

CELECOXIB VERSUS DICLOFENAC AND OMEPRAZOLE IN REDUCING THE RISK OF RECURRENT ULCER BLEEDING IN PATIENTS WITH ARTHRITIS

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ABSTRACT

Background Current guidelines recommend that patients at risk for ulcer disease who require treatment for arthritis receive nonsteroidal antiinflammatory drugs (NSAIDs) that are selective for cyclooxygenase-2 or the combination of a nonselective NSAID with a proton-pump inhibitor. We assessed whether celecoxib would be similar to diclofenac plus omeprazole in reducing the risk of recurrent ulcer bleeding in patients at high risk for bleeding.

Methods We studied patients who used NSAIDs for arthritis and who presented with ulcer bleeding. After their ulcers had healed, we randomly assigned patients who were negative for *Helicobacter pylori* to receive either 200 mg of celecoxib twice daily plus daily placebo or 75 mg of diclofenac twice daily plus 20 mg of omeprazole daily for six months. The end point was recurrent ulcer bleeding.

Results In the intention-to-treat analysis, which included 287 patients (144 receiving celecoxib and 143 receiving diclofenac plus omeprazole), recurrent ulcer bleeding occurred in 7 patients receiving celecoxib and 9 receiving diclofenac plus omeprazole. The probability of recurrent bleeding during the six-month period was 4.9 percent (95 percent confidence interval, 3.1 to 6.7) for patients who received celecoxib and 6.4 percent (95 percent confidence interval, 4.3 to 8.4) for patients who received diclofenac plus omeprazole (difference, -1.5 percentage points; 95 percent confidence interval for the difference, -6.8 to 3.8). Renal adverse events, including hypertension, peripheral edema, and renal failure, occurred in 24.3 percent of the patients receiving celecoxib and 30.8 percent of those receiving diclofenac plus omeprazole.

Conclusions Among patients with a recent history of ulcer bleeding, treatment with celecoxib was as effective as treatment with diclofenac plus omeprazole, with respect to the prevention of recurrent bleeding. Renal toxic effects are common in high-risk patients receiving celecoxib or diclofenac plus omeprazole. (N Engl J Med 2002;347:2104-10.)

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NONSTEROIDAL antiinflammatory drugs (NSAIDs) are one of the most widely prescribed classes of drugs worldwide, with nearly \$2 billion spent in the United States yearly on prescription NSAIDs alone.¹ Gastrointestinal toxic effects induced by NSAIDs are common. In the United States, an estimated 107,000 patients are hospitalized and 16,500 die each year as a result of NSAID-related ulcer complications.² Patients with a history of ulcer bleeding who use NSAIDs are at the highest risk for ulcer complications.^{3,4}

Current evidence indicates that concurrent therapy with NSAIDs and proton-pump inhibitors or misoprostol reduces the risk of ulcers^{5,6} and ulcer complications.⁷⁻⁹ Because proton-pump inhibitors are well tolerated, their use as prophylaxis has been recommended for patients at high risk for ulcer complications.^{10,11} However, lack of compliance may limit the usefulness of this strategy, especially in elderly people who are already receiving multiple drugs.

An alternative strategy to reduce the risk of ulcer complications is to replace conventional, nonselective NSAIDs with NSAIDs that are selective for cyclooxygenase-2 (COX-2). There is good evidence that the COX-2-selective NSAIDs celecoxib and rofecoxib are effective antiinflammatory agents and inflict minimal gastric injury.¹²⁻¹⁵ In one study, the incidence of gastric ulcers in patients receiving a COX-2-selective NSAID was equivalent to that in patients receiving a placebo.¹² Two large-scale randomized trials, the Vioxx Gastrointestinal Outcomes Research Study¹⁵ and the Celecoxib Long-Term Arthritis Safety Study (CLASS),¹⁶ have shown that treatment with COX-2-selective NSAIDs causes fewer clinical upper gastrointestinal tract events than treatment with nonselective NSAIDs. The American College of Rheumatology guidelines for the management of osteoarthritis recommend a COX-2-selective NSAID as an alternative to a nonselective NSAID in patients at risk for ulcer disease.¹⁷

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The gastric-safety profile of COX-2-selective NSAIDs in patients at high risk for ulcer complications is less well defined than that in patients with average levels of risk.¹ In CLASS, which enrolled almost 8000 subjects, only about 1.5 percent of the study population had a history of gastrointestinal bleeding. Patients with a recent history of gastroduodenal ulcers were also excluded.¹⁶ The generalizability of the data from this study to patients at high risk is uncertain. In addition, CLASS failed to demonstrate a significant reduction in ulcer complications in patients taking celecoxib, as compared with patients taking nonselective NSAIDs.¹⁶ Whether COX-2-selective NSAIDs are similar to the combination of a nonselective NSAID plus a proton-pump inhibitor for patients at high risk for ulcer complications has not been investigated.

Our study was a six-month, prospective, randomized, double-blind trial that compared celecoxib with the combination of diclofenac plus omeprazole for patients presenting with ulcer bleeding. We compared celecoxib administered at a dose of 200 mg twice daily (the maximal dose for rheumatoid arthritis and twice the maximal dose for osteoarthritis approved by the Food and Drug Administration [FDA]) with commonly used therapeutic doses of diclofenac plus omeprazole. We hypothesized that treatment with celecoxib would not be inferior to combined therapy with diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients at high risk.

METHODS

Study Population

This study was conducted at the Endoscopy Center of the Prince of Wales Hospital in Hong Kong, China. We screened consecutive patients with rheumatoid arthritis, osteoarthritis, and other forms of arthritis who presented with ulcer bleeding confirmed by endoscopy. The inclusion criteria were ulcer healing as confirmed by follow-up endoscopy, a negative test for *Helicobacter pylori* or successful eradication of *H. pylori* according to histologic findings, and anticipated regular use of NSAIDs for the duration of the trial. The exclusion criteria were concomitant use of anticoagulant agents or corticosteroids; a history of gastric or duodenal surgery other than a patch repair; and the presence of erosive esophagitis, gastric-outlet obstruction, renal failure (defined by a serum creatinine level of more than 2.2 mg per deciliter [200 μ mol per liter]), terminal illness, or cancer.

Study Design

The protocol was approved by the clinical-trial ethics committee of the Chinese University of Hong Kong, and all participants provided written informed consent. Before enrollment, the patients underwent a physical examination, laboratory testing, and an assessment of arthritis. The assessment of arthritis included the patient's global assessment of disease activity, scored on a scale of 1 (no limitation of normal activities) to 5 (inability to carry out all normal activities), and the patient's assessment of arthritis pain, marked on a visual-analogue scale ranging from 0 mm (no pain) to 100 mm (severe pain).¹³

Eligible patients were randomly assigned to receive either 200 mg of celecoxib (Celebrex, Pharmacia) twice daily plus omeprazole pla-

cebo daily or 75 mg of extended-release diclofenac (Voltaren XR, Novartis) twice daily plus 20 mg of omeprazole (Losec, AstraZeneca) daily for six months. Randomization was carried out with a computer-generated list of random numbers. An independent staff assigned treatments according to consecutive numbers in sealed envelopes. Double-blinding was achieved by repackaging diclofenac and celecoxib as identical-appearing red capsules and omeprazole and its placebo as identical-appearing green capsules, according to the International Good Manufacturing Practice Guidelines for Pharmaceuticals. Consecutively numbered, sealed bottles of the study drugs were dispensed by a research nurse.

The patients were permitted to take antacids, acetaminophen, non-NSAID analgesics, and disease-modifying antirheumatic drugs. During the study, NSAIDs other than diclofenac (except for low-dose aspirin [up to 325 mg daily]), misoprostol, histamine H₂-receptor antagonists, sucralfate, and proton-pump inhibitors other than omeprazole were prohibited for all patients.

Assessments

After randomization, the patients were contacted by telephone at month 1 and returned to the endoscopy center at month 2 and every two months thereafter until the end of the study. At each visit, hemoglobin levels, serum biochemical values, drug compliance, efficacy, and safety were assessed. Drug compliance was assessed by pill counts. Assessment of treatment efficacy included the patient's global assessment of disease activity and the patient's assessment of arthritis pain. Assessment of safety was based on the physical examination, laboratory tests, and observed or reported adverse events. A direct telephone line was provided so that the patients could report any serious adverse events between the scheduled visits. Patients who discontinued the study drugs before the study ended were followed until the end of the study to determine whether gastrointestinal events had occurred.

Study End Points

The primary end point was recurrent ulcer bleeding within six months as defined by prespecified criteria — namely, hematemesis or melena documented by the admitting medical officer, with ulcers or bleeding erosions confirmed by endoscopy, or a decrease in the hemoglobin level of at least 2 g per deciliter in the presence of endoscopically proved ulcers or bleeding erosions. An ulcer was defined as a circumscribed mucosal break that was at least 0.5 cm in diameter and had a perceptible depth, and a bleeding erosion was defined as a flat mucosal break of any size that occurred in the presence of blood in the stomach. Endoscopy was performed in a treatment-blinded fashion. Members of an independent, blinded adjudication committee determined whether recurrent bleeding had occurred according to the prespecified criteria. Only events that were confirmed by the adjudication committee were included in the analysis. Secondary end points included the efficacy of treatments, recurrent ulcer bleeding among patients not taking low-dose aspirin, and other adverse events.

Statistical Analysis

We determined the sample size on the assumptions that about 4 percent of patients receiving diclofenac plus omeprazole would have recurrent ulcer bleeding within six months⁹ and that celecoxib would not be found inferior to diclofenac plus omeprazole if the upper limit of the 95 percent confidence interval for the difference in recurrent bleeding did not exceed 6 percentage points. According to the method described by Roebuck and Kuhn,¹⁸ a sample of 132 patients in each treatment group would give the study a power of 80 percent at a 5 percent level of significance with the use of a one-sided equivalence test of proportions. On the assumption that we would not be able to evaluate 10 percent of the patients, a total sample of 290 patients was required.

One planned interim analysis was performed in September 2000

to compare the safety of the two treatments. To decide whether to terminate the trial if one treatment was markedly inferior to the other, we used a predefined early-stopping rule that specified a level of significance of 0.001.¹⁹ The interim analysis, which included data from 130 patients, did not justify early termination.²⁰ The final analysis was performed in June 2002, after 287 patients had completed the study. Data analyses were carried out exclusively by a data-review committee.

The homogeneity of the treatment groups at base line was analyzed by Pearson's chi-square test for categorical data, Fisher's exact test for types of arthritis, and Student's t-test for continuous variables.²¹ Efficacy variables were analyzed by repeated-measures analysis of variance, with time as the within-subject factor and treatment as the between-subject factor, to test for any time or group difference. The term for the interaction between group and time was also inspected to determine whether the changes over time were the same in the two treatment groups with use of SPSS software (version 10.0).

The Kaplan–Meier method was used to estimate the likelihood of reaching the end point of recurrent ulcer bleeding within six months in the intention-to-treat population, which was defined as all patients who had taken at least one dose of study medication.²² The log-rank test was used to compare time-to-event curves in the two treatment groups. Failure to take at least 70 percent of the study drugs or use of prohibited drugs was considered a violation of the protocol. All P values and 95 percent confidence intervals are two-sided.

RESULTS

Patients

Between January 2000 and December 2001, we screened 396 patients taking NSAIDs for arthritis who presented with ulcer bleeding, and we enrolled 290 patients. The reasons for exclusion were the absence of an indication for prolonged NSAID therapy (34 patients), renal failure (26 patients), cancer (14 patients), failure to provide consent (14 patients), esophagitis (10 patients), unhealed ulcer (4 patients), and concomitant use of anticoagulant agents (4 patients). Three patients who withdrew consent after randomization and did not take any study medication were excluded from the analysis. Two hundred eighty-seven patients were included in the intention-to-treat analysis: 144 were randomly assigned to receive celecoxib, and 143 were assigned to receive diclofenac plus omeprazole (Table 1).

Ninety-two percent of the patients in the two treatment groups took at least 70 percent of the study drugs. The rates of discontinuation of medications were similar in the two groups: 13.3 percent in the

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	CELECOXIB (N=144)	DICLOFENAC PLUS OMEPRAZOLE (N=143)
Male sex — no. of patients (%)	61 (42.4)	65 (45.5)
Age — yr	66.5±14.2	68.8±13.2
Current smoking — no. of patients (%)	15 (10.4)	20 (14.0)
Current alcohol drinking — no. of patients (%)	16 (11.1)	13 (9.1)
Location of bleeding ulcers — no. of patients (%)		
Gastric	86 (59.7)	80 (55.9)
Duodenal	52 (36.1)	48 (33.6)
Gastric and duodenal	6 (4.2)	15 (10.5)
More than 1 episode of ulcer bleeding — no. of patients (%)	30 (20.8)	33 (23.1)
Diameter of ulcer — cm	1.0±0.7	1.0±0.7
Ulcer ≥2 cm in diameter — no. of patients (%)	24 (16.7)	22 (15.4)
Ulcer with active bleeding or nonbleeding visible vessels — no. of patients (%)	39 (27.1)	32 (22.4)
Transfusion required — no. of patients (%)	67 (46.5)	54 (37.8)
Type of arthritis — no. of patients (%)		
Osteoarthritis	123 (85.4)	127 (88.8)
Rheumatoid arthritis	5 (3.5)	2 (1.4)
Other	16 (11.1)	14 (9.8)
Coexisting medical condition — no. of patients (%)†	76 (52.8)	78 (54.5)
More than 1 coexisting medical condition — no. of patients (%)	30 (20.8)	28 (19.6)
Serum creatinine >1.2 mg/dl (106 μmol/liter) — no. of patients (%)	37 (25.7)	27 (18.9)
Concomitant use of low-dose aspirin — no. of patients (%)	9 (6.2)	18 (12.6)
Previous <i>Helicobacter pylori</i> infection — no. of patients (%)	77 (53.5)	75 (52.4)

*Plus–minus values are means ±SD.

†Medical conditions included ischemic heart disease, heart failure, stroke, cirrhosis, chronic obstructive airway disease, renal diseases, and diabetes with renal and vascular complications.

celecoxib group (10.5 percent because of adverse events, 1.4 percent because of a lack of efficacy, and 1.4 percent for other reasons) and 11.9 percent in the diclofenac-plus-omeprazole group (9.8 percent because of adverse events, 1.4 percent because of a lack of efficacy, and 0.7 percent for other reasons). No patient who discontinued medications early had recurrent ulcer bleeding or anemia within the six-month follow-up period. One patient in each group was lost to follow-up and could not be evaluated at six months, and one patient in each group died; all other patients completed the planned six months of follow-up.

Efficacy

The patients' global assessments of disease activity and their assessments of arthritis pain did not differ between the two treatment groups at any visit (Table 2). The proportions of patients who discontinued medications or used nonstudy NSAIDs because of a lack of efficacy of the study drugs were low (2.8 percent in the celecoxib group and 2.1 percent in the diclofenac-plus-omeprazole group).

Serious Gastrointestinal Events

Twenty-four cases of serious gastrointestinal events were evaluated by the adjudication committee. The committee identified 16 cases of recurrent ulcer bleeding, 7 in the celecoxib group and 9 in the diclofenac-plus-omeprazole group. All except 1 had recurrent bleeding from gastric ulcers; in 13 patients, the ulcer recurred at the same site. The median diameter of the recurrent ulcers was 1.5 cm (range, 0.5 to 4.0). Six patients required endoscopic control of bleeding, and four required blood transfusion (median, 3 units; range, 2 to 4). The remaining eight patients with gastrointestinal events did not meet the prespecified cri-

teria for recurrent ulcer bleeding: two were in the celecoxib group (one had colitis and one had colonic angiodysplasia) and six were in the diclofenac-plus-omeprazole group (one had colonic angiodysplasia, one had colon cancer, and four had anemia due to occult gastrointestinal bleeding of unknown origin).

The probability of recurrent ulcer bleeding during the six-month study was 4.9 percent for patients who received celecoxib and 6.4 percent for patients who received diclofenac plus omeprazole (difference, -1.5 percentage points; 95 percent confidence interval for the difference, -6.8 to 3.8) (Fig. 1 and Table 3). A per-protocol analysis of 263 patients showed that the probability of recurrent bleeding was 3.9 percent in the celecoxib group and 5.7 percent in the diclofenac-plus-omeprazole group (difference, -1.8 percentage points; 95 percent confidence interval for the difference, -7.0 to 3.4).

Of the 260 patients who did not take concomitant low-dose aspirin, 6 in the celecoxib group and 7 in the diclofenac-plus-omeprazole group had recurrent ulcer bleeding. The probability of recurrent bleeding was 4.5 percent in the celecoxib group and 5.6 percent in the diclofenac-plus-omeprazole group (difference, -1.2 percentage points; 95 percent confidence interval for the difference, -6.3 to 3.9) (Table 3).

One patient who received diclofenac plus omeprazole had peritonitis and died after four weeks of treatment. Postmortem examination revealed small-bowel infarction and multiple perforations.

Other Adverse Events

The adverse events leading to discontinuation of treatment were similar in the two treatment groups (Table 4). Renal adverse events, including hypertension, peripheral edema, and renal failure, were common. Among patients with renal impairment at base line, 51.4 percent of those receiving celecoxib and 40.7 percent of those receiving diclofenac plus omeprazole had renal adverse events. One patient in the celecoxib group died of lung cancer and one in the diclofenac-plus-omeprazole group had colon cancer during the study period. Both events were considered unrelated to the study medication.

DISCUSSION

We set out to test the hypothesis that treatment with celecoxib would not be inferior to combined therapy with diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding among patients at high risk. Most of the patients enrolled in this study had one or more risk factors in addition to a recent history of ulcer bleeding, such as old age and coexisting medical conditions. We found that among these patients at high risk, the incidence of recurrent ulcer bleeding is similar in those given celecoxib at twice the maximal

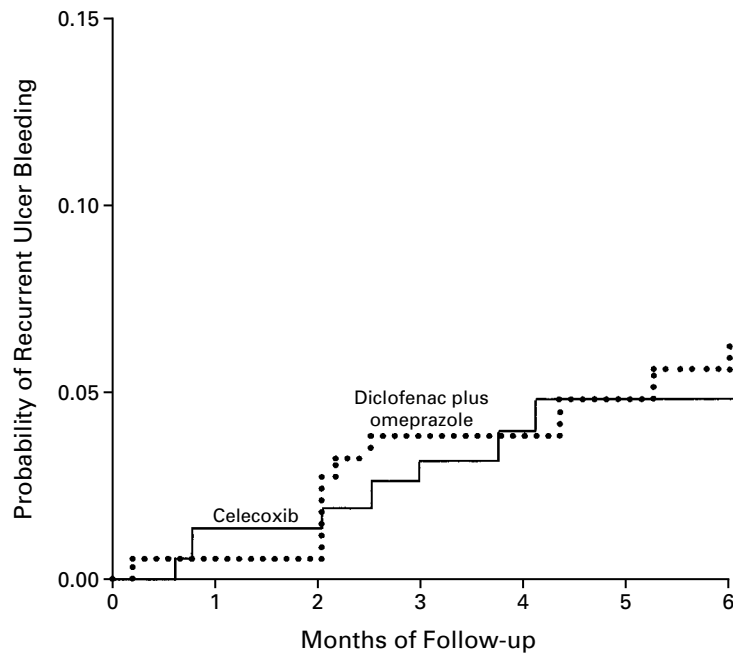
TABLE 2. EFFICACY OF CELECOXIB AND DICLOFENAC PLUS OMEPRAZOLE FOR ARTHRITIS.*

TIME	DISEASE-ACTIVITY SCORE†		PAIN SCALE‡	
	CELECOXIB	DICLOFENAC PLUS OMEPRAZOLE	CELECOXIB	DICLOFENAC PLUS OMEPRAZOLE
Base line	3.2±0.7	3.3±0.8	60.7±21.0	66.5±19.1
Month 2	2.6±0.9	2.5±1.0	43.1±25.1	43.9±25.6
Month 4	2.4±0.9	2.3±0.9	36.8±24.4	34.2±24.4
Month 6	2.1±1.1	2.1±1.0	33.4±25.2	30.3±24.4

*Plus-minus values are means ±SD.

†Scores for the patient's assessment of global disease activity ranged from 1 (no limitation of normal activities) to 5 (inability to carry out all normal activities).

‡The patient's assessment of arthritis pain was marked on a visual-analogue scale ranging from 0 mm (no pain) to 100 mm (severe pain).



NO. AT RISK	
Celecoxib	144 142 141 137 136 135 135
Diclofenac plus omeprazole	143 142 138 135 135 134 132

Figure 1. Cumulative Probability of Recurrent Ulcer Bleeding in the Group Receiving Celecoxib and the Group Receiving Diclofenac plus Omeprazole.

The difference between groups was not significant (P=0.60 by the log-rank test).

TABLE 3. KAPLAN-MEIER ESTIMATES OF THE LIKELIHOOD OF RECURRENT ULCER BLEEDING AT SIX MONTHS.*

PATIENTS	PROBABILITY OF RECURRENT BLEEDING		DIFFERENCE IN THE PROBABILITY OF RECURRENT BLEEDING†
	CELECOXIB	DICLOFENAC PLUS OMEPRAZOLE	
	percent (95% CI)		percentage points (95% CI)
All patients	4.9 (3.1 to 6.7)	6.4 (4.3 to 8.4)	-1.5 (-6.8 to 3.8)
Patients who did not take concomitant aspirin	4.5 (2.7 to 6.3)	5.6 (3.6 to 7.7)	-1.2 (-6.3 to 3.9)

*P=0.60 by the log-rank test for the difference between treatment groups. CI denotes confidence interval.

†Celecoxib was to be considered not inferior to diclofenac plus omeprazole if the upper limit of the 95 percent confidence interval for the difference in the probability of recurrent bleeding did not exceed 6 percentage points. Negative values favored celecoxib, and positive values favored diclofenac plus omeprazole.

dose approved by the FDA for osteoarthritis and those given diclofenac plus omeprazole.

The gastric-safety profile of COX-2-selective NSAIDs remains a matter of concern for clinicians and patients. CLASS, the study whose results were presented at the FDA hearings, failed to demonstrate

a significant difference in the incidence of ulcer complications between patients receiving celecoxib and those receiving diclofenac.²³ Among patients receiving celecoxib, the incidence of ulcer complications continued to rise beyond six months.²³ It was argued that the lack of advantage of celecoxib over diclofenac

TABLE 4. INCIDENCE OF ADVERSE EVENTS.

EVENT	CELECOXIB (N=144)	DICLOFENAC PLUS OMEPRAZOLE (N=143)
	no. of patients (%)	
Gastrointestinal		
Dyspepsia	22 (15.3)	12 (8.4)
Nausea, heartburn, or diarrhea	1 (0.7)	2 (1.4)
Total	23 (16.0)	14 (9.8)
Discontinued medication	6 (4.2)	5 (3.5)
Renal		
Hypertension	20 (13.9)	27 (18.9)
Peripheral edema	7 (4.9)	8 (5.6)
Renal failure*	8 (5.6)	9 (6.3)
Total	35 (24.3)	44 (30.8)
Discontinued medication	7 (4.9)	7 (4.9)
Cardiovascular		
Myocardial infarction	1 (0.7)	0
Angina	1 (0.7)	2 (1.4)
Total	2 (1.4)	2 (1.4)
Discontinued medication	2 (1.4)	2 (1.4)

*Renal failure was defined by a progressive rise in the creatinine level to above 2.2 mg per deciliter (200 μmol per liter). There were no significant differences between the groups.

was due to a large and differential dropout of susceptible patients who received diclofenac.²⁴ In addition, concurrent use of low-dose aspirin may have negated the protective effect of celecoxib.¹⁶ Whether the failure of CLASS to find a difference between the two treatments was related to the study design or the inadequacy of celecoxib remains controversial. Although our findings suggest that celecoxib is an alternative to combined therapy with diclofenac and omeprazole, the risk of recurrent bleeding with either treatment was high (4.9 percent of those in the celecoxib group and 6.4 percent of those in the diclofenac-plus-omeprazole group had recurrent bleeding within six months). Our findings suggest that neither regimen can completely protect patients at high risk from recurrent ulcer complications.

Previous studies reported a very low incidence of renal adverse events associated with COX-2-selective NSAIDs, ranging from 0 to 5 percent.^{13,15,16} In contrast, we found renal adverse events in more than 20 percent of the patients receiving celecoxib. There was no advantage of celecoxib over diclofenac plus omeprazole in terms of such events. The substantial proportion of our patients with coexisting medical conditions, such as renal diseases, diabetic nephropathy, and heart failure, probably accounts for the high incidence of renal adverse events. Studies have shown that inhibition of COX-2 reduces creatinine clearance in the elderly²⁵ and causes fluid retention in salt-depleted subjects.²⁶ The renal toxicity of COX-2-selective

NSAIDs in susceptible persons is probably similar to that of nonselective NSAIDs.

Our study had several limitations. First, the study was not powered to assess the effect of concomitant low-dose aspirin on the risk of recurrent bleeding. Second, the exclusion of patients with active ulcers may have contributed to the favorable outcome among patients receiving celecoxib. Studies in animals have shown that inhibition of COX-2 delays ulcer healing.^{27,28} It is uncertain whether COX-2-selective NSAIDs would precipitate ulcer complications in patients with active ulcers. Third, our study was not designed to determine the risk reduction achieved by celecoxib or diclofenac plus omeprazole in patients at high risk. We previously reported that about 19 percent of patients with a recent episode of ulcer bleeding who took a nonselective NSAID had recurrent bleeding within six months.⁹ It would therefore be unethical to prescribe diclofenac without prophylaxis to patients at high risk.

In summary, among patients with a recent history of ulcer bleeding, treatment with celecoxib was as effective as treatment with diclofenac plus omeprazole, with respect to the prevention of recurrent bleeding. Renal adverse events are common in susceptible patients receiving celecoxib or diclofenac plus omeprazole. Neither regimen can completely eliminate the risk of recurrent ulcer complications in patients at high risk. Subsequent studies will be needed to address whether the combination of a COX-2-selective NSAID with a proton-pump inhibitor or misoprostol will eliminate the risk of ulcer complications for patients with multiple risk factors.

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