GI tract, regardless of the source, is approximately 10 times more common than perforation, and perforation is about 4 times more frequent than obstruction.<sup>6</sup>

#### NSAID Gastropathy

NSAIDs cause far more GUs than DUs, but serious adverse events (eg, POBs and PUBs) occur more often in the presence of DUs, which have been linked to *Helicobacter pylori* infection or other factors, rather than NSAID use.<sup>11</sup> Most NSAID-associated ulcers in the antrum, which are often found during surgery for complications, are not the result of acute topical effects. These ulcers can arise over time, even with NSAID prodrugs such as cinoril or nabumetone or when dosed as rectal or topical preparations. NSAID lesions in endoscopic trials occur most often in the stomach, especially in the corpus and fundus, but the complicated lesions, which the surgeon finds, are mostly in the gastric antrum, pyloric channel, and duodenal bulb. When endoscopy is performed shortly after hospitalization of patients with NSAID-associated complications, ulcers are only part of the problem. As mentioned, Lanas et al<sup>8</sup>

have shown that among those with bleeding on NSAIDs, 60% come from nonulcer sources, and more than half of these are from the lower GI tract. The relation between perforation and NSAID use is closer, but even for this complication, more than one fourth of the perforations occur in sites devoid of GUs or DUs.

#### Time to Highest Risk

Gabriel et al,<sup>12</sup> in a meta-analysis, showed that in the first month of NSAID

*Gabriel et al, in a meta-analysis, showed that in less than 1 month of NSAID therapy the summary odds ratio for developing a GI event (crude risk) was 8 (CI 6.37 to 10.06) and for 3 months of exposure the odds ratio was 1.92 (CI 1.19 to 3.13).*

therapy the summary odds ratio for developing a GI event (crude risk) was 8 (CI 6.37 to 10.06) and for 3 months of exposure the odds ratio was 1.92 (CI 1.19 to 3.13). This time-dependent odds ratio reduction may be the result of the depletion of NSAID-susceptible individuals out of the remaining population. For example, NSAID users who experience GI symptoms such as nausea, dyspepsia, or ulcers within the first month of NSAID therapy, stop the treatment. Therefore, an important factor to consider when analyzing the NSAID-associated complications is the clinical trial population. The majority of patients who have participated in clinical trials that examine the efficacy and tolerability of NSAIDs for arthritis treatment have taken NSAIDs prior to enrollment: in these patients, the odds ratio is 2.0. The crude risk estimates are population-based, which include all patients, even those at high risk for complications.

Over 75% of all NSAID users take the drug for less than 1 month, which is the time period when the risk is highest in

NSAID-naive patients. In most long-term NSAID trials, high-risk patients are excluded from study entry. The assumption can be made that a 50% reduction in relative risk among a low-risk population would begin to approach the background risk of a comparable population assigned a placebo. In the VIGOR<sup>2</sup> (rofecoxib versus naproxen) and CLASS<sup>6</sup> (celecoxib versus ibuprofen or diclofenac in nonaspirin users) trials, there is evidence of early increased events in the comparator group taking nonselective NSAIDs.

#### **Comorbidity, Increase in Risk of GI Complications**

McMahon et al<sup>13</sup> examined the relationship between newly prescribed NSAIDs and GI hemorrhage among the population of Tayside, Scotland, and reported a 3-fold increase in the risk of GI complications in patients in whom NSAID use was the sole risk factor (ie, no prior history of GI complications). However, in patients with 1 or more additional risk factors present (eg, a history of peptic ulcer, previous GI bleed, previous GI complication, warfarin therapy, etc), the total number of adverse events was increased, but there were no significant differences between NSAID users and non-NSAID users. The morbidity rate from peptic ulcer complications is so high in patients with other risk factors that the addition of traditional NSAIDs has little effect on the total GI risk. Because the baseline risk of complications in patients with comorbid conditions is very high, the additional risk attributable to NSAIDs appears insignificant. The clinician must think carefully before prescribing a traditional NSAID to these patients.

#### **Aspirin, COX-2 Specific Inhibitors, and GI Complications**

The VIGOR<sup>2</sup> and the CLASS<sup>6</sup> trials compared twice the maximum chronic dose of a COX-2 specific inhibitor with standard doses of traditional NSAIDs and addressed the question of whether a COX-2 inhibitor decreases GI complications. The two trials differ in that low-

dose aspirin (a selective COX-1 inhibitor) was allowed in the CLASS trial but not in the VIGOR trial. Rofecoxib was shown to have a significantly lower GI toxicity than naproxen ( $P<0.005$ ), but in the CLASS study<sup>6</sup> increased tolerability to celecoxib could not be demonstrated versus ibuprofen or diclofenac. However, when aspirin users were excluded from the analysis, a significant reduction in ulcer complication rates was reported in the celecoxib group ( $P=0.04$  [total GI complications were not reported]). The CLASS trial demonstrated that the improved risk obtained by using a selective COX-2 inhibitor could be lost by combining it with aspirin, a selective COX-1 inhibitor. This suggests that the benefit of COX-2 selective inhibitors is the reduction of bleeding due to platelet dysfunction.

#### **Results, Number Needed to Treat, and Economics**

According to the VIGOR trial,<sup>2</sup> the rate of upper GI clinical events was 2.1% in the rofecoxib group compared with 4.5% in the naproxen group, a significant reduction. The RRR of clinical upper GI events was 54%. Complicated upper GI events were also significantly decreased in the rofecoxib group ( $P=0.6$ ) compared with the naproxen group ( $P=1.4$ , RRR of 57%) as well as significantly fewer lower and upper GI bleeding events (RRR of 62%). If the absolute risk reduction (ie, the crude difference in rate of complications between the 2 groups) is considered in this study, then the number needed to treat (NNT) is 41 (ie, a clinician would have to treat 41 people with rofecoxib instead of naproxen to prevent 1 clinical event), 125 to prevent one of the most serious events, and 56 to prevent a GI bleeding episode. These numbers are possibly confirmed by the post-hoc subgroup analysis of nonaspirin users in the CLASS study. Celecoxib was associated with a lower incidence of symptomatic ulcers compared with ibuprofen and diclofenac (0.44 vs 1.27,  $P=0.04$ ). The clinical event rate in nonaspirin users represents a 50% RRR (1.40 vs 2.91,  $P=0.02$ ) in the cele-

coxib group. The NNT to prevent a single clinical event with celecoxib in non-aspirin users was 100.<sup>4</sup> To evaluate whether the NNT is low enough to warrant using a COX-2 selective inhibitor versus a traditional NSAID, a comparison with a large statin trial may be instructive. It has been shown that the yearly NNT to prevent 1 coronary event ranges from about 65 to 265 depending on the severity of the event. Clinicians have demonstrated that they feel that these NNTs do justify using statins to prevent coronary events.

### Summary

Studies have shown that COX-2 inhibitors significantly reduce the risk of ulcers and upper GI complications in nonaspirin users.<sup>2,3,6</sup> Endoscopic ulcers are decreased by 70% to 75% at 6 months with an NNT of 3 to 9. Clinical upper GI events are decreased by 50% at 1 year, with an NNT between 41 and 100. Complicated upper GI events, at least from the VIGOR study, were decreased by 57% at 1 year with an NNT of 125. The debate concerning whether a 50% to 60% decrease in RR is sufficient continues.

An unanswered question remains: Do COX-2 inhibitors decrease the risk of clinical events to the placebo level? Unfortunately, a very large equivalence trial comparing placebo with COX-2 specific inhibitors in tens of thousands of patients may be needed to definitively answer that question. Because of the ethical issues related to treating significant long-term suffering with a placebo, this study will most likely never be done.

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