

COMPARISON OF UPPER GASTROINTESTINAL TOXICITY OF ROFECOXIB AND NAPROXEN IN PATIENTS WITH RHEUMATOID ARTHRITIS

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ABSTRACT

Background Each year, clinical upper gastrointestinal events occur in 2 to 4 percent of patients who are taking nonselective nonsteroidal antiinflammatory drugs (NSAIDs). We assessed whether rofecoxib, a selective inhibitor of cyclooxygenase-2, would be associated with a lower incidence of clinically important upper gastrointestinal events than is the nonselective NSAID naproxen among patients with rheumatoid arthritis.

Methods We randomly assigned 8076 patients who were at least 50 years of age (or at least 40 years of age and receiving long-term glucocorticoid therapy) and who had rheumatoid arthritis to receive either 50 mg of rofecoxib daily or 500 mg of naproxen twice daily. The primary end point was confirmed clinical upper gastrointestinal events (gastroduodenal perforation or obstruction, upper gastrointestinal bleeding, and symptomatic gastroduodenal ulcers).

Results Rofecoxib and naproxen had similar efficacy against rheumatoid arthritis. During a median follow-up of 9.0 months, 2.1 confirmed gastrointestinal events per 100 patient-years occurred with rofecoxib, as compared with 4.5 per 100 patient-years with naproxen (relative risk, 0.5; 95 percent confidence interval, 0.3 to 0.6; $P < 0.001$). The respective rates of complicated confirmed events (perforation, obstruction, and severe upper gastrointestinal bleeding) were 0.6 per 100 patient-years and 1.4 per 100 patient-years (relative risk, 0.4; 95 percent confidence interval, 0.2 to 0.8; $P = 0.005$). The incidence of myocardial infarction was lower among patients in the naproxen group than among those in the rofecoxib group (0.1 percent vs. 0.4 percent; relative risk, 0.2; 95 percent confidence interval, 0.1 to 0.7); the overall mortality rate and the rate of death from cardiovascular causes were similar in the two groups.

Conclusions In patients with rheumatoid arthritis, treatment with rofecoxib, a selective inhibitor of cyclooxygenase-2, is associated with significantly fewer clinically important upper gastrointestinal events than treatment with naproxen, a nonselective inhibitor. (N Engl J Med 2000;343:1520-8.)

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NONSTEROIDAL antiinflammatory drugs (NSAIDs) are among the most commonly used medications in the world.¹ A major factor limiting their use is gastrointestinal toxicity. Although endoscopic studies reveal that gastric or duodenal ulcers develop in 15 to 30 percent of patients who regularly take NSAIDs,² the chief concern is clinically important gastrointestinal problems, such as bleeding. It has been estimated that more than 100,000 patients are hospitalized and 16,500 die each year in the United States as a result of NSAID-associated gastrointestinal events.^{3,4}

Most NSAIDs inhibit both cyclooxygenase-1 and cyclooxygenase-2, isoenzymes involved in the synthesis of prostaglandins.⁵ Cyclooxygenase-1 is constitutively expressed and generates prostanoids involved in the maintenance of the integrity of gastrointestinal mucosa and platelet aggregation,⁶ whereas at sites of inflammation, cyclooxygenase-2 is induced to generate prostaglandins that mediate inflammation and pain.⁷ The antiinflammatory effects of nonselective NSAIDs (those that inhibit both cyclooxygenase-1 and cyclooxygenase-2) therefore appear to be mediated through the inhibition of cyclooxygenase-2,⁸ whereas their harmful effects in the gastrointestinal tract as well as their antiplatelet effects are believed to occur primarily through the inhibition of cyclooxygenase-1.⁵

Agents that selectively inhibit cyclooxygenase-2 have antiinflammatory and analgesic effects that are simi-

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lar to those of nonselective NSAIDs,⁹⁻¹² but they induced significantly fewer ulcers in endoscopic trials.¹²⁻¹⁵ Whether such a decrease in the number of ulcers translates into a similar decrease in the number of clinical gastrointestinal events is a matter of controversy. We performed a prospective, randomized, double-blind comparison of rofecoxib and naproxen in more than 8000 patients with rheumatoid arthritis.

METHODS

Study Population

Patients with rheumatoid arthritis who were at least 50 years old (or at least 40 years old and receiving long-term glucocorticoid therapy) and who were expected to require NSAIDs for at least one year were eligible. Patients were excluded if they had a history of another type of inflammatory arthritis, upper gastrointestinal surgery, or inflammatory bowel disease; an estimated creatinine clearance of 30 ml or less per minute; a positive test for fecal occult blood (this test was performed at base line in all patients); an unstable medical condition; a history of cancer or alcohol or drug abuse in the five years before the study; a history of cerebrovascular events in the two years before the study; or a history of myocardial infarction or coronary bypass in the year before the study. Patients with morbid obesity and those who required or who had been receiving treatment with aspirin, ticlopidine, anticoagulants, cyclosporine, misoprostol, sucralfate, or proton-pump inhibitors or treatment with histamine H₂-receptor antagonists in prescription-strength doses were also excluded from the study. Patients enrolled in the study were not thought to require the use of these agents by their treating physicians.

Study Design

The study was conducted at 301 centers in 22 countries. Three to 14 days after discontinuing NSAIDs, eligible patients were randomly assigned to receive either 50 mg of rofecoxib (Vioxx, Merck, Whitehouse Station, N.J.) once daily or 500 mg of naproxen (Novopharm Biotech, Toronto) twice daily. The groups were stratified according to the presence or absence of a history of gastroduodenal ulcer, upper gastrointestinal bleeding, and gastroduodenal perforation. Blinding was achieved through the use of a matching placebo for each study medication.

Patients were permitted to take acetaminophen, non-NSAID analgesic medications, glucocorticoids, and disease-modifying drugs (e.g., methotrexate) to control their rheumatoid arthritis. Patients were also allowed to take antacids and H₂-receptor antagonists in the following maximal doses: ranitidine, 150 mg daily; famotidine, 20 mg daily; cimetidine, 400 mg daily; and nizatidine, 150 mg daily. Nonstudy NSAIDs were not allowed. After randomization, the patients returned to the clinic at six weeks and at four months and every four months thereafter until the end of the study. Patients were contacted by telephone at week 10 and every four months thereafter. Compliance was assessed by pill counts at clinic visits and by questioning of patients during the scheduled telephone calls. Serum was obtained from all patients for *Helicobacter pylori* testing (HM-CAP, Enteric Products, Stonybrook, N.Y.). Investigators were not informed of the results of these tests during the study.

The institutional review board or ethics review committee at each center approved the protocol, and all patients gave written informed consent. A steering committee oversaw the study design, conduct of the trial, analyses of data, and drafting of this report. This committee was composed of 14 members, 2 of whom were employees of the sponsoring pharmaceutical company. An independent data and safety monitoring board monitored the patients' safety. An independent, external (end-point) committee whose members were unaware of the patients' treatment assignments reviewed the data to determine which patients had reached the study end points. Because highly selective cyclooxygenase-2 inhibitors do not inhibit

platelet aggregation, which is mediated by cyclooxygenase-1, there was a possibility that the incidence of thrombotic cardiovascular events would be lower among patients treated with nonselective cyclooxygenase inhibitors than among those treated with cyclooxygenase-2-selective inhibitors. Therefore, cardiovascular events were also assessed for a future meta-analysis by independent committees whose members were unaware of the patients' treatment assignments. A separate analysis of these events, however, was not specified in the study design.

Study End Points

Patients who had potential clinical upper gastrointestinal events were evaluated and treated according to the standard practice of the physicians who were caring for them. Patients who stopped taking the study medication before the study ended were followed until the end of the study to determine whether an upper gastrointestinal event had occurred. Only events that were confirmed by the end-point committee according to prespecified criteria (Table 1) and that occurred during treatment or within 14 days after the discontinuation of treatment were included in the primary analysis.

In addition, the protocol called for the analysis of all episodes of gastrointestinal bleeding, including confirmed and unconfirmed episodes of upper gastrointestinal bleeding, and bleeding from a site beyond the duodenum that resulted in hospitalization, discontinuation of treatment, or a decrease in the hemoglobin level of at least 2 g per deciliter.

Assessment of Efficacy

For each patient both the investigator and the patient answered a Global Assessment of Disease Activity question at base line (after the discontinuation of prestudy NSAIDs), 6 weeks, 4 months, and 12 months and at the end of the study or when treatment was discontinued. The score can range from 0 ("very well") to 4 ("very poor"), and higher scores indicate more disease activity. The Modified Health Assessment questionnaire was administered only to patients enrolled at centers in the United States at base line, at six weeks, and at the end of the study or when treatment was discontinued. This questionnaire evaluates the extent of functional disability in eight types of tasks performed on a daily basis. The level of effort required to perform each task is assessed on a 4-point scale on which a score of 0 indicates no difficulty in performing the task and a score of 3 indicates an inability to perform the task.¹⁶ Higher scores indicate more severe disability.

Statistical Analysis

The primary hypothesis was that the risk of confirmed upper gastrointestinal events (gastroduodenal perforation or obstruction, upper gastrointestinal bleeding, and symptomatic gastroduodenal ulcers) would be lower among patients who were taking rofecoxib than among those who were taking naproxen. Secondary hypotheses were that the risk of confirmed complicated events (perforation, obstruction, and severe upper gastrointestinal bleeding) and the risk of both confirmed and unconfirmed upper gastrointestinal events would be lower among patients who were taking rofecoxib.

Cox proportional-hazards analysis was used to compare the effect of treatment; the presence or absence of a history of gastrointestinal events was a stratification factor in the analysis.^{17,18} The scores for the Global Assessment of Disease Activity question and Modified Health Assessment questionnaire were analyzed in terms of the mean change from base line during the treatment period. The primary population for analysis comprised all randomized patients. Subgroup analyses were conducted with use of Cox regression analysis.^{17,18} Interactions between treatments and subgroups were assessed to determine whether the effect of rofecoxib as compared with that of naproxen was consistent in the subgroups. We assessed data on general safety by evaluating 95 percent confidence intervals of the differences in the proportions of the treatment groups with each adverse event.¹⁹ All statistical tests were two-sided.

TABLE 1. CRITERIA FOR GASTROINTESTINAL EVENTS.

EVENT	CRITERIA REQUIRED FOR CONFIRMATION OF EVENT
Perforation due to nonmalignant gastric or duodenal ulcer	Evidence of perforation on endoscopy, at surgery, on radiography (evidence of free intraabdominal air or extravasation of contrast medium), or at autopsy
Obstruction due to gastric or duodenal ulcer	Occurrence of nausea and vomiting ≥ 24 hours postprandially and evidence of narrowing of distal portion of stomach or duodenum as a result of a nonmalignant ulcer on endoscopy, at surgery, on radiography, or at autopsy
Upper gastrointestinal bleeding	Episode of hematemesis or aspiration of bloody gastric fluid witnessed by health care provider; episode of melena witnessed by health care provider; evidence of active bleeding on endoscopy, at surgery, or on angiography; positive test for fecal occult blood with documented upper gastrointestinal lesion judged to be the source and associated with either clinically significant bleeding or decrease in volume* or evidence of visible vessel, clot, or pigmented spot on ulcer at endoscopy; or episode of hematemesis or melena reported by patient with upper gastrointestinal lesion judged to be the source and associated with either clinically significant bleeding or decrease in volume* or evidence of visible vessel, clot, or pigmented spot on ulcer at endoscopy
Gastric or duodenal ulcer	Evidence of gastric or duodenal ulcer on endoscopy, at surgery, on contrast-enhanced radiography of the upper gastrointestinal tract, or at autopsy

*A decrease in volume was defined by the finding of a decrease in hemoglobin of at least 2 g per deciliter; by the finding of an orthostatically induced change in pulse of more than 20, change in systolic blood pressure of more than 20 mm Hg, or change in diastolic blood pressure of more than 10 mm Hg; by the finding of other evidence of a clinically significant reduction in circulatory volume (e.g., clinically significant hypotension that is corrected by volume replacement); or by the need for blood transfusion.

RESULTS

Characteristics of the Patients

Between January 1999 and July 1999, we screened 9539 patients and enrolled 8076; 4047 were randomly assigned to receive rofecoxib, and 4029 to receive naproxen. The major reasons for exclusion were a contraindication to prolonged NSAID therapy (in the case of 246 patients), a positive test for fecal occult blood (203 patients), and a failure to meet inclusion criteria (355 patients). The median follow-up was 9.0 months in both treatment groups (range, 0.5 to 13). A total of 5742 patients (71.1 percent) continued to take their assigned medication until the end of the study. Rates of discontinuation were similar in the two groups: 29.3 percent in the rofecoxib group (16.4 percent because of adverse events, 6.3 percent because of a lack of efficacy, and 6.6 percent for other reasons) and 28.5 percent in the naproxen group (16.1 percent because of adverse events, 6.5 percent because of a lack of efficacy, and 5.9 percent for other reasons). Ninety-nine percent of the patients in both groups took their medication on at least 75 percent of the study days. The base-line characteristics were similar in the two groups (Table 2).

Efficacy

Rofecoxib and naproxen had similar efficacy against rheumatoid arthritis (Table 3). In addition, the rates of discontinuation of treatment owing to a lack of efficacy were low in both groups (6.3 percent in the rofecoxib group and 6.5 percent in the naproxen group).

Adverse Gastrointestinal Events

Confirmed upper gastrointestinal events occurred in 177 patients. In 53 of these patients the event was complicated. An additional 13 patients had events that were reported by investigators but that were judged by the end-point committee to be unconfirmed.

The time to the development of a confirmed upper gastrointestinal event is shown in Figure 1. The rates per 100 patient-years and incidences of the pre-specified clinical events are shown in Tables 4 and 5, respectively. The relative risk of confirmed upper gastrointestinal events for patients in the rofecoxib group as compared with those in the naproxen group was 0.5 (95 percent confidence interval, 0.3 to 0.6; $P < 0.001$), whereas the relative risk of complicated confirmed upper gastrointestinal events was 0.4 (95 percent confidence interval, 0.2 to 0.8; $P = 0.005$). The relative risk of complicated upper gastrointestinal bleeding for patients in the rofecoxib group as compared with those in the naproxen group was 0.4 (95 percent confidence interval, 0.2 to 0.7; $P = 0.004$), whereas the relative risk of bleeding beyond the duodenum was 0.5 (95 percent confidence interval, 0.2 to 0.9; $P = 0.03$).

A per-protocol analysis of the 7925 patients without substantial protocol violations demonstrated relative risks of confirmed upper gastrointestinal events and complicated confirmed events of 0.4 (95 percent confidence interval, 0.3 to 0.6; $P < 0.001$) and 0.4 (95 percent confidence interval, 0.2 to 0.7; $P = 0.003$), respectively. The results of an intention-to-treat analysis of all confirmed upper gastrointestinal

TABLE 2. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	ROFECOXIB GROUP (N=4047)	NAPROXEN GROUP (N=4029)
Age — yr	58±9	58±10
Female sex — no. (%)	3223 (79.6)	3215 (79.8)
Race or ethnic group — no. (%)		
White	2761 (68.2)	2750 (68.3)
Black	207 (5.1)	202 (5.0)
Asian	101 (2.5)	85 (2.1)
Hispanic	501 (12.4)	516 (12.8)
Other	477 (11.8)	476 (11.8)
Duration of disease — no. (%)		
Unknown	3 (0.1)	6 (0.1)
<2 yr	430 (10.6)	455 (11.3)
2–10 yr	1991 (49.2)	1996 (49.5)
>10 yr	1623 (40.1)	1572 (39.0)
Positive test for rheumatoid factor — no. (%)	2946 (72.8)	2967 (73.6)
Prior use of NSAIDs — no. (%)	3321 (82.1)	3331 (82.7)
Treatment for rheumatoid arthritis — no. (%)		
Glucocorticoids	2260 (55.8)	2263 (56.2)
Methotrexate	2263 (55.9)	2269 (56.3)
Other disease-modifying drugs	1847 (45.6)	1826 (45.3)
Low-dose H ₂ -receptor antagonists — no. (%)†	365 (9.0)	335 (8.3)
History of clinical gastrointestinal events	314 (7.7)	316 (7.8)
Global Disease Activity score‡		
Patient's assessment	2.0±0.9	2.0±0.9
Investigator's assessment	1.9±0.8	1.9±0.8
American College of Rheumatology functional class — no. (%)§		
I	881 (21.8)	830 (20.6)
II	2160 (53.4)	2199 (54.6)
III	928 (22.9)	932 (23.1)
IV	78 (1.9)	68 (1.7)

*Plus-minus values are means ±SD. NSAIDs denotes nonselective nonsteroidal antiinflammatory drugs.

†A low dose was defined as a maximal daily dose of 150 mg of ranitidine, 20 mg of famotidine, 400 mg of cimetidine, and 150 mg of nizatidine.

‡Scores can range from 0 ("very well") to 4 ("very poor"). Higher scores indicate more disease activity.

§According to the American College of Rheumatology's system of classification, functional class I indicates complete ability to perform usual activities of daily living, and class IV indicates limited ability to perform usual activities of daily living.

events throughout the study, including those that occurred at any time after the discontinuation of treatment, were similar and remained statistically significant (data not shown).

Subgroup analyses showed the following relative risks of clinical gastrointestinal events among the patients in the rofecoxib group as compared with those in the naproxen group: patients with no prior gastrointestinal events (relative risk, 0.5; 95 percent confidence interval, 0.3 to 0.7), patients with prior gastrointestinal events (relative risk, 0.4; 95 percent confidence interval, 0.2 to 0.8), patients with no glucocorticoid therapy at base line (relative risk, 0.7; 95 percent confidence interval, 0.4 to 1.2), and pa-

tients with glucocorticoid therapy at base line (relative risk, 0.4; 95 percent confidence interval, 0.2 to 0.6). The relative risks in these subgroups and the other prespecified subgroups (defined according to sex, race or ethnic group, and location of study center) were not significantly different, indicating that there was no significant interaction between the treatments and the subgroups.

Treatment with rofecoxib was associated with a significantly lower incidence of clinical gastrointestinal events regardless of the results of serologic tests for *H. pylori*. However, the relative risks of clinical events among *H. pylori*-negative patients and *H. pylori*-positive patients were significantly different ($P=0.04$, data not shown). Finally, the relative risk of gastrointestinal events remained significantly lower (0.1; 95 percent confidence interval, 0.02 to 1.0) in the rofecoxib group than in the naproxen group even in a subgroup at very low risk (i.e., patients who were younger than 65 years, who were negative for *H. pylori*, who had no history of a clinical gastrointestinal event, and who were not taking glucocorticoids at base line).

General Safety

The safety of both rofecoxib and naproxen was similar to that reported in previous studies.^{20,21} The mortality rate was 0.5 percent in the rofecoxib group and 0.4 percent in the naproxen group. The rate of death from cardiovascular causes was 0.2 percent in both groups. Ischemic cerebrovascular events occurred in 0.2 percent of the patients in each group. Myocardial infarctions were less common in the naproxen group than in the rofecoxib group (0.1 percent vs. 0.4 percent; 95 percent confidence interval for the difference, 0.1 to 0.6 percent; relative risk, 0.2; 95 percent confidence interval, 0.1 to 0.7). Four percent of the study subjects met the criteria of the Food and Drug Administration (FDA) for the use of aspirin for secondary cardiovascular prophylaxis (presence of a history of myocardial infarction, angina, cerebrovascular accident, transient ischemic attack, angioplasty, or coronary bypass)²² but were not taking low-dose aspirin therapy. These patients accounted for 38 percent of the patients in the study who had myocardial infarctions. In the other patients the difference in the rate of myocardial infarction between groups was not significant (0.2 percent in the rofecoxib group and 0.1 percent in the naproxen group). When the data showing a reduction in the rate of myocardial infarction in the naproxen group became available after the completion of this trial, Merck, the manufacturer of rofecoxib, notified all investigators in ongoing studies of a change in the exclusion criteria to allow patients to use low-dose aspirin. There was no association between hypertension and myocardial infarction; only a single patient (in the rofecoxib group) had both hypertension and a myocardial infarction as adverse events.

TABLE 3. EFFECTIVENESS OF ROFECOXIB AND NAPROXEN FOR RHEUMATOID ARTHRITIS.*

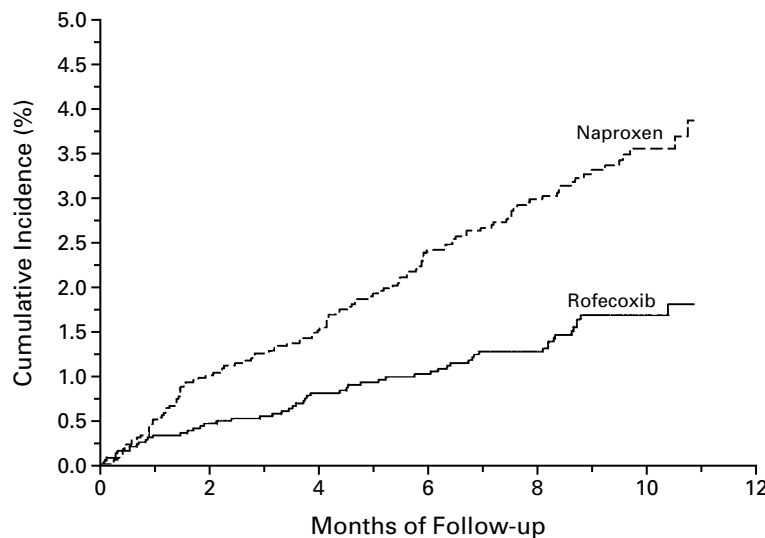
VARIABLE	BASE-LINE SCORE		CHANGE IN SCORE DURING TREATMENT		LEAST-SQUARES MEAN DIFFERENCE BETWEEN GROUPS (95% CI)†
	ROFECOXIB GROUP	NAPROXEN GROUP	ROFECOXIB GROUP	NAPROXEN GROUP	
Global Disease Activity score‡					
Patient's assessment	1.96±0.93	1.99±0.94	-0.51±0.93	-0.53±0.94	0.00 (-0.03 to 0.03)
Investigator's assessment	1.85±0.80	1.87±0.78	-0.49±0.84	-0.52±0.85	0.01 (-0.02 to 0.04)
Modified Health Assessment score§	0.59±0.49	0.59±0.49	-0.11±0.37	-0.12±0.36	0.01 (-0.01 to 0.04)

*Plus-minus values are means ±SD.

†The values were calculated by analysis of variance in a model that included treatment assignment and presence or absence of a history of gastrointestinal events and the base-line value as covariates. CI denotes confidence interval.

‡Scores can range from 0 ("very well") to 4 ("very poor"). Higher scores indicate more disease activity.

§Scores can range from 0 (no difficulty in performing a task) to 3 (unable to perform the task). Higher scores indicate more severe disability. The questionnaire was administered only to patients enrolled at centers in the United States (1735 in the rofecoxib group and 1732 in the naproxen group).



No. AT RISK	0	2	4	6	8	10	12
Rofecoxib	4047	3641	3402	3180	2806	1073	533
Naproxen	4029	3644	3389	3163	2796	1071	513

Figure 1. Cumulative Incidence of the Primary End Point of a Confirmed Upper Gastrointestinal Event among All Randomized Patients.

The most common adverse events leading to discontinuation of treatment, excluding the gastrointestinal end points, were dyspepsia, abdominal pain, epigastric discomfort, nausea, and heartburn. In the rofecoxib group, significantly fewer patients discontinued treatment as a result of any one of these five upper gastrointestinal symptoms than in the naprox-

en group (3.5 percent vs. 4.9 percent). The rates of discontinuation for any gastrointestinal events, including gastrointestinal end points, were also significantly lower in the rofecoxib group than in the naproxen group (7.8 percent vs. 10.6 percent). The incidence of adverse effects related to renal function was low and was similar in the two groups (1.2 percent in the ro-

TABLE 4. INCIDENCE OF GASTROINTESTINAL EVENTS IN THE TREATMENT GROUPS.

TYPE OF EVENT	ROFECOXIB GROUP (N=4047)	NAPROXEN GROUP (N=4029)	ROFECOXIB GROUP (N=4047)	NAPROXEN GROUP (N=4029)	RELATIVE RISK (95% CI)*	P VALUE
	no. with event		rate/100 patient-yr			
Confirmed upper gastrointestinal events	56	121	2.1	4.5	0.5 (0.3–0.6)	<0.001
Complicated confirmed upper gastrointestinal events	16	37	0.6	1.4	0.4 (0.2–0.8)	0.005
Confirmed and unconfirmed upper gastrointestinal events†	58	132	2.2	4.9	0.4 (0.3–0.6)	<0.001
Complicated confirmed and unconfirmed upper gastrointestinal events‡	17	42	0.6	1.6	0.4 (0.2–0.7)	0.002
All episodes of gastrointestinal bleeding	31	82	1.1	3.0	0.4 (0.3–0.6)	<0.001

*CI denotes confidence interval.

†The analysis includes 13 events that were reported by investigators but were considered to be unconfirmed by the end-point committee.

‡The analysis includes six events that were reported by investigators but that were considered to be unconfirmed by the end-point committee.

TABLE 5. INCIDENCE OF CONFIRMED UPPER GASTROINTESTINAL EVENTS.*

TYPE OF UPPER GASTROINTESTINAL EVENT	ALL CONFIRMED UPPER GASTROINTESTINAL EVENTS		ALL COMPLICATED CONFIRMED UPPER GASTROINTESTINAL EVENTS	
	ROFECOXIB GROUP (N=4047)	NAPROXEN GROUP (N=4029)	ROFECOXIB GROUP (N=4047)	NAPROXEN GROUP (N=4029)
	number (percent)			
Perforations†	3 (0.1)‡	4 (0.1)	3 (0.1)	4 (0.1)
Gastric ulcer	28 (0.7)	81 (2.0)	1 (<0.1)	6 (0.1)
Duodenal ulcer	27 (0.7)	39 (1.0)	3 (0.1)	5 (0.1)
Obstruction†	1 (<0.1)	0	1 (<0.1)	0
Bleeding	14 (0.3)	35 (0.9)	12 (0.3)§	32 (0.8)¶
Total	56 (1.4)	121 (3.0)	16 (0.4)	37 (0.9)

*Patients may have been included in more than one column, but each is counted only once in the total.

†Perforations and obstructions are complicated events by definition.

‡Two confirmed upper gastrointestinal events occurred after only one dose of rofecoxib and most likely resulted from prior use of nonselective nonsteroidal antiinflammatory drugs.

§The cause or source of bleeding was gastric ulcers in five patients, duodenal ulcers in five, and other upper gastrointestinal source in three. One patient in the rofecoxib group had both a gastric and a duodenal ulcer.

¶The cause or source of bleeding was gastric ulcers in 16 patients, duodenal ulcers in 9, and other upper gastrointestinal sources in 7.

fecoxib group and 0.9 percent in the naproxen group); only 0.2 percent of patients in each group discontinued treatment because of these adverse effects.

DISCUSSION

We found that, in patients with rheumatoid arthritis, treatment with rofecoxib at twice the maximal dose approved by the FDA for long-term use resulted in sig-

nificantly lower rates of clinically important upper gastrointestinal events and complicated upper gastrointestinal events than did treatment with a standard dose (1000 mg per day) of naproxen. We also found that the incidence of complicated upper gastrointestinal bleeding and bleeding from beyond the duodenum was significantly lower among patients who received rofecoxib. Only 41 patients would need to be treated

with rofecoxib rather than naproxen to avert one clinical upper gastrointestinal event in a one-year period. Although the optimal dose of rofecoxib for the treatment of rheumatoid arthritis has yet to be determined, data from a prior study indicate that maximal efficacy is achieved at a daily dose of 25 mg.²³

A prospective study that compared NSAIDs alone with NSAIDs plus misoprostol reported that 0.95 percent of patients with rheumatoid arthritis who were taking an NSAID alone had upper gastrointestinal complications over a period of six months,²⁴ with a relative reduction in the risk of such complications with combination treatment of 40 percent during this period. These results are similar to our finding of a cumulative incidence of serious upper gastrointestinal events over a six-month period of 0.75 percent in the naproxen group and a relative reduction in risk of 67 percent in the rofecoxib group (data not shown). A 50 percent reduction in the incidence of clinically important upper gastrointestinal events with rofecoxib as compared with a nonselective NSAID was also found in a prespecified combined analysis of eight double-blind studies that included 4921 patients with osteoarthritis, none of whom received glucocorticoids.²⁵ Patients with rheumatoid arthritis have a higher risk of upper gastrointestinal events than do patients with osteoarthritis.⁴ Thus, the results of our study extend the results of the combined analysis to a group of patients at higher risk of bleeding.

The results of a randomized, double-blind comparison of the cyclooxygenase-2-selective inhibitor celecoxib and the nonselective NSAIDs ibuprofen and diclofenac were recently published.²⁶ In this trial of 7968 patients, 73 percent of whom had osteoarthritis and 27 percent of whom had rheumatoid arthritis, data were reported from the first 6 months of a study period that extended for up to 13 months. Treatment with celecoxib was associated with a non-significant ($P=0.09$) trend toward a decrease in the incidence of the primary end point (complicated ulcers and erosions) and a significant decrease ($P=0.02$) in the incidence of the secondary end point (complicated and symptomatic ulcers).

The incidence of clinically important gastrointestinal events was lower in the rofecoxib group than in the naproxen group in all subgroups we examined. Concomitant glucocorticoid and NSAID therapy has been reported to be associated with a higher risk of a clinical gastrointestinal event than is NSAID therapy alone.⁴ Therefore, a larger reduction in the incidence of events might have been expected in the subgroup that received both an NSAID and glucocorticoids. There was a greater reduction in the relative risk of events in the subgroup of patients who were taking glucocorticoids at base line than in the subgroup of patients who were not taking glucocorticoids at base line, but the difference between the groups was not significant.

Whether ulcers identified by endoscopic examination are markers of a clinical gastrointestinal event has been a matter of controversy. The relative reduction in the risk of such ulcers in two identical studies that compared 50 mg of rofecoxib daily with 800 mg of ibuprofen three times a day was 71 percent at six months.^{13,14} Thus, our findings support the concept that the results of endoscopic studies of ulcers can be extrapolated to clinical gastrointestinal events.

In prior endoscopic studies, the frequency of ulcers was similar in patients taking rofecoxib and those taking placebo.^{13,14} We could not include a placebo group, and no studies have yet assessed whether a cyclooxygenase-2-selective inhibitor or the combination of nonselective NSAIDs plus gastroprotective drugs (such as misoprostol and proton-pump inhibitors) will achieve similar results.

Gastrointestinal symptoms are extremely common with NSAID therapy, as demonstrated by the fact that, in our study, the five most common adverse events leading to the discontinuation of treatment were upper gastrointestinal symptoms. Although gastrointestinal symptoms are poorly correlated with endoscopic findings of ulcers or clinical gastrointestinal events,²⁷ significantly fewer patients in the rofecoxib group than in the naproxen group discontinued treatment because of gastrointestinal symptoms.

The overall mortality rate was similar in the two groups, as were the rates of death from gastrointestinal events and from cardiovascular causes. The rate of myocardial infarction was significantly lower in the naproxen group than in the rofecoxib group (0.1 percent vs. 0.4 percent). This difference was primarily accounted for by the high rate of myocardial infarction among the 4 percent of the study population with the highest risk of a myocardial infarction, for whom low-dose aspirin is indicated.²² The difference in the rates of myocardial infarction between the rofecoxib and naproxen groups was not significant among the patients without indications for aspirin therapy as secondary prophylaxis.

Naproxen inhibits the production of thromboxane by 95 percent and inhibits platelet aggregation by 88 percent, and this effect is maintained throughout the dosing interval²⁸; therefore, the effects of regular use of naproxen may be similar to those of aspirin. Flurbiprofen, another NSAID that is a potent inhibitor of platelet-derived thromboxane, led to a 70 percent reduction in the rate of reinfarction as compared with placebo among patients in whom acute myocardial infarction was successfully treated with thrombolysis, angioplasty, or both.²⁹

Analyses of 7535 patients in double-blind trials comparing rofecoxib with placebo and other NSAIDs (diclofenac, ibuprofen, and nabumetone) that do not produce sustained, maximal inhibition of platelet aggregation revealed similar rates of myocardial infarction in all groups³⁰ (and unpublished data). Thus, our

results are consistent with the theory that naproxen has a coronary protective effect and highlight the fact that rofecoxib does not provide this type of protection owing to its selective inhibition of cyclooxygenase-2 at its therapeutic dose and at higher doses. The finding that naproxen therapy was associated with a lower rate of myocardial infarction needs further confirmation in larger studies.

In summary, the use of the cyclooxygenase-2-selective inhibitor rofecoxib resulted in significantly fewer clinically important upper gastrointestinal events than did treatment with naproxen, a nonselective NSAID. The two drugs had similar rates of clinical effectiveness.

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APPENDIX

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REFERENCES

- Misoprostol for co-prescription with NSAIDs. *Drug Ther Bull* 1990; 28:25-6.

2. Laine L. Nonsteroidal anti-inflammatory drug gastropathy. *Gastrointest Endosc Clin North Am* 1996;6:489-504.
3. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of non-steroidal antiinflammatory drugs. *N Engl J Med* 1999;340:1888-99. [Erratum, *N Engl J Med* 1999;341:548.]
4. Singh G, Rosen Ramey D. NSAID induced gastrointestinal complications: the ARAMIS perspective — 1997. *J Rheumatol Suppl* 1998;51:8-16.
5. Cryer B. Nonsteroidal anti-inflammatory drugs and gastrointestinal disease. In: Feldman M, Schar Schmidt BF, Sleisenger MH, eds. *Sleisenger and Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management*. 6th ed. Vol. 1. Philadelphia: W.B. Saunders, 1998:343-57.
6. Meade EA, Smith WL, DeWitt DL. Differential inhibition of prostaglandin endoperoxide synthase (cyclooxygenase) isoenzymes by aspirin and other non-steroidal anti-inflammatory drugs. *J Biol Chem* 1993;268:6610-4.
7. Fosslein E. Adverse effects of nonsteroidal anti-inflammatory drugs on the gastrointestinal system. *Ann Clin Lab Sci* 1998;28:67-81.
8. Mitchell JA, Akarasereonont P, Thiemeermann C, Flower RJ, Vane JR. Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. *Proc Natl Acad Sci U S A* 1993;90:11693-7.
9. Day R, Morrison B, Luza A, et al. A randomized trial of the efficacy and tolerability of the COX-2 inhibitor rofecoxib vs ibuprofen in patients with osteoarthritis. *Arch Intern Med* 2000;160:1781-7.
10. Cannon GW, Caldwell JR, Holt P, et al. Rofecoxib, a specific inhibitor of cyclooxygenase 2, with clinical efficacy comparable with that of diclofenac sodium: results of a one-year, randomized, clinical trial in patients with osteoarthritis of the knee and hip. *Arthritis Rheum* 2000;43:978-87.
11. Ehrlich EW, Schnitzer TJ, McIlwain H, et al. Effect of specific COX-2 inhibition in osteoarthritis of the knee: a 6 week double blind, placebo controlled pilot study of rofecoxib. *J Rheumatol* 1999;26:2438-47.
12. 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;282:1921-8.
13. Laine L, Harper S, Simon T, 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. *Gastroenterology* 1999;117:776-83.
14. Hawkey C, Laine L, Simon T, et al. Comparison of the effect of rofecoxib (a cyclooxygenase 2 inhibitor), ibuprofen, and placebo on the gastroduodenal mucosa of patients with osteoarthritis: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2000;43:370-7.
15. Emery P, Zeidler H, Kvien KT, et al. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. *Lancet* 1999;354:2106-11.
16. Pincus T, Summey JA, Soraci SA Jr, Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. *Arthritis Rheum* 1983;26:1346-53.
17. Cox DR. Regression models and life-tables. *J Stat Soc [B]* 1972;34:187-220.
18. *Idem*. Partial likelihood. *Biometrika* 1975;62:269-76.
19. Fleiss JL. *Statistical methods for rates and proportions*. 2nd ed. New York: John Wiley, 1981.
20. Vioxx (rofecoxib tablets and oral suspension). Whitehouse Station, N.J.: Merck, 1999 (package insert).
21. Naproxen. Nutley, N.J.: Roche Laboratories, 1999 (package insert).
22. Genuine Bayer aspirin. Morristown, N.J.: Bayer Consumer Care Division, 1999 (package insert).
23. Schnitzer TJ, Truitt K, Fleischmann R, et al. The safety profile, tolerability, and effective dose range of rofecoxib in the treatment of rheumatoid arthritis. *Clin Ther* 1999;21:1688-702.
24. Silverstein FE, Graham DY, Senior JR, 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;123:241-9.
25. Langman MJ, Jensen DM, Watson DJ, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. *JAMA* 1999;282:1929-33.
26. 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;284:1247-55.
27. Singh G, Ramey DR, Morfeld D, Shi H, Hatoum HT, Fries JF. Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis: a prospective observational cohort study. *Arch Intern Med* 1996;156:1530-6.
28. VanHecken A, Schwartz JJ, Depré M, et al. Comparative inhibitory activity of rofecoxib, meloxicam, diclofenac, ibuprofen and naproxen on COX-2 versus COX-1 in healthy volunteers. *J Clin Pharmacol* 2000;40:1109-20.
29. Brochier ML. Evaluation of flurbiprofen for prevention of reinfarction and reocclusion after successful thrombolysis or angioplasty in acute myocardial infarction: the Flurbiprofen French Trial. *Eur Heart J* 1993;14:951-7.
30. Daniels B, Seidenberg B. Cardiovascular safety profile of rofecoxib in controlled clinical trials. *Arthritis Rheum* 1999;42:Suppl:S143. abstract.