# Gastrointestinal Toxicity With Celecoxib vs Nonsteroidal Anti-inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis

## The CLASS Study: A Randomized Controlled Trial

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**Context** Conventional nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with a spectrum of toxic effects, notably gastrointestinal (GI) effects, because of inhibition of cyclooxygenase (COX)-1. Whether COX-2–specific inhibitors are associated with fewer clinical GI toxic effects is unknown.

**Objective** To determine whether celecoxib, a COX-2–specific inhibitor, is associated with a lower incidence of significant upper GI toxic effects and other adverse effects compared with conventional NSAIDs.

**Design** The Celecoxib Long-term Arthritis Safety Study (CLASS), a double-blind, randomized controlled trial conducted from September 1998 to March 2000.

**Setting** Three hundred eighty-six clinical sites in the United States and Canada.

**Participants** A total of 8059 patients (≥18 years old) with osteoarthritis (OA) or rheumatoid arthritis (RA) were enrolled in the study, and 7968 received at least 1 dose of study drug. A total of 4573 patients (57%) received treatment for 6 months.

**Interventions** Patients were randomly assigned to receive celecoxib, 400 mg twice per day (2 and 4 times the maximum RA and OA dosages, respectively; n=3987); ibuprofen, 800 mg 3 times per day (n=1985); or diclofenac, 75 mg twice per day (n=1996). Aspirin use for cardiovascular prophylaxis (≤325 mg/d) was permitted.

**Main Outcome Measures** Incidence of prospectively defined symptomatic upper GI ulcers and ulcer complications (bleeding, perforation, and obstruction) and other adverse effects during the 6-month treatment period.

**Results** For all patients, the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib vs NSAIDs were 0.76% vs 1.45% ($P=.09$) and 2.08% vs 3.54% ($P=.02$), respectively. For patients not taking aspirin, the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib vs NSAIDs were 0.44% vs 1.27% ($P=.04$) and 1.40% vs 2.91% ($P=.02$). For patients taking aspirin, the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib vs NSAIDs were 2.01% vs 2.12% ($P=.92$) and 4.70% vs 6.00% ($P=.49$). Fewer celecoxib-treated patients than NSAID-treated patients experienced chronic GI blood loss, GI intolerance, hepatotoxicity, or renal toxicity. No difference was noted in the incidence of cardiovascular events between celecoxib and NSAIDs, irrespective of aspirin use.

**Conclusions** In this study, celecoxib, at dosages greater than those indicated clinically, was associated with a lower incidence of symptomatic ulcers and ulcer complications combined, as well as other clinically important toxic effects, compared with NSAIDs at standard dosages. The decrease in upper GI toxicity was strongest among patients not taking aspirin concomitantly.

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For patients with musculoskeletal disorders, conventional nonsteroidal anti-inflammatory drugs (NSAIDs) are a mainstay of clinical care.[1-3] Well-established limitations of NSAID therapy, however, include the risk of developing significant injury to the upper gastrointestinal (GI) tract.[4-10] The annualized incidence rate of symptomatic GI ulcers and ulcer complications in NSAID users ranges from 2% to 4% (1%-2% for ulcer complications alone).[11-13] NSAID-related ulcer complications are estimated to lead to

**For editorial comment see p 1297.**

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107 000 hospitalizations and 16 500 deaths yearly in the United States.[16]

NSAIDs inhibit cyclooxygenase (COX), the enzyme responsible for conversion of arachidonic acid to prostaglandins.[16] COX exists in 2 isoforms.[17] COX-1 is a ubiquitous constitutive isozyme producing prostaglandins responsible for homeostatic functions such as maintenance of GI mucosal integrity.[17] COX-2 is largely a cytokine-induced isozyme producing prostaglandins that mediate pain and inflammation.[17] NSAIDs inhibit both COX-1 and COX-2 to varying degrees.[18,19] Thus, the therapeutic effects of conventional NSAIDs are derived from inhibition of COX-2, while the adverse effects of these agents, particularly in the upper GI tract, arise from inhibition of COX-1 activity.

Celecoxib, a COX-2–specific inhibitor, recently was approved by the US Food and Drug Administration (FDA) for symptomatic treatment of rheumatoid arthritis (RA) and osteoarthritis (OA). To determine whether the COX-2 specificity of celecoxib is associated with lower COX-1–related adverse effects, we compared celecoxib administered at 2 and 4 times the maximum FDA-approved effective dosages for RA and OA, respectively, with commonly used therapeutic dosages of ibuprofen and diclofenac. The dosage of celecoxib exceeded the maximum dosage approved by the FDA for OA and RA to permit a safety assessment of the higher dosages. However, based on previous studies,[20,21] exceeding the dosages approved by the FDA would not improve patients' symptom relief. The dosages of ibuprofen and diclofenac were based on prescription data; 48% and 60% of OA and RA patients, respectively, who received ibuprofen were prescribed a dosage of at least 2400 mg/d, and 36% and 57% of OA and RA patients, respectively, who received diclofenac were prescribed a dosage of at least 150 mg/d.[22]

## METHODS

### Study Population

Outpatients aged 18 years or older were eligible to participate in the study if, on screening, they were diagnosed as having RA or OA evident for at least 3 months and were expected to require continuous treatment with an NSAID for the duration of the trial. Patients were excluded from study participation if at screening they had active GI, renal, hepatic, or coagulation disorders; malignancy (unless removed surgically with no recurrence within 5 years); esophageal or gastroduodenal ulceration within the previous 30 days; history of gastric or duodenal surgery other than an oversew; or known immediate-type hypersensitivity to COX-2 inhibitors, sulfonamides, ibuprofen, or diclofenac. Women were excluded if they were pregnant, might have become pregnant, or were lactating.

### Study Protocol

This prospective, randomized double-blind trial was conducted at 386 centers in the United States and Canada from September 1998 to March 2000 in accordance with the principles of good clinical practice and the Declaration of Helsinki. The protocol was approved by the institutional review board at each study site, and all patients provided written informed consent. Prior to enrollment, patients completed a physical examination and clinical laboratory testing. After a baseline visit, follow-up clinic visits took place at weeks 4, 13, and 26 after the initial dose of medication, and every 13 weeks thereafter. All patients were provided an opportunity to complete a minimum of 6 months of treatment.

Patients withdrawing from study participation prior to 6 months were classified as follows: preexisting violation of entry criteria, protocol noncompliance (investigator-defined failure to comply with the requirements of the protocol, eg, failure to take at least 70% of the study medication in any 13-week interval), treatment failure (investigator-defined failure of study medication to control arthritis signs and symptoms), or adverse effect (investigator-defined signs or symptoms unrelated to arthritis; see "Clinical Assessments" herein). These patients nonetheless were followed up for end-point evaluation for 2 months or until study termination.

### Treatment

Patients were randomly assigned to receive treatments (celecoxib, 400 mg twice per day; ibuprofen, 800 mg 3 times per day; or diclofenac, 75 mg twice per day) on a 2:1:1 basis by an interactive voice response system (ClinPhone, Nottingham, England) according to a computer-generated randomization schedule. All treatment regimens were blinded and double dummy. Treatment assignment for 3 patients was unblinded by study site personnel during trial conduct (1 at the investigation site, 2 via the interactive voice response system). None of these patients experienced a study outcome event. One celecoxib patient experienced diverticular bleeding; 2 patients (1 celecoxib and 1 diclofenac) experienced non–GI-related adverse events; and in no instance was the treatment assignment made known to personnel of the drug company (Pharmacia, Skokie, Ill) or to members of the oversight committees prior to final review of all end points by a GI events committee.

### Concomitant Medications

NSAIDs (except for stable dosages of aspirin up to 325 mg/d); antiulcer drugs (except for occasional antacid use); antibiotics used alone or in combination with omeprazole, lansoprazole, and ranitidine for treatment of *Helicobacter pylori* infection; and antineoplastics (except methotrexate or azathioprine for RA) were prohibited during the study. Use of oral, intramuscular, and intra-articular glucocorticoids and disease-modifying antirheumatic drugs was permitted.

### Clinical Assessments

Investigators were instructed to identify and report all potential upper GI ulcer complications. Evaluation of such events was outlined in a prespecified algorithm structured to reproduce clinical practice norms. Evaluation was required for any of the following presentations: hematemesis; melena; acute

hypovolemia/hypotension; development of postural dizziness, lightheadedness, or syncope; history of dark stool, hematochezia, or anal or rectal bleeding; development of new anemia (defined as a hematocrit level outside of the reference range) or a decrease in hematocrit of at least 5 percentage points; development of dyspepsia, abdominal pain, or nausea or vomiting; or development of occult blood-positive stools. Endoscopy was encouraged to document bleeding lesions but could also be performed if indicated by the investigator's clinical judgment.

All documentation relating to potential ulcer complications was forwarded to a GI events committee (J.L.G., G.E., N.M.A., and W.F.S). The committee collectively reviewed each case in a treatment-blinded fashion and assigned it by unanimous consensus as either meeting or not meeting the definition of an upper GI ulcer complication (TABLE 1). Symptomatic ulcers consisted of cases that did not meet the definition of an ulcer complication but did have endoscopic or x-ray evidence of a gastric or duodenal ulcer as judged by the committee. All patients with symptomatic ulcers or ulcer complications were withdrawn from the study and included in the analysis as having had a study end point.

Adverse effect data were collected at each visit (and as reported spontaneously) using the following question: "Since your last visit, have you experienced or do you currently have any symptoms that are not associated with your arthritis?" All affirmative responses were recorded regardless of severity or relationship to study drug. Laboratory data were also collected at each visit and as indicated according to the investigators' discretion. Clinically significant changes in hematocrit and hemoglobin were predefined as decreases of at least 10 percentage points and 20 g/L, respectively. Clinically significant changes in serum urea nitrogen and creatinine were predefined as values at 6-month follow-up of at least 40 mg/dL (14.3 mmol/L) and 1.8 mg/dL (159 μmol/L), respectively. Clinically significant changes in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were predefined as increases to at least 3 times the upper limit of normal. Trial safety (eg, serious adverse effects) was monitored in a treatment-blinded fashion during the study by the data safety monitoring board (G.F., T.P., A.W., and R.M.).

**Table 1.** Protocol-Specified Definitions and Adjudication Criteria for Ulcer Complications

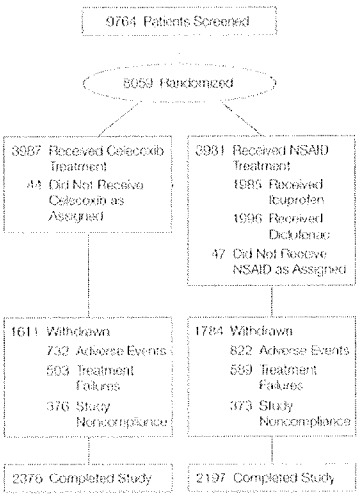
| Event | Criteria for Confirmed Event |
|---|---|
| Gastric or duodenal perforation | Perforated lesion requiring surgery. Could involve a laparoscopic repair, but only if evidence of the perforation was unequivocal, such as free air in the abdomen visible on radiograph or peritoneal signs on physical examination. |
| Gastric outlet obstruction | Gastric outlet obstruction requiring diagnosis by investigator; diagnosis was required to be supported by endoscopy (eg, ulcer with a tight edematous pyloric channel) or by radiographic results (eg, dilated stomach, delayed barium emptying with clinical evidence of outlet obstruction and with an ulcer in the channel, severe outlet narrowing and edema) |
| Upper gastrointestinal bleeding | Hematemesis with a lesion (ulcer or large erosion) on endoscopy or radiograph<br>Lesion (ulcer or large erosion) on endoscopy with evidence of active bleeding or stigmata of a recent hemorrhage (visible vessel or clot attached to the base of an ulcer)<br>Melena with a lesion (ulcer or large erosion) on endoscopy or radiograph<br>Occult blood-positive stool with a lesion (ulcer or large erosion) on endoscopy or radiograph and with evidence of serious bleeding, including at least 1 of the following:<br>Decrease from baseline in hematocrit of ≥5 percentage points or in hemoglobin of ≥15 g/L<br>Postural vital sign changes (increase in heart rate of ≥20/min and/or decrease in systolic blood pressure of ≥20 mm Hg and/or in diastolic blood pressure of ≥10 mm Hg)<br>Transfusion of ≥2 units of blood<br>Blood in stomach on endoscopy or nasogastric aspiration |

## Statistical Analysis

Sample size calculations were based on the assumption that the annualized incidence of upper GI ulcer complications would be 0.3% for celecoxib and 1.2% for NSAIDs. To detect this difference with a 2-sided .05 significance level with statistical power of 85% and assuming a 35% withdrawal rate, a sample size of approximately 4000 patients was required for the celecoxib group and 2000 patients were needed for each of the 2 NSAID groups.

Homogeneity of the treatment groups at baseline was analyzed using the $\chi^2$ test for categorical data and 2-way analysis of variance with treatment and center effects for continuous-valued data. Statistical analyses were conducted on the intent-to-treat population, defined a priori in the protocol as consisting of all patients who received at least 1 dose of assigned study medication. An additional prespecified analysis was performed on the population of patients not taking aspirin (since aspirin use was a predefined risk factor for GI events). Time-to-event analyses of upper GI ulcer complications alone or combined with symptomatic ulcers were performed based on cumulative event rates (symptomatic ulcers and/or ulcer complications) for the 6-month study period and are expressed as annualized incidence rates (number of events per 100 patient-years of exposure or percentage). The log-rank test was used to compare time-to-event curves among treatment groups. Based on the recommendation of the GI events committee and as specified by the protocol a priori, upper GI ulcer complications were defined as a study end point (ie, an uncensored event) if they occurred within the 6-month treatment period and occurred 48 hours after the first dose day or before 14 days after the last known dose of study drug (to avoid confounding due to prestudy or poststudy NSAID use). Patients who had upper GI ulcer complications outside of the specified

**Figure 1.** Flowchart of Patient Disposition at 6 Months




time frame were censored for purposes of time-to-event analysis. This recommendation was based on the pharmacologic washout period for most common NSAIDs and evidence in the literature of carryover effects of NSAIDs in terms of GI toxic effects.[8,23] Analyses were conducted with and without these censored patients. The effects of potential risk factors for the development of an ulcer complication (including but not limited to concurrent aspirin use) were analyzed by Cox proportional hazards models. The incidences of treatment-emergent adverse effects or clinical laboratory changes in the different treatment groups during the 6 months were compared using the Fisher exact test. All *P* values and 95% confidence intervals (CIs) are 2-sided. No significant differences in adverse events were noted by sex, so results are presented with women and men combined. Adverse events for diclofenac and ibuprofen were similar except for liver enzyme elevations, for which results are presented separately.

## RESULTS

A total of 8059 patients were randomized (FIGURE 1). Ninety-one patients did not receive study drug (32 were randomized and found to be ineligible prior to administration of study drug; 59 withdrew consent prior to taking study drug). Of these 91 patients, 44 were randomized to celecoxib and 47 were randomized to NSAIDs.

A total of 7968 patients received at least 1 dose of medication. Of these, 3987 patients were treated with celecoxib, 400 mg twice per day, and 3981 patients were treated with NSAIDs (1985 received ibuprofen, 800 mg 3 times per day, and 1996 received diclofenac, 75 mg twice per day). The celecoxib and NSAID groups had 1441 and 1384 total patient-years of exposure, respectively. Baseline characteristics did not differ significantly between groups (TABLE 2). More than 20% of the patients were taking low-dosage aspirin (≤325 mg/d). Approximately 57% of the patients (n=4573) completed 6 months of treatment (Figure 1). More patients in the NSAID treatment group withdrew from the study for either adverse effects (n=822 [20.6%]) or lack of therapeutic efficacy (n=589 [14.8%]) than did celecoxib-treated patients (n=732 [18.4%] and n=503 [12.6%], respectively; *P*=.01 and *P*=.005; Figure 1). No patients were lost to follow-up (ie, a cause of withdrawal was determined for all patients who withdrew).

**Table 2.** Baseline Patient Characteristics*

| Characteristics | Celecoxib Group (n = 3987) | NSAID Group (n = 3981) |
|---|---|---|
| Age, mean (range), y | 60.6 (20-89) | 59.8 (18-90) |
| >65 y, % | 39.1 | 37.3 |
| >75 y, % | 12.2 | 11.4 |
| Women, % | 68.5 | 69.1 |
| Race/ethnicity, % | | |
| White | 88.5 | 87.9 |
| Black | 7.5 | 8.2 |
| Hispanic | 2.7 | 2.8 |
| Asian | 0.7 | 0.8 |
| Other | 0.6 | 0.6 |
| Primary rheumatoid arthritis, % | 27.3 | 27.5 |
| Duration of disease, mean (SD), y | | |
| Osteoarthritis | 10.3 (9.7) | 10.1 (9.9) |
| Rheumatoid arthritis | 11.3 (9.9) | 10.7 (9.6) |
| NSAID therapy at study entry, % | 81.4 | 81.6 |
| Ibuprofen | 21.7 | 20.9 |
| Diclofenac | 13.6 | 14.0 |
| Potential risk factor, % | | |
| History of gastrointestinal bleeding | 1.7 | 1.5 |
| History of gastrointestinal ulcer | 8.4 | 8.1 |
| *Helicobacter pylori* infection, % | 38.5 | 38.2 |
| Tobacco use, % | 15.8 | 14.9 |
| Alcohol use, % | 30.9 | 30.1 |
| Concurrent medications, % | | |
| Aspirin (≤325 mg/d) | 20.9 | 20.4 |
| Corticosteroids | 30.6 | 29.5 |
| Anticoagulants | 1.1 | 1.1 |

*NSAID indicates nonsteroidal anti-inflammatory drug.

### GI Toxicity

A total of 260 cases were selected by the GI events committee for adjudication. The committee identified 35 upper GI ulcer complications and another 48 cases that represented symptomatic but uncomplicated gastroduodenal ulcers (TABLE 3). Four upper GI ulcer complications (2 in celecoxib-treated patients and 2 in NSAID-treated patients) were censored according to predetermined criteria (see "Methods" section). The remaining 177 cases not meeting the definition of gastroduodenal ulcer or ulcer

complication were assigned a diagnosis from the categories listed in Table 3.

The annualized incidence of upper GI ulcer complications in celecoxib-treated patients was 0.76% (11 events/1441 patient-years) vs an incidence of 1.45% (20 events/1384 patient-years) for patients taking NSAIDs ($P=.09$; FIGURE 2A). The relative risk (RR) for celecoxib compared with NSAIDs was 0.53 (95% CI, 0.26-1.11). The annualized incidence of upper GI ulcer complications plus symptomatic ulcers with celecoxib was 2.08% (30 events/1441 patient-years) vs 3.54% (49 events/1384 patient-years) for patients taking NSAIDs ($P=.02$; Figure 2A). The RR for celecoxib compared with NSAIDs was 0.59 (95% CI, 0.38-0.94).

Inclusion of the 2 censored events in each group did not alter the interpretation of results. For upper GI ulcer complications, the rates without censoring were 0.90% (13 events/1441 patient-years) and 1.59% (22 events/1384 patient-years) for celecoxib and NSAIDs, respectively ($P=.11$). For upper GI ulcer complications plus symptomatic ulcers, the rates were 2.22% (32 events/1441 patient-years) and 3.68% (51 events/1384 patient-years) for celecoxib and NSAIDs, respectively ($P=.03$). Corticosteroid use was not significantly associated with the incidence of upper GI ulcer complications in either treatment group (RR, 0.2 and 0.6 for patients treated with celecoxib and NSAIDs, respectively; $P=.13$ and $P=.27$).

### GI Toxicity With Aspirin Use

Based on time-to-event analyses using a Cox proportional hazard model, low-dosage aspirin use was found to have a significant effect on the incidence of upper GI ulcer complications in celecoxib-treated patients. Within the celecoxib treatment group, the RR of an upper GI ulcer complication was 4.3 with low-dosage aspirin use: 6 events in 833 patients taking low-dosage aspirin vs 5 events in 3154 non–aspirin users ($P=.01$). Low-dosage aspirin use did not have a significant effect on the rate of upper GI ulcer complications in patients receiving NSAIDs (RR, 1.7; $P=.29$).

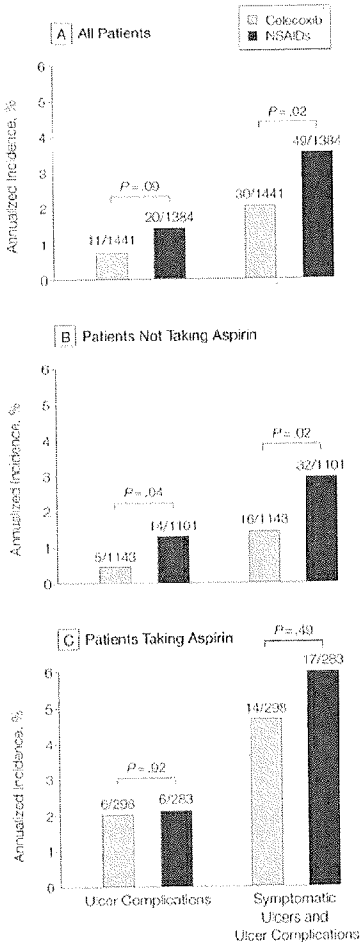
When the non–aspirin-using cohort was examined, 2 upper GI ulcer complications were censored (1 in each group). The annualized incidence of upper GI ulcer complications in non–aspirin users was significantly lower with celecoxib vs NSAIDs (0.44% [5 events/1143 patient-years] vs 1.27% [14 events/1101 patient-years]; $P=.04$; Figure 2B). The RR for celecoxib compared with NSAIDs was 0.35 (95% CI, 0.14-0.98). The annualized incidence

**Table 3.** Adjudicated Cases Meeting and Not Meeting Prespecialized Definitions of Gastroduodenal Ulcers and Ulcer Complications*

| | Celecoxib Group (n = 3987) | NSAID Group (n = 3981) |
|---|---|---|
| Total No. of cases adjudicated | 111 | 149‡ |
| No. of adjudicated cases not meeting the definition of a gastroduodenal ulcer or ulcer complication | | |
| Esophageal disease | 23 | 21 |
| Gastroduodenitis | 12 | 21 |
| Colonic or small bowel disease | 10 | 7 |
| Nonulcer bleeding | 10 | 17 |
| Miscellaneous GI symptoms | 18 | 20 |
| Anemia | 5 | 12 |
| Cholelithiasis | 1 | 0 |
| Total | 79 | 98 |
| No. of adjudicated cases meeting the definition of a gastroduodenal ulcer or ulcer complication | | |
| Gastroduodenal ulcers | 19 | 29 |
| Ulcer complications† | 13 | 22 |
| Upper GI bleeding | 10 | 20 |
| Perforation | 0 | 0 |
| Gastric outlet obstruction | 1 | 0 |
| Total | 32 | 51 |

*NSAID indicates nonsteroidal anti-inflammatory drug; GI, gastrointestinal.
†$P=.001$ vs celecoxib group.
‡Four ulcer complications (2 in the celecoxib group and 2 in the NSAID group) were censored from the analysis because of the timing of the event based on a priori–specified definitions.

**Figure 2.** Annualized Incidence of Upper Gastrointestinal Tract Ulcer Complications Alone and With Symptomatic Gastroduodenal Ulcers




Numbers above bars indicate events per patient-years of exposure. NSAIDs indicates nonsteroidal anti-inflammatory drugs.

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