



Outcomes studies of the gastrointestinal safety of cyclooxygenase-2 inhibitors

JAMES M. SCHEIMAN, MD

■ ABSTRACT

Short-term endoscopic studies of the highly selective cyclooxygenase-2 (COX-2) inhibitors (coxibs) rofecoxib and celecoxib have shown that these agents are well tolerated and have efficacy equivalent to nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) with fewer adverse effects on the upper gastrointestinal (GI) tract. These studies are limited, however, as the detection of endoscopic lesions is not well correlated with symptomatic ulcers and ulcer complications. Outcomes studies of the GI safety are, therefore, essential to understanding how coxibs are likely to perform in a clinical practice setting. Four large outcomes studies (Vioxx Gastrointestinal Outcomes Research, VIGOR; Assessment of Difference Between Vioxx and Naproxen to Ascertain Gastrointestinal Tolerability and Effectiveness trial, ADVANTAGE; Celecoxib Long-term Arthritis Safety Study, CLASS; and the Successive Celecoxib Efficacy and Safety Studies, SUCCESS) examined the GI safety of rofecoxib and celecoxib in over 39,000 patients with osteoarthritis

or rheumatoid arthritis. Results of these studies showed that patients taking a supratherapeutic dose of rofecoxib or celecoxib had significantly lower rates of GI-related adverse events than those taking a non-selective NSAID (naproxen, ibuprofen, or diclofenac). Reduced risk of upper GI events was seen in patients with multiple risk factors and in patients using low-dose aspirin and corticosteroids concomitantly with a coxib. Results of large outcomes studies provide support for the COX-2 hypothesis and demonstrate the long-term safety and tolerability of coxibs.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line therapy in patients with osteoarthritis (OA) who do not respond to nonpharmacologic modalities. NSAID use is widespread, with more than 30 billion over-the-counter tablets sold and 70 million prescriptions filled annually in the United States.¹

Most NSAIDs inhibit both forms of cyclooxygenase (COX), the enzyme that catalyzes prostaglandin synthesis. COX-1, which is constitutively expressed, generates prostaglandins critical to gastrointestinal (GI) mucosal defenses.² COX-2 is induced at sites of inflammation and generates prostaglandins that mediate inflammation and pain.³ As a result of COX-1 inhibition, nonselective NSAIDs have detrimental effects on the GI mucosa. GI-related serious adverse effects affect as many as 30% of those using NSAIDs, resulting in 103,000 hospitalizations annually.¹ The negative outcomes of NSAID use have provided the impetus to develop drugs that specifically inhibit COX-2 and therefore control pain and inflammation without damage to the GI mucosa.⁴

From the University of Michigan Medical School, Ann Arbor. Address correspondence to J.M.S., Associate Professor of Internal Medicine, Gastroenterology, University of Michigan Medical School, 3912 Taubman Center, Box 0362, Ann Arbor, MI 48109-0362; e-mail: jscheima@umich.edu.

Disclosure. The author has indicated that he has received grant or research support from AstraZeneca, Byk-Gulden, Pfizer, Merck, and SmithKline Beecham; has been a consultant for AstraZeneca, Merck, NitroMed, and McNeil; and is on the speakers' bureaus of AstraZeneca, TAP, Merck, Wyeth, Pfizer, and Boehringer Ingelheim.

TABLE 1Comparison of characteristics of the VIGOR and CLASS trials¹¹⁻¹³

Characteristic	VIGOR (n = 8,076)	CLASS (n = 7,968)
Patients		
Disease, %		
Rheumatoid arthritis	100	27.4
Osteoarthritis	0	72.6
Concomitant medications, %		
Aspirin use (< 325 mg)	0	20.7
Glucocorticoids	56.0	30.1
Anticoagulants	0	1.1
<i>Helicobacter pylori</i> infection, %	43.0	38.4
Previous GI perforation, ulcer, or bleeding, %	7.8	9.9
End points		
Primary	Symptomatic ulcers	Ulcer complications
Secondary	Ulcer complications	Symptomatic ulcers
Treatment		
Drug	Rofecoxib 50 mg/day	Celecoxib 800 mg/day
Comparator(s)	Naproxen 1,000 mg/day	Ibuprofen 2,400 mg/day Diclofenac 150 mg/day
Duration	9 months (median)	6 months
Analysis	5,396 patient-years Intent to treat	2,825 patient-years 6 months reported

The US Food and Drug Administration (FDA) has approved two drugs that specifically inhibit the COX-2 enzyme (coxibs), rofecoxib and celecoxib. These drugs were shown in 12- and 24-week clinical studies to have efficacy similar to that of nonselective NSAIDs for the treatment of OA and rheumatoid arthritis (RA) with lower risk of GI complications.⁵⁻⁷ As serious GI adverse events (perforation, obstruction, and bleeding) have an annual incidence of only 0.2% to 0.3%, large numbers of patients are necessary to accumulate sufficient events for safety studies.⁸ To overcome this, endoscopic evidence of lesions has been used as a surrogate measure of serious upper GI events. Endoscopic results, however, do not necessarily correlate with GI complications.⁹ Of patients with a break in the gastric mucosa of equal to or greater than 3 mm in size, approximately 25% have an ulcer, and 1% to 4% will have a clinically significant GI complication. In addition, reduced incidence of endoscopic lesions, such as that resulting from use of misoprostol or proton pump inhibitors, does not reflect an equivalent reduction in risk of serious GI complications.¹⁰ Long-term studies in large numbers of patients are therefore necessary for assessment of GI safety. To be relevant, these studies should report incident events of clinical significance (eg, hospitalizations or serious GI

events), and patients should be those with risk factors generalizable to real-world clinical settings. The results of four outcomes studies characterizing the long-term GI safety of coxibs are reviewed here.

■ OUTCOMES STUDIES OF COXIBS

Several large, long-term studies have examined the GI safety outcomes of coxibs. Rofecoxib studies include the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial and the Assessment of Difference Between Vioxx and Naproxen to Ascertain Gastrointestinal Tolerability and Effectiveness (ADVANTAGE) trial. Trials of celecoxib include the Celecoxib Long-term Arthritis Safety Study (CLASS) and the Successive Celecoxib Efficacy and Safety Studies (SUCCESS). A summary of VIGOR and CLASS trials is shown in **Table 1**.¹¹⁻¹³

■ VIGOR

The VIGOR trial compared twice the recommended dose of rofecoxib (50 mg daily) with the most common dose of naproxen (1000 mg daily) in 8,076 patients with RA (**Table 1**).¹¹ VIGOR was a 13-month, placebo-controlled, double-blind trial con-

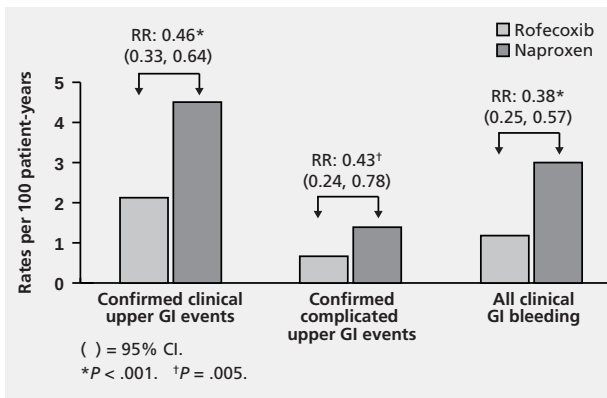


FIGURE 1. Summary of clinical end points for the VIGOR trial.¹³

ducted prospectively in 301 centers in 22 countries. Median treatment was 9 months. Patients over 50 years of age and using NSAIDs for at least 1 year were included. Those with a positive fecal blood test, and those using aspirin, anticoagulants, antiplatelet agents, or prescribed antiulcer medications, were excluded from VIGOR.

The primary end point of VIGOR was symptomatic ulcers, including clinical upper GI events of perforation, obstruction, and bleeding. The secondary end point was complicated upper GI events (perforation; obstruction; and major bleeding resulting in ≥ 2 -g drop in hemoglobin, transfusion, or hypotension).¹¹ The RA patient population of VIGOR was selected because RA patients use NSAIDs chronically and have a substantially higher risk of NSAID-related GI events than do patients with OA.

Rofecoxib significantly decreased the incidence of all GI end points studied in VIGOR (Figure 1).¹³ The comparative event rates for all upper GI end points for rofecoxib compared with naproxen were 2.1 and 4.5 per 100 patient-years, respectively, resulting in a relative risk (RR) of 0.46 (95% confidence interval [CI], 0.33–0.64; $P < .001$). For complicated upper GI events, the rates were 0.6 and 1.4 per 100 patient-years for rofecoxib and naproxen, respectively (RR = 0.43; 95% CI, 0.24–0.78; $P = .005$). All GI bleeding rates for rofecoxib and naproxen were 1.1 and 3.0 per 100 patient-years, respectively (RR = 0.38; 95% CI, 0.25–0.57; $P = .001$).¹¹

The time to GI end point events is shown in Figure 2.¹³ Patients randomized to rofecoxib had half the risk of perforation, obstruction, and major bleeding as those receiving naproxen (RR = 0.5; 95% CI, 0.33–0.64; $P < .001$). The lower incidence of GI events in the rofecoxib group was apparent after the

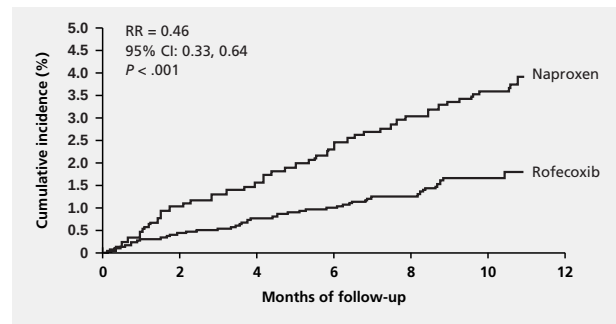


FIGURE 2. Time to confirmed clinical primary end point in VIGOR.¹³

first month, and new events occurred at a significantly lower rate than in the naproxen group for the remainder of the study.¹¹

The rates of discontinuation due to lack of efficacy for rofecoxib and naproxen were comparable (6.3% and 6.5%, respectively).¹¹ The rate of discontinuation for any GI events (including clinical end points) was significantly lower in the rofecoxib group compared with the naproxen group (7.8% and 10.6%, respectively; $P < .05$).¹¹ There was significantly less use of prescribed H_2 -receptor antagonists, proton pump inhibitors, or prostaglandin analogs in the rofecoxib group compared with the naproxen group (11.2% vs 14.5%, RR = 0.77; 95% CI, 0.68–0.87).¹⁴

Analysis of risk factors among VIGOR participants showed that those factors independently associated with increased risk of GI events included advanced age, prior history of clinical GI events or GI symptoms, arthritic disease severity, and prior H_2 -receptor antagonist use. Corticosteroids are among the major risk factors for ulcers and ulcer complications.¹ The prevalence of steroid use in VIGOR was 56%, suggesting that patients had a high baseline risk. The subgroup of patients in VIGOR using steroids at study entry had a significantly increased risk of GI clinical events (RR = 1.59; 95% CI, 1.15–2.18, $P = .005$).¹⁵

In patients receiving rofecoxib, RR of clinical GI events among the group with risk factors (≥ 65 years of age, history of ulcer or GI event, *Helicobacter pylori*-positive, or steroid user) was reduced by 51%, similar to the 54% reduction in risk for the entire rofecoxib group. The RR reduction in the low-risk group (that is, none of the four risk factors) receiving rofecoxib was 88% (Figure 3).^{13,15} The probability of GI complications in patients taking NSAIDs depends on preexisting risk factors, and these data show that rofecoxib can reduce risk incrementally in patients both with

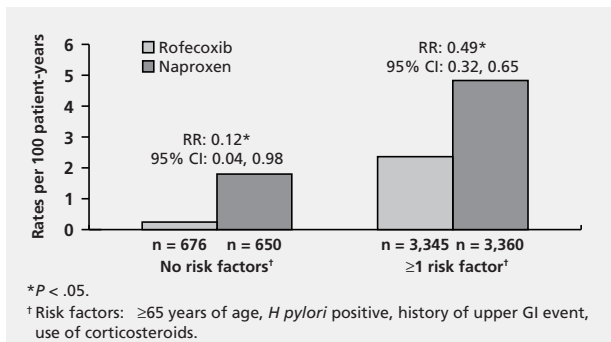


FIGURE 3. Relative risk (RR) of confirmed upper GI events by risk category in VIGOR.¹³

and without multiple risk factors.

VIGOR also compared the efficacy of rofecoxib 50 mg daily to naproxen 500 mg twice daily for a median of 9 months. Global Assessment Disease Activity scores were assessed by patients and physicians as well as by using the Modified Health Assessment Score. The results showed that rofecoxib was indistinguishable from naproxen on all efficacy measures.¹¹

■ ADVANTAGE

ADVANTAGE was a 12-week, double-blind, randomized, prospective trial in 5,597 patients with OA in the United States and Sweden who were randomized to receive rofecoxib (25 mg daily) or naproxen (500 mg twice daily). Patients using low-dose aspirin (<81 mg/day) were included in the trial. The primary end point of ADVANTAGE was GI tolerability as defined by the incidence of discontinuations due to GI adverse events. The secondary end point was use of concomitant medication to treat GI symptoms.¹⁶ Most patients (71%) were women, and the mean age of study participants was 63 years old. Twelve percent of patients used low-dose aspirin during the trial, and baseline characteristics of the treatment groups were similar.

At study end, a significantly lower rate of GI adverse event-related discontinuations occurred with rofecoxib (5.9% vs 8.1% for rofecoxib vs naproxen; $P = .005$). Significantly fewer patients receiving rofecoxib (9.1%) required concomitant GI medications compared with patients receiving naproxen (11.2%; $P = .014$). Concomitant use of low-dose aspirin did not significantly affect relative rates of discontinuation due to adverse events, serious adverse events, or drug-related adverse events.¹⁶ While ADVANTAGE was limited to 12 weeks, the results are important because they show

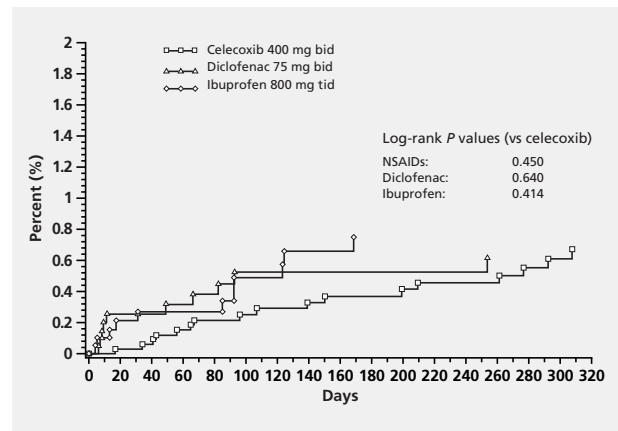


FIGURE 4. Time to upper gastrointestinal outcomes in the CLASS trial. Results are for entire study using intent-to-treat analysis.¹⁸

that concomitant use of low-dose aspirin with rofecoxib does not significantly increase risk of adverse events.

■ CLASS

The CLASS trial (Table 1) was carried out in 7,968 patients from 386 centers in the United States and Canada and compared celecoxib (400 mg twice daily; two and four times the maximum dosage for RA and OA, respectively) with two nonselective NSAIDs: diclofenac (75 mg twice daily) or ibuprofen (800 mg thrice daily).¹² While ibuprofen is nonselective, diclofenac has a COX-1/COX-2 IC_{50} (concentration that inhibits 50%) ratio similar to that of celecoxib (29 vs 30 for diclofenac and celecoxib, respectively).¹⁷ CLASS enrolled patients from September 1998 to March 2000; 57% of enrolled patients received treatment for 6 months. Only data from the first 6 months of the trial have been published.¹² However, 9-month (median) data were presented in February 2001 to the FDA and are available on the FDA website.¹⁸ Efficacy was not reported for CLASS.

The primary end point in CLASS was the incidence of ulcer complications (ulcer perforation, gastric outlet obstruction, or upper GI bleeding). The secondary end point was complicated and symptomatic ulcer events. Patients taking low-dose aspirin (≤ 325 mg/day) were allowed to enroll.

In CLASS, the annualized incidence rates for upper GI ulcer complications were 0.76% and 1.45% for celecoxib and NSAIDs, respectively ($P = .09$).¹² While the difference in rates favored celecoxib, it did not reach statistical significance. Comparison of the time

GI outcomes with coxibs

Long-term outcomes studies provide the best evidence for gastrointestinal (GI) safety of coxibs in patients with arthritis and preexisting risk factors.

Prospective studies in over 39,000 arthritis patients compared the long-term GI safety of coxibs and non-steroidal anti-inflammatory drugs (NSAIDs).

Outcomes studies show rofecoxib and celecoxib have favorable GI safety profiles at supratherapeutic doses and significantly decrease GI adverse events compared with NSAIDs.

The magnitude of the safety advantage of coxibs in the setting of concomitant aspirin use remains unresolved.

Coxibs decrease risk of upper GI ulcers and ulcer complications in patients with and without ulcer risk factors.

to primary end point for the entire study is shown in **Figure 4**.¹⁸ The cumulative rate of complicated ulcer favored celecoxib within the first month of the study, and this trend continued at 6 months ($P = .09$). There were no further GI events in the ibuprofen group after day 170, and the last event in the diclofenac group occurred at day 250. At study end, the trend favoring celecoxib was no longer apparent ($P = .45$).¹⁸

A caveat of unbiased time-to-event analysis is that the basis of withdrawal from the study (censoring) must be independent of the outcome event being measured. Treatment-emergent symptoms (dyspepsia, abdominal pain, diarrhea, nausea, and vomiting) were found to be a significant risk factor for the primary and secondary end points of CLASS, particularly in patients receiving diclofenac. The RR of ulcer complications in patients with moderate-to-severe GI symptoms vs patients without moderate-to-severe GI symptoms was 3.9 overall and 13.8 for diclofenac.¹⁸ The RR of symptomatic ulcer plus ulcer complications in patients with moderate-to-severe GI symptoms vs patients without moderate-to-severe GI symptoms was 6.3 overall and 11.5 for diclofenac. More patients in the diclofenac group withdrew owing to GI symptoms than did patients in the other treatment groups (9.5% for diclofenac vs 7.5% for celecoxib and ibuprofen; $P < .05$). As early withdrawal of patients in the diclofenac group could have biased results, celecoxib and diclofenac could not be meaningfully compared in an intent-to-treat analysis in CLASS.¹⁸

For the secondary end point of CLASS, patients in the celecoxib group had significantly lower rates of symptomatic and complicated ulcers than those

in the NSAID group; annualized incidence rates were 2.08% and 3.54% for celecoxib and NSAIDs, respectively ($P = .02$).¹²

There are several possible explanations for why the primary end point of the CLASS trial was not met. The design of the CLASS study may have provided inadequate statistical power to demonstrate a decrease in primary end point events with celecoxib. CLASS was designed with power to detect a 75% reduction in risk, while the results were closer to a 50% reduction.

The inability to demonstrate a statistically significant difference in end point rates of the treatment groups may also reflect the higher-than-expected event rate in the celecoxib group. The annualized event rate in CLASS patients receiving celecoxib (0.76%) was almost four times that predicted from previous trials (0.2%).¹² This likely reflects the 21% of participants using aspirin during the trial, about twice the number in other trials of celecoxib.⁶ Among aspirin users, the annualized incidence of complicated ulcers was similar in the celecoxib and NSAID groups (2.01% vs 2.12%; $P = .92$) as were the rates of symptomatic and/or complicated ulcers (4.7% vs 6.0%; $P = .49$). Overall, the RR of ulcer complication for participants taking celecoxib and aspirin concomitantly, compared with those taking celecoxib without aspirin, was 4.5 ($P = .01$).¹² The increased risk of adding aspirin to celecoxib in CLASS participants was comparable to the risk incurred by a moderate dose of an NSAID alone and about half the risk of taking aspirin concomitantly with a nonselective NSAID.¹⁹ When CLASS participants not using aspirin were examined in a posthoc analysis, the rate of annualized incidence of complicated ulcers was significantly lower in those taking celecoxib than in those taking NSAIDs (0.44% vs 1.27%; $P = .04$; **Figure 5**),¹² and event rates were similar to those of other celecoxib trials.¹² These results suggest that aspirin use may offset the GI benefits of celecoxib use.

For reasons that are unclear, the rate of withdrawals in CLASS (40.4% and 44.8% in the celecoxib and NSAID groups, respectively) was considerably higher than that in other coxib trials. The withdrawal rate for adverse events was significantly higher in patients receiving NSAIDs compared with those receiving celecoxib (20.6% vs 18.4%, respectively; $P < .01$).¹²

■ SUCCESS

SUCCESS was a 12-week, double-blind, randomized trial in 13,274 patients that compared the incidence of upper GI hospitalizations in patients with

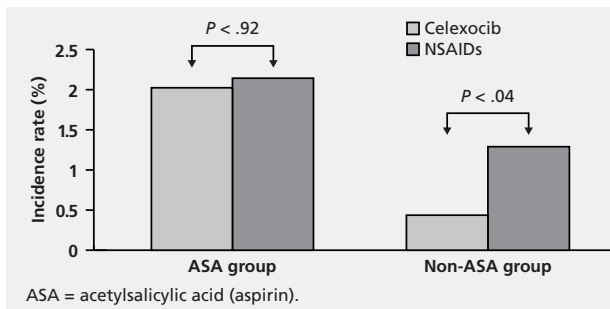


FIGURE 5. Annualized incidence of primary end point for CLASS trial (complicated ulcers) among users and nonusers of low-dose aspirin (ASA).¹²

(Adapted with permission from Silverstein et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study—a randomized controlled trial. JAMA 2000; 284:1247-1255.)

OA taking celecoxib (200 or 400 mg daily), diclofenac (100 mg daily), or naproxen (1,000 mg daily).²⁰ In an effort to closely parallel a general practice, patients and clinicians reported clinically significant GI events, which were then adjudicated as ulcer complications and symptomatic ulcers (as defined in CLASS). The rate of hospitalization was significantly lower in the celecoxib group (1.17 vs 2.34 per 100 patient-years for celecoxib vs NSAIDs), resulting in an RR of 0.5 (95% CI, 0.28–0.90; $P < .02$).²⁰ For the primary end point of ulcers plus ulcer complications, the rates per 100 patient-years as determined by a blinded panel were 0.32 and 1.27 for celecoxib vs NSAIDs, respectively (RR = 0.25; 95% CI, 0.09–0.67; $P < .006$).

In SUCCESS, there were significantly fewer nuisance symptoms in the celecoxib group compared with the NSAID group. Symptoms of dyspepsia, abdominal pain, or nausea were reported by 4.8%, 4.8%, and 2.4%, respectively, in the celecoxib group, and by 5.9%, 6.2%, and 3.4%, respectively, in the NSAID group ($P < .05$, celecoxib vs NSAIDs for all categories). In addition, fewer patients taking celecoxib (5.2%) than taking NSAIDs (6.8%) withdrew due to GI-related adverse events ($P < .05$).²¹

SUCCESS also measured efficacy in patients with OA. Results of the trial showed that both dosages (200 and 400 mg daily) of celecoxib were as efficacious as NSAIDs.²²

■ COMMENTS

The results of long-term trials of coxibs provide evidence supporting the hypothesis that COX-2-specific

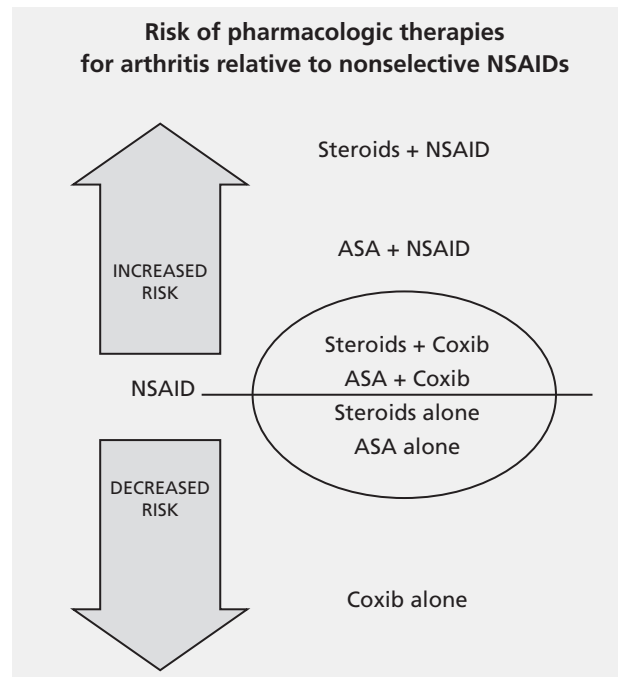


FIGURE 6. Risk of upper GI adverse events associated with pharmacologic therapies in patients with arthritis. Risks are relative to common NSAIDs as approximated from prospective studies. Risks vary with dose and individual agents.^{11,12,19}

inhibition results in relief from arthritis symptoms without accompanying deleterious effects on mucosal defenses. Perhaps more importantly, these studies offer insight into how coxibs might be expected to perform in a real-world clinical setting. The clinical end points of these trials—ulcers and ulcer complications—are more valid than surrogate endoscopic measures commonly used in short-term trials. Furthermore, by striving for a naturalistic setting, the study design and entry criteria of these trials produced findings that can be generalized to most patients encountered in clinical practice. The results of coxib outcomes studies also revealed the ability of coxibs to reduce GI risk even when patients face a combination of other risk factors such as advanced age, steroid use, or *H pylori* infection.

Patients with RA commonly use low-dose aspirin for cardiovascular prophylaxis. While the risk of aspirin use to the upper GI tract is recognized, the increased risk incurred by those taking low-dose aspirin and a coxib has been controversial. In the ADVANTAGE trial, concomitant use of aspirin with rofecoxib resulted in no significant effect on GI adverse events, discontinuations, or symptomatic ulcers. In CLASS, low-dose aspirin was an independent risk factor for ulcers in patients taking celecoxib,

and aspirin offset the GI benefit of celecoxib. In contrast to CLASS, SUCCESS showed that—relative to concomitant nonselective NSAIDs and aspirin—the risk of GI adverse events is substantially reduced with concomitant celecoxib and aspirin, albeit to a lesser degree than celecoxib without aspirin (**Figure 6**).^{11,12,19} With the exception of CLASS, favorable outcomes of these trials suggest that in patients using coxibs for relief of arthritis symptoms, the cardiovascular benefits of low-dose aspirin may weigh against the incremental risk of GI events. For patients at high risk for ulcer complications, cotherapy may be required when a coxib is prescribed with aspirin.

Other controversy has centered on possible inhibitory effects of coxibs on the protective effects of aspirin. A detailed analysis revealed that coxibs do not inhibit platelet aggregation and do not contraindicate

low-dose aspirin therapy for appropriate patients.²³ In particular, rofecoxib (and other nonselective NSAIDs except ibuprofen) does not inhibit the beneficial effects of aspirin.²⁴

In conclusion, four coxib outcomes studies (VIGOR, ADVANTAGE, CLASS, and SUCCESS) were conducted in over 39,000 patients with OA and RA. These studies showed that the COX-2-specific inhibitors, rofecoxib and celecoxib, resulted in significantly fewer clinically important upper GI adverse events than did nonselective NSAIDs, while having similar efficacy. Treatment of large numbers of patients has helped to define the role of selective COX-2 inhibitors in symptom management in arthritis while providing convincing evidence that coxibs can reduce the risk of symptomatic ulcers and ulcer complications.

REFERENCES

- Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med* 1999; 340:1888–1899.
- Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nat New Biol* 1971; 231:232–235.
- Crofford LJ, Lipsky PE, Brooks P, Abramson SB, Simon LS, van de Putte LBA. Basic biology and clinical application of specific cyclooxygenase-2 inhibitors. *Arthritis Rheum* 2000; 43:4–13.
- FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001; 345:433–442.
- Emery P, Zeidler H, Kvien TK, et al. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. *Lancet* 1999; 354:2106–2111.
- Simon LS, Weaver AL, Graham DY, et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *JAMA* 1999; 282:1921–1928.
- Laine L, Harper S, Simon T, et al, for the Rofecoxib Osteoarthritis Endoscopy Study Group. A randomized trial comparing the effect of rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. *Gastroenterology* 1999; 117:776–783.
- Goldstein JL, Silverstein FE, Agrawal NM, et al. Reduced risk of upper gastrointestinal ulcer complications with celecoxib, a novel COX-2 inhibitor. *Am J Gastroenterol* 2000; 95:1681–1690.
- Lipsky PE, Abramson SB, Crofford L, DuBois RN, Simon LS, van de Putte LBA. The classification of cyclooxygenase inhibitors. *J Rheumatol* 1998; 25:2298–2303.
- Singh G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. *Am J Med* 1998; 105:31S–38S.
- 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.
- Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study—a randomized controlled trial. *JAMA* 2000; 284:1247–1255.
- Reicin A. VIOXX Gastrointestinal Outcomes Research (VIGOR). Merck & Co., Inc; West Point, PA. FDA Arthritis Advisory Committee; February 8, 2001.
- Laine L, Bombardier C, Ramey DR, Watson DJ, Pellissier JM, Reicin A. Less use of gastrointestinal (GI) protective agents and GI-related procedures with rofecoxib vs naproxen in the VIGOR (VIOXX GI Outcomes Research) study [abstract]. European League Against Rheumatism, Prague, Czech Republic, June 13–16, 2001.
- Reicin A, Shapiro D, Sperling R. Risk factors for clinical gastrointestinal events and high/low risk subgroup analyses from the VIGOR study [abstract]. European League Against Rheumatism, Prague, Czech Republic, June 13–16, 2001.
- Geba GP, Lisse JR, Polis AB, et al. Gastrointestinal tolerability in primary care patients treated with naproxen or rofecoxib for osteoarthritis (OA): the ADVANTAGE trial [abstract]. European League Against Rheumatism, Prague, Czech Republic, June 13–16, 2001.
- Patrono C, Patrignani P, Garcia Rodriguez LA. Cyclooxygenase-selective inhibition of prostanoid formation: transducing biochemical selectivity into clinical read-outs. *J Clin Invest* 2001; 108:7–13.
- Food and Drug Administration. CLASS Advisory Committee Briefing Document. Rockville, MD: Food and Drug Administration; Center for Drug Evaluation and Research; 2001. Available at: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_01_searle.pdf. Accessed November 3, 2001.
- Garcia Rodriguez LA, Hernandez-Diaz S. The risk of upper gastrointestinal complications associated with nonsteroidal anti-inflammatory drugs, glucocorticoids, acetaminophen, and combinations of these agents. *Arthritis Res* 2001; 3:98–101.
- Goldstein JL, Eisen G, Bensen W, et al. SUCCESS in osteoarthritis (OA) trial: celecoxib significantly reduces the risk of upper gastrointestinal (UGI) hospitalizations compared to diclofenac and naproxen in 13,274 randomized patients with OA [abstract]. European League Against Rheumatism, Prague, Czech Republic, June 13–16, 2001.
- Goldstein JL, Agrawal N, Eisen G, et al. Significantly improved upper gastrointestinal (UGI) tolerability with celecoxib, a COX-2 specific inhibitor, compared with conventional NSAIDs. The SUCCESS I trial [abstract]. European League Against Rheumatism, Prague, Czech Republic, June 13–16, 2001.
- Singh G, Goldstein J, Agrawal N, et al. COX-2 specific inhibitors—is there any benefit of using these agents in patients on low dose aspirin [abstract]. European League Against Rheumatism, Prague, Czech Republic, June 13–16, 2001.
- Strand V, Hochberg MC. The risk of cardiovascular thrombotic events with COX-2 selective inhibitors. *Arthritis Rheum* 2002; 47 in press.
- Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001; 345:1809–1817.