CLINICAL–ALIMENTARY TRACT

Peptic Ulcer and Bleeding Events Associated With Rofecoxib in a 3-Year Colorectal Adenoma Chemoprevention Trial

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Background & Aims: Our aim was to establish the incidence of symptomatic upper gastrointestinal ulcers, ulcer perforation, ulcer obstruction, or bleeding episodes (PUBs) associated with the use of selective cyclooxygenase-2 inhibitors at standard clinical doses compared with placebo. We report here on the PUB outcomes associated with the use of rofecoxib 25 mg in a 3-year, multicenter, double-blind, placebo-controlled trial designed to determine the effect of rofecoxib on the risk of recurrent neoplastic polyps of the colon. **Methods:** A total of 2587 patients with a history of colorectal adenomas underwent randomization to 25 mg/day of rofecoxib or to placebo. Investigator-reported PUBs were adjudicated by an external blinded committee. Kaplan–Meier and Cox proportional hazards techniques were used to estimate incidence and relative risks of PUBs in an intention-to-treat analysis. **Results:** Patients assigned to rofecoxib had a higher incidence of confirmed PUBs than those randomized to placebo (.88 vs .18 events per 100 patient-years; relative risk, 4.9; 95% confidence interval, 1.98–14.54). The incidence of confirmed complicated PUBs (ulcer perforation, obstruction, or bleeds) was low, but was numerically higher in the rofecoxib than in the placebo group (.23 vs .06 events per 100 patient-years; relative risk, 3.8; 95% confidence interval, .72–37.46; $P = .14$). Rofecoxib increased the incidence of confirmed PUBs vs placebo in both low-dose aspirin users and nonusers. **Conclusions:** Among patients with a history of colorectal adenomas, the long-term use of 25 mg/day of rofecoxib was associated with an increased risk of clinically relevant upper gastrointestinal events when compared with placebo.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used widely for the treatment of pain and inflammation in various rheumatic conditions, but may cause gastrointestinal (GI) ulceration and bleeding, presumably as a result of inhibition of the cyclooxygenase-1 (COX-1)-mediated production of prostaglandins. Selective inhibitors of COX-2 were developed to provide analgesic and anti-inflammatory efficacy similar to nonselective COX inhibitors, but with reduced upper-GI side effects.¹

Several placebo-controlled endoscopy studies of osteoarthritis or rheumatoid arthritis patients have reported that the use of COX-2-selective inhibitors is associated with rates of endoscopically determined gastroduodenal ulcers lower than in patients taking nonselective NSAIDs^{2–5} and either similar^{2–4} or slightly higher⁵ than observed in patients taking placebo. Two long-term (12-mo) outcome studies, VIGOR⁶ (VIOXX Gastrointestinal Outcomes Research) and Therapeutic Arthritis Research and Gastrointestinal Event Trial,⁷ have shown that both rofecoxib and lumiracoxib were associated with reduced risks of upper-GI complications and symptomatic gastroduodenal ulcers in comparison with nonselective NSAIDs. However, a celecoxib outcomes study, Celecoxib Long-term Arthritis Safety Study, reported an incidence of upper-GI complications similar to that observed with traditional NSAIDs, although when upper-GI complications were combined with symptomatic peptic ulcers, celecoxib also was superior to nonselective NSAIDs.⁸ In a more recent short-term (12-wk) trial that compared lower

Abbreviations used in this paper: APPROVe, Adenomatous Polyp Prevention On Vioxx; CI, confidence interval; COX, cyclooxygenase; GI, gastrointestinal; PUBs, symptomatic gastroduodenal ulcers, gastroduodenal ulcer perforation, obstruction or bleeds; PPI, proton pump inhibitor; VIGOR, VIOXX Gastrointestinal Outcomes Research.

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doses of celecoxib with traditional NSAIDs,⁹ patients taking celecoxib had a lower rate of ulcer complications and upper gastrointestinal events than those taking traditional NSAIDs.

The relevance of those findings to clinical practice is unclear because the doses of COX-2 inhibitors in these trials,⁶⁻⁸ but not the doses of the NSAID comparators, were higher than those routinely used clinically. Furthermore, a coherent understanding of the data from the endoscopy studies and the outcomes studies has not been possible because of the lack of a placebo group in the outcomes studies.⁶⁻⁹ Also, information on the incidence of GI side effects associated with the use of these compounds for other indications in patients without musculoskeletal diseases (eg, cancer prevention) is limited.

The Adenomatous Polyp Prevention On Vioxx (APPROVe) trial was designed to evaluate the hypothesis that adenomatous polyp recurrence would be reduced in patients receiving rofecoxib, a selective COX-2 inhibitor, for 3 years. Investigator-reported symptomatic upper-GI ulcers, ulcer perforation, obstruction, or bleeds (PUBs) were adjudicated by an independent committee, and all safety data were monitored regularly by an external safety monitoring committee. We report here the upper-GI side effects observed in the study. The primary efficacy and tolerability data from this study, and the cardiovascular outcomes, are the subject of separate reports.^{10,11}

Materials and Methods

The design of the study has been described in detail elsewhere.^{10,11} In brief, enrollment occurred from February 2000 to November 2001 at 108 centers in 29 countries. Men and women at least 40 years old were eligible if they had undergone removal of at least 1 histologically confirmed large-bowel adenoma within 12 weeks of study entry. Only patients who were not anticipated to need chronic NSAID therapy (including analgesic doses of aspirin) during the study and/or patients who had not been taking NSAIDs on a chronic basis, defined as 7 or more total days of each month for the 2 consecutive months before the screening visit, were enrolled. Low-dose aspirin for cardiovascular protection (≤ 100 mg/day) was allowed, although limited to a maximum of 20% of patients at baseline, to minimize the ability of low-dose aspirin to mask the possible chemopreventive effects of rofecoxib. Individuals with a history of ulcer or dyspepsia were eligible. Patients with uncontrolled hypertension ($>165/95$ mm Hg), angina or congestive heart failure at rest or with minimal activity, evidence of occult GI bleeding, or history of small- or large-bowel resection were excluded.

Written informed consent was obtained from all patients enrolled. The study was approved by the institutional review board for each center. The active treatment period was preceded by a 6-week single-blind placebo

run-in to assess patient compliance with study medication. Patients who took at least 80% of their tablets during the placebo run-in were assigned randomly to receive either 1 rofecoxib 25-mg tablet or 1 identical-appearing placebo tablet daily for 3 years. The computer-derived randomization was stratified by clinical center and low-dose aspirin use, with a blocking factor of 2. Patients, investigators, and study-sponsor personnel involved in study monitoring were blinded to the treatment allocation schedule. Follow-up evaluation continued until 2 weeks after the last dose of study treatment. There were in-person clinic visits at randomization and at weeks 4, 17, 35, 52, 69, 86, 104, 121, 138, 156, and after discontinuation of treatment. At each visit, patients were asked if they experienced any symptoms or side effects; compliance also was monitored. Vital signs were measured at each clinic visit during the study.

Before the start of the trial, a previously described standard procedure was instituted for investigators to report PUBs for adjudication.¹⁰ The definition of a PUB event in this trial was identical to that reported previously in GI outcome studies with rofecoxib,⁶ and included either the diagnosis of a gastroduodenal symptomatic ulcer, or the occurrence of ulcer perforation, nonmalignant ulcer gastric outlet obstruction, or upper-GI bleeding. Clinical documentation of investigator-reported candidate PUBs was reviewed by a blinded, external adjudication committee. The committee determined whether a suspected PUB was confirmed (confirmed PUB), and whether it was a complicated event by virtue of the presence of clinically significant upper-GI bleeding, obstruction, or perforation, using predefined criteria (confirmed complicated PUB). Confirmed PUBs, the primary GI end point, were included in the analysis. Data presented here include events occurring on study drug and up to 14 days after the last dose. An independent external safety monitoring board met periodically to review the safety data provided by an unblinded statistician who was not otherwise involved in the study.

The clinical investigators also recorded more minor GI adverse events, including episodes of dyspepsia, abdominal pain, and upper-abdominal pain among many others; however, these were not adjudicated. Discontinuation because of a GI system adverse experience including abdominal pain, was prespecified for comparison.

Statistical Analysis

The analysis, performed using SAS software version 8.2 (SAS Institute, Cary, NC), included all randomized patients who took at least 1 dose of study medication. We used a Cox proportional hazards model with treatment as the only factor to compute hazard ratios (relative risks) and 95% confidence intervals (CIs), and Kaplan-Meier techniques to estimate cumulative proportions of patients experiencing confirmed PUBs over time. Subgroup analyses for confirmed PUBs were performed to assess the uniformity of treatment effect across sub-

Table 1. Patient Characteristics

	Treatment group	
	Rofecoxib (N = 1287)	Placebo (N = 1300)
Male, n (%)	804 (62.5)	805 (61.9)
Mean age, (y)	59.4	59.4
Ulcer history, n (%)	93 (7.2)	94 (7.2)
Alcohol user at baseline, n (%)	773 (60.1)	764 (58.8)
Caffeine user at baseline, n (%)	1167 (90.7)	1168 (89.8)
Ex/current tobacco user at baseline, n (%)	776 (60.3)	774 (59.5)
Low-dose (≤ 100 mg/day) aspirin user at baseline, n (%)	213 (16.6)	204 (15.7)
Low-dose aspirin user during trial, n (%) ^a	233 (18.1)	236 (18.2)
Any dose aspirin user during trial, n (%) ^b	245 (19.0)	245 (18.8)
Antisecretory drug user at baseline, n (%) ^c	266 (20.7)	275 (21.2)
Antisecretory drug user during trial, n (%) ^d	454 (35.3)	432 (33.2)
Proton pump inhibitor user at baseline, n (%) ^e	185 (14.4)	205 (15.8)
Proton pump inhibitor user during trial, n (%) ^f	354 (27.5)	341 (26.2)

^aDefined as a patient who took ≤ 100 mg/day aspirin for at least 50% of the time while on study therapy and did not start any of these medications after a PUB event.

^bDefined as a patient who took any dose of aspirin or aspirin-containing products for at least 50% of the time while on study therapy and did not start any of these medications after a PUB event.

^cDefined as a patient who took ≥ 1 dose of H₂-blocker or PPI at baseline.

^dDefined as a patient who took ≥ 1 dose of H₂-blocker or PPI while on study therapy.

^eDefined as a patient who took ≥ 1 dose of PPI before randomization.

^fDefined as a patient who took ≥ 1 dose of PPI while on study therapy.

groups (ie, interactions). There were no stratification factors or covariates in the analysis models because the number of events was small. Demographic and clinical data also were tested one at a time to assess whether the variable was a significant risk factor for PUBs in the entire population of the study. Interaction assessment was not reported if data were too sparse (eg, 0 events in some of the groups). PUB events were monitored up until 14 days after the last dose of study medication. The last date a patient took any study medication was on October 24, 2004. The last reported PUB event occurred on September 29, 2004. All reported PUB events were adjudicated and the last date that cases were adjudicated was on December 9, 2004. The data reported here are those available to the authors as of April 27, 2006.

Results

Demographics and Characteristics of Participants

A total of 3260 patients were screened for inclusion in the study, 2612 were considered eligible and 2587 were randomized to rofecoxib 25 mg or placebo; all took at least one dose of study medication, and therefore all 2587 were included in the analysis. The treatment groups were similar with regard to measured baseline characteristics including age, sex, and GI risk factors (Table 1).

At baseline, low-dose aspirin (≤ 100 mg/day) was taken by 16.6% of patients randomized to rofecoxib and 15.7% of those assigned to placebo. The use of other medications, including antisecretory agents such as H₂-blockers or proton pump inhibitors (PPIs), both at baseline and

during the study, was similar in the 2 groups (Table 1). At the time the study was terminated because of increased cardiovascular risk with long-term use of rofecoxib (September 2004), 870 patients in the rofecoxib group and 980 patients in the placebo group had completed the 3 years of study treatment, with a mean on-drug exposure time of 2.30 years in the rofecoxib group and 2.48 years in the placebo group.

Upper-GI PUBs

A total of 27 patients in the rofecoxib group had a confirmed PUB (20 uncomplicated and 7 complicated) during 3067 patient-years of follow-up evaluation (.88 events per 100 patient-years; 95% CI, 0.58–1.28). In the placebo group there were 6 patients with PUBs (4 uncomplicated

Figure 1. Cumulative incidence of confirmed PUBs with rofecoxib 25 mg/day and placebo over time.

Figure 2. Types of confirmed PUBs with rofecoxib 25 mg/day and placebo. The gastric or duodenal ulcer event rate include both symptomatic uncomplicated ulcers and complicated ulcers. Complicated events (7 in the rofecoxib group and 2 in the placebo group) were all upper GI bleeding events and included 3 cases of gastric ulcer and 1 of duodenal ulcer in the rofecoxib group; no gastric or duodenal ulcer cases were identified in the 2 cases of upper GI bleeding in the placebo group. Twenty patients in the rofecoxib group had uncomplicated symptomatic ulcers (4 patients had gastric ulcers, 14 had duodenal ulcers, and 2 patients had both gastric and duodenal ulcers). Four patients in the placebo group had uncomplicated symptomatic ulcers (3 patients had gastric ulcers and 1 had a duodenal ulcer). There were 2 rofecoxib patients that had both complicated and uncomplicated PUBs. They are not counted in the 20 patients with uncomplicated symptomatic ulcers.

and 2 complicated) during 3342 patient-years of follow-up evaluation (.18 events per 100 patient-years; 95% CI, .07–.39; absolute difference: .70 events per 100 patient-years; 95% CI, 0.34–1.06). The relative risk was 4.9 (95% CI, 1.98–14.5) (Figure 1). The risk of both duodenal ulcers and gastric ulcers was increased in the rofecoxib group, although the

increase seemed greater for the former (Figure 2). The rates of confirmed complicated PUBs were .23 (95% CI, .09–.43) and .06 (95% CI, .01–.22) events per 100 patient-years in the rofecoxib and placebo groups, respectively ($P = .14$) (absolute difference, .17 events per 100 patient-years; 95% CI, -.02 to .35). The corresponding rates of confirmed symptomatic uncomplicated ulcers were .65 (95% CI, .40–1.01) and .12 (95% CI, .03–.31) per 100 patient-years ($P < .001$) (absolute difference, .53 events per 100 patient-years; 95% CI, 0.22–.84). There were no deaths associated with the PUB events. One patient who was taking placebo died of disseminated intravascular coagulation, renal failure, and hepatic failure 10 days after colonoscopy complicated by colonic perforation, but this event was not counted as a PUB in the analysis because it was located in the large bowel.

Confirmed PUBs were more than 3 times more frequent in the rofecoxib treatment group than in the placebo group both among those who did not use low-dose aspirin during the trial ($P = .005$) and among those who did use aspirin either at baseline or during the study ($P = .014$) (Table 2). Further subgroup analyses were performed to test whether there were differences in the relative risk (rofecoxib vs placebo) of confirmed PUBs according to the presence of potential modifying risk factors such as age, sex, race, caffeine or alcohol use, and smoking. There were no significant treatment-by-subgroup interactions except for alcohol use, which seemed to increase the PUB risk among rofecoxib subjects (Table 3).

In this study, ulcer history was a risk factor for PUBs relative risk (RR, 3.32; 95% CI, 1.36–8.09), but the data were too sparse to determine whether ulcer history increased the PUB risk among subjects taking rofecoxib relative to placebo. Data regarding the use of either H₂-receptor antagonists or PPIs and rates of PUBs in our population are reported in Table 3.

Table 2. Summary of Rates and Relative Risks for Confirmed PUBs According to Aspirin Use

	Rofecoxib 25 mg (N = 1287)			Placebo (N = 1300)			Treatment Comparison
	No. at risk	No. of events	Rate/100 patient-yr (95% CI)	No. at risk	No. of events	Rate/100 patient-yr (95% CI)	Relative risk (95% CI)
Low-dose (≤ 100 mg/day) aspirin user at baseline							
No	1074	20	.78 (.47–1.20)	1096	6	.21 (.08–.46)	3.67 (1.42–11.17)
Yes	213	7	1.43 (.57–2.94)	204	0	.00 (.00–.73)	Undefined
Low-dose aspirin user during trial ^a							
No	1054	18	.71 (.42–1.13)	1064	6	.22 (.08–.48)	3.25 (1.24–10.00)
Yes	233	9	1.66 (.76–3.16)	236	0	.00 (.00–.61)	Undefined
Any dose aspirin user during trial ^b							
No	1043	18	.72 (.43–1.14)	1055	6	.22 (.08–.48)	3.25 (1.24–10.01)
Yes	244	9	1.59 (.73–3.01)	245	0	.00 (.00–.58)	Undefined

^aDefined as a patient who took ≤ 100 mg of aspirin or aspirin-containing products for at least 50% of the time while on study therapy and did not start any of these medications after a PUB event.

^bDefined as a patient who took any dose of aspirin or aspirin-containing products for at least 50% of the time while on study therapy and did not start any of these medications after a PUB event.

Table 3. Summary of Rates and Relative Risks for Confirmed PUBs According to Different Risk Factors

	Rofecoxib 25 mg (N = 1287)			Placebo (N = 1300)			Treatment comparison	
	No. at risk	No. of events	Rate/100 patient-year (95% CI)	No. at risk	No. of events	Rate/100 patient-year (95% CI)	Relative risk (95% CI)	P value, subgroup-by-treatment interaction
Age, (y)								.684
<65	903	17	.77 (.45–1.23)	914	3	.13 (.03–.37)	6.11 (1.77–32.52)	
≥65	384	10	1.16 (.56–2.14)	386	3	.31 (.06–.91)	3.75 (.96–21.19)	
Sex ^a								.331
Male	804	22	1.13 (.71–1.71)	805	4	.19 (.05–.48)	5.99 (2.03–23.90)	
Female	483	5	.45 (.15–1.05)	495	2	.16 (.02–.59)	2.74 (.45–28.73)	
Race ^a								.082
White	1082	20	.77 (.47–1.19)	1086	2	.07 (.01–.26)	10.78 (2.62–95.09)	
Other	205	7	1.51 (.61–3.11)	214	4	.74 (.20–1.90)	2.04 (.52–9.48)	
Caffeine user								.224
No	119	3	1.03 (.21–3.01)	132	2	.56 (.07–2.04)	1.83 (.21–21.87)	
Yes	1167	24	.87 (.55–1.29)	1168	4	.13 (.04–.34)	6.47 (2.22–25.66)	
Alcohol user								.028
No	505	7	.59 (.24–1.21)	527	5	.38 (.12–.89)	1.55 (.42–6.19)	
Yes	773	20	1.08 (.66–1.67)	764	1	.05 (.00–.28)	21.66 (3.46–897.64)	
Current cigarette user								.329
No	1007	16	.66 (.38–1.07)	1015	5	.19 (.06–.44)	3.45 (1.21–12.05)	
Yes	280	11	1.74 (.87–3.11)	285	1	.14 (.00–.78)	12.49 (1.82–537.66)	
History of upper-GI ulcers ^a								^b
No	1194	20	.70 (.43–1.08)	1206	6	.19 (.07–.42)	3.61 (1.40–11.00)	
Yes	93	7	3.47 (1.39–7.15)	94	0	.00 (.00–1.55)	(Undefined)	
Use of H2-RA before PUB event								.093
No	1114	22	.83 (.52–1.26)	1142	3	.10 (.02–.30)	8.16 (1.60–30.50)	
Yes	173	5	1.16 (.38–2.71)	158	3	.73 (.15–2.14)	1.59 (.31–10.24)	
Use of PPI before PUB event								.832
No	951	19	.85 (.51–1.32)	970	5	.20 (.06–.47)	4.23 (1.53–14.49)	
Yes	336	8	.97 (.42–1.92)	330	1	.12 (.00–.44)	8.24 (1.10–365.71)	
Region ^a								^b
US	660	10	.64 (.31–1.18)	669	0	.00 (.00–.22)	(Undefined)	
Non-US	627	17	1.13 (.66–1.81)	631	6	.36 (.13–.78)	3.17 (1.19–9.81)	

^aThese variables were found to be associated as risk factors for PUBs.

^bData were too sparse for interaction assessment.

Other GI Adverse Events

Reports of other GI adverse events were collected during the trial but these were not adjudicated. Treatment discontinuation because of a gastrointestinal adverse experience occurred in 2.95% (95% CI, 2.03–3.88) of patients taking rofecoxib and 2.23% (95% CI, 1.43–3.04) of patients taking placebo ($P = .27$). Among other specific side effects commonly associated with NSAID use such as dyspepsia, abdominal pain, or upper abdominal pain,¹² the proportion of patients who reported having one or more of these side effects was 18.6% in the rofecoxib group and 18.5% in the placebo arm.

Discussion

In this randomized, placebo-controlled adenoma chemoprevention trial, we found that, among patients with a history of colorectal adenomas, long-term treatment with standard doses of the COX-2-selective inhibitor rofecoxib was associated with an increased risk of confirmed PUBs compared with placebo. Our findings are supported by results from a previous smaller long-term trial in elderly patients with mild cognitive impairment that also reported an increase in upper-GI events for rofecoxib vs placebo.¹³

It is notable, however, that the absolute rate of PUBs in patients taking rofecoxib was low in this study, lower than in the VIGOR trial,⁶ and much lower than that ascribed to conventional NSAIDs.^{6–8} The reasons for the difference in rates found in patients taking rofecoxib in this study and in the VIGOR trial are not clear, but the 3 main differences between the 2 studies are the dose (50 mg/day in VIGOR vs 25 mg/day in APPROVe), the nature of the baseline disease (rheumatoid arthritis in VIGOR vs a much healthier population in this study), and the use of PPIs by some patients in the APPROVe study. Other potential factors such as naive vs chronic users of NSAIDs, or concomitant low-dose aspirin, might have tended to increase PUB rates in APPROVe.

In contrast to previous experience in patients taking nonselective NSAIDs, rofecoxib was associated with a greater increase of duodenal ulcers than of gastric ulcers. This anatomic pattern of ulcer occurrence is consistent with similar findings obtained in previous studies with rofecoxib, including the VIGOR trial⁶ and Alzheimer disease studies (Alise Reicin, personal communication, March 2006). Because *Helicobacter pylori* infection is the main factor involved in the pathogenesis of duodenal ulcers and previous analyses have reported that *H pylori* infection is a risk factor for peptic ulcer events in patients taking rofecoxib,¹⁴ it would have been of interest to know the *H pylori* status of our patients. Unfortunately, this was not evaluated systematically in this trial.

The only factor identified that significantly modified the relationship between rofecoxib use and PUB risk was alcohol intake. Patients who used alcohol had a rofecoxib rela-

tive risk for developing PUBs that was much higher than those who did not drink alcohol. Alcohol has been identified as a risk factor for upper-GI bleeding in patients taking aspirin and NSAIDs in some observational studies,^{15,16} but other studies including randomized controlled trials did not confirm this.^{14,17} On the other hand, alcohol may prolong the bleeding time after NSAID/aspirin use,¹⁸ but there are no data regarding a possible interaction with coxib use. Furthermore, it must be noted that the definition of alcohol use in this and other studies^{15–18} is vague and includes patients using different types of alcohol and different doses from infrequent to heavy use.

Dyspepsia is a frequent side effect of NSAID use.¹ Coxib use has been associated with a lower frequency of this side effect when compared with nonselective NSAIDs.¹² In this study, the frequency of reported dyspepsia and/or abdominal pain (including upper-abdominal pain) by the investigators was similar in patients and controls, findings consistent with the better profile (coxibs have a lower incidence of dyspepsia when compared to nonselective NSAIDs) described for coxibs than for nonselective NSAIDs.

Our study had limitations that should be taken into account when considering the clinical implications and conclusions obtained. Although the study procedures, event adjudication, and predefined analysis plan addressed GI outcomes, the study was not designed primarily for this analysis. As a result, we may not have optimally identified and categorized all potential GI events that occurred during the trial. A second important limitation is that patients who usually take COX-2-selective inhibitors may be older and have a higher risk of GI complications than our patients,^{12,19} differences that may affect the risk of PUBs and complications when taking this class of drugs. Finally, the study did not compare rofecoxib users with patients taking other analgesics, for example, acetaminophen. Except for prevention studies, such as the one described here, most patients would take a COX inhibitor for some painful condition (eg, arthritis). The results of the present study show that the risk of upper-GI toxicity is greater with COX-2-selective inhibitors than with no therapy (placebo), but that the absolute risk is low. Physicians and their patients should weigh the potential risks and benefits of the use of this class of drugs.

Appendix

The Steering Committee for the APPROVe trial consisted of John A. Baron, MD (Chair), Robert S. Bresalier, MD, Robert S. Sandler, MD, Robert Riddell, MD, Dion Morton, MD, Angel Lanas, MD, Bettina Oxenius MD,* James A. Bolognese MStat,* and Kevin Horgan, MD.*

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References

- Hawkey CJ, Langman MJ. Non-steroidal anti-inflammatory drugs: overall risks and management. Complementary roles for COX-2 inhibitors and proton pump inhibitors. *Gut* 2003;52:600–608.
- Lanza FL, Rack MF, Simon TJ, Quan H, Bolognese JA, Hoover ME, et al. Specific inhibition of cyclooxygenase-2 with MK-0966 is associated with less gastroduodenal damage than either aspirin or ibuprofen. *Aliment Pharmacol Ther* 1999;13:761–767.
- Laine L, Harper S, Simon T, Bath R, Johanson J, Schwartz H, et al. 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. Rofecoxib Osteoarthritis Endoscopy Study Group. *Gastroenterology* 1999;117:776–783.
- Hawkey CJ, Laine L, Simon T, Quan H, Shingo S, Evans J, et al. Incidence of gastroduodenal ulcers in patients with rheumatoid arthritis after 12 weeks of rofecoxib, naproxen, or placebo: a multicentre, randomised, double blind study. *Gut* 2003;52:820–826.
- Hunt RH, Harper S, Watson DJ, Yu C, Quan H, Lee M, Evans JK, Oxenius B. The gastrointestinal safety of the COX-2 selective inhibitor etoricoxib assessed by both endoscopy and analysis of upper gastrointestinal events. *Am J Gastroenterol* 2003;98:1725–1733.
- Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR study group. *N Engl J Med* 2000;343:1520–1530.
- Schnitzer TJ, Burmester GR, Mysler E, Hochberg MC, Doherty M, Ehsam E, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. *Lancet* 2004;364:665–674.
- Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA* 2000;284:1247–1255.
- Singh G, Fort JG, Goldstein JL, Levy RA, Hanrahan PS, Belo AE, et al. Celecoxib versus naproxen and diclofenac in osteoarthritis patients. SUCCESS-I study. *Am J Med* 2006;119:255–266.
- Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;352:1092–1102.
- Bresalier RS, Sandler RS, Bolognese J, Quan H, Oxenius B, Joseph R, et al. A randomized trial of rofecoxib to prevent colorectal adenomas: the Approve trial. *Gastroenterology* 2005;128(Suppl 2):200, A-35.
- Watson DJ, Harper SE, Zhao PL, Quan H, Bolognese JA, Simon TJ. Gastrointestinal tolerability of the selective cyclooxygenase-2 (COX-2) inhibitor rofecoxib compared with nonselective COX-1 and COX-2 inhibitors in osteoarthritis. *Arch Intern Med* 2000;160:2998–3003.
- Thal LJ, Ferris SH, Kirby L, Block GA, Lines CR, Yuen E, Assaid C, Nessly ML, Norman BA, Baranak CC, Reines SA. A randomized, double-blind, study of rofecoxib in patients with mild cognitive impairment. *Neuropsychopharmacology* 2005;30:1204–1215.
- Laine L, Bombardier C, Hawkey CJ, Davis B, Shapiro D, Brett C, Reicin A. Stratifying the risk of NSAID-related upper gastrointestinal clinical events: results of a double-blind outcomes study in patients with rheumatoid arthritis. *Gastroenterology* 2002;123:1006–1012.
- Kaufman DW, Kelly JP, Wiholm BE, Laszlo A, Sheehan JE, Koff RS, et al. The risk of acute major upper gastrointestinal bleeding among users of aspirin and ibuprofen at various levels of alcohol consumption. *Am J Gastroenterol* 1999;94:3189–3196.
- Garcia Rodriguez LA, Cattaruzzi C, Trocon MG, Agostinis L. Risk of hospitalization for upper gastrointestinal tract bleeding associated with ketorolac, other nonsteroidal anti-inflammatory drugs, calcium antagonists, and other antihypertensive drugs. *Arch Intern Med* 1998;158:33–39.
- Holvoet J, Terriere L, Van Hee W, Verbist L, Fierens E, Hautekeete ML. Relation of upper gastrointestinal bleeding to non-steroidal anti-inflammatory drugs and aspirin: a case-control study. *Gut* 1991;32:730–734.
- Schefer AI. Effects of nonsteroidal antiinflammatory drugs on platelet function and systemic hemostasis. *J Clin Pharmacol* 1995;35:209–219.
- Silverstein FE, Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1995;123:241–249.

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