

Ulcer Formation With Low-Dose Enteric-Coated Aspirin and the Effect of COX-2 Selective Inhibition: A Double-Blind Trial

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Background & Aims: We assessed the risk of ulcers with low-dose aspirin and the interaction of low-dose aspirin with a COX-2 selective inhibitor in a double-blind trial that compared placebo, low-dose aspirin, rofecoxib + low-dose aspirin, and ibuprofen. **Methods:** Osteoarthritis patients ≥ 50 years of age without ulcers or erosive esophagitis at baseline endoscopy were assigned randomly to placebo, enteric-coated aspirin 81 mg/day, rofecoxib 25 mg combined with aspirin 81 mg/day, or ibuprofen 800 mg 3 times a day. Repeat endoscopies were performed at 6 and 12 weeks. **Results:** The 12-week cumulative incidence of ulcers was placebo (N = 381) 5.8%, aspirin (N = 387) 7.3%, rofecoxib combined with aspirin (N = 377) 16.1%, and ibuprofen (N = 374) 17.1% ($P < 0.001$ for rofecoxib combined with aspirin and for ibuprofen vs. each of placebo and aspirin). Over 12 weeks, mean increases in the number of erosions were placebo 0.17, aspirin 0.85 ($P = 0.002$ vs. placebo), rofecoxib combined with aspirin 1.67, and ibuprofen 1.91 (both $P < 0.001$ vs. aspirin and placebo). **Conclusions:** Low-dose aspirin alone did not significantly increase ulcer incidence. Addition of a cyclooxygenase-2 (COX-2) selective inhibitor to low-dose aspirin increased ulcer incidence, to a rate not significantly less than a nonselective nonsteroidal anti-inflammatory drug (NSAID) alone. Determining the relative impact of COX-2 selective inhibitors and nonselective NSAIDs on gastrointestinal mucosal injury in low-dose aspirin users will require further study.

Aspirin is used widely as an antithrombotic drug for prevention of cardiovascular and cerebrovascular events.¹⁻³ Low-dose aspirin, generally defined as 75-325 mg/day, provides an antiplatelet effect caused by near-complete inhibition of platelet thromboxane B₂ production.^{1,2}

Low-dose aspirin also is associated with a significant risk for developing serious gastrointestinal (GI) complications, such as bleeding, even at daily doses of 75 mg.^{4,5} Furthermore, although enteric coating may decrease gastric mucosal damage in short-term endoscopic studies,⁶ it does not decrease the risk for upper GI bleeding compared with plain aspirin.^{7,8} Surprisingly, no random-

ized clinical trials have explored the development of ulcers in patients taking low-dose plain or enteric-coated aspirin.

Patients taking low-dose aspirin frequently require treatment of pain or inflammation with a nonsteroidal anti-inflammatory drug (NSAID). However, concomitant NSAID use is a major risk factor for GI bleeding, increasing the risk 2-4-fold as compared with low-dose aspirin alone.^{8,9} COX-2 selective inhibitors significantly decrease the development of ulcers and clinical GI events as compared with traditional nonselective NSAIDs,¹⁰⁻¹³ suggesting that they would be safer than nonselective NSAIDs in patients taking low-dose aspirin. However, no randomized clinical trials designed to study the interaction of low-dose aspirin and COX-2 selective inhibitors in patients have been published.

We therefore performed a 12-week, double-blind, placebo-controlled, endoscopic trial in 1615 patients with osteoarthritis to determine the rates of ulcer formation with a standard U.S. dose and formulation of low-dose aspirin (81-mg enteric-coated), alone and in combination with the COX-2 selective inhibitor, rofecoxib. The most clinically relevant comparison would be aspirin plus rofecoxib vs. aspirin plus a nonselective NSAID in patients requiring low-dose aspirin for vascular prophylaxis. However, because a placebo group was required (because no information on ulcer formation with low-dose aspirin was available) ethical considerations precluded the inclusion of patients requiring aspirin for vascular prophylaxis. Furthermore, the risk of combining aspirin and a nonselective NSAID in osteoarthritis patients not requiring aspirin and not allowed to receive protective medications such as proton pump inhibitors or misoprostol was felt to be too great to be acceptable.

Therefore, we compared aspirin plus rofecoxib with a nonselective NSAID, ibuprofen alone, in patients who

Abbreviations used in this paper: CI, confidence interval; GI, gastrointestinal.

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were not taking any dose of aspirin. We reasoned that if our primary hypothesis, patients treated with rofecoxib plus low-dose aspirin would have a lower incidence of ulcers than those treated with ibuprofen alone, was confirmed, then this would adequately document that rofecoxib causes less ulcers than a nonselective NSAID in patients taking low-dose aspirin.

Patients and Methods

Patients ≥ 50 years old with a diagnosis of osteoarthritis who were expected to require treatment for 3 months were eligible; female patients were required to be postmenopausal or have a negative pregnancy test at entry and use appropriate contraception. Exclusion criteria included requirement for cardiovascular prophylaxis with aspirin or other antiplatelet therapy, including history of stroke or transient ischemic attack, or history of angina, myocardial infarction, coronary angioplasty, or coronary artery bypass graft (investigators were told explicitly that patients requiring aspirin for cardiovascular prophylaxis could not have their aspirin discontinued and be enrolled in the study); other rheumatologic disease; upper GI or biliary surgery; renal insufficiency; uncontrolled hypertension; symptomatic congestive heart failure; malignancy within 5 years; inflammatory bowel disease; bleeding diathesis or anticoagulant therapy; positive fecal occult blood test at baseline; ulcer, pyloric obstruction, or erosive esophagitis at baseline endoscopy; requirement for proton pump inhibitors, H_2 -receptor antagonists, misoprostol, or sucralfate; corticosteroid use (other than intra-articular) within 1 month of study entry; alcohol abuse or use of illicit drugs; allergy or hypersensitivity to acetaminophen, aspirin, or other NSAID; blood transfusion within 4 weeks; and clinically significant laboratory abnormalities at baseline. Patients with gastric or duodenal erosions at baseline endoscopy (regardless of the number of erosions) were not excluded.

Patient eligibility was determined in a prestudy screening visit 2 weeks before their baseline visit. At this time, all NSAIDs, antibiotics, and GI cotherapy medications were discontinued; patients requiring chronic GI medications (e.g., for reflux) were not included in the trial. After endoscopy at the baseline visit, eligible patients were assigned randomly using a computer-generated schedule of random numbers with concealed allocation. Patients were stratified based on a history of upper GI clinical events (hemorrhage, perforation, or symptomatic ulcer). Patients received 1 of 4 treatments: placebo, 81-mg enteric-coated aspirin once daily, 81-mg enteric-coated aspirin plus 25-mg rofecoxib once daily, or 800-mg ibuprofen 3 times a day. Patients received identical-appearing blister packs with medications or matching placebos to maintain blinding. Patients also received acetaminophen 325-mg tablets to treat osteoarthritis pain and antacid tablets (Gelusil, Warner-Lambert, Morris Plains, NJ) for treatment of minor upper GI symptoms as necessary.

Patients had repeat visits with clinical and laboratory evaluation at weeks 3, 6, 9, and 12, as well as 2 weeks after the end

of the study (week 14). Repeat upper endoscopies were performed at weeks 6 and 12. Unscheduled endoscopies could be performed if a patient developed moderate to severe upper GI symptoms for ≥ 2 days or at the discretion of the investigator. Patients with an ulcer at endoscopy were discontinued from the study and received ulcer treatment. Compliance was measured by tablet count at each visit.

The primary end point was a gastroduodenal ulceration, defined as a mucosal break ≥ 3 mm in length (measured by close application of an open endoscopic biopsy forceps) with unequivocal depth by 12 weeks. We also assessed ulcers ≥ 5 mm and the change in number of gastric and duodenal erosions. Efficacy evaluation was not an objective of the study, but patient global assessment of disease activity and acetaminophen use were measured throughout the study.

The primary hypothesis was that the cumulative proportion of patients who developed gastric and/or duodenal ulcers by 12 weeks would be lower with rofecoxib plus aspirin rather than with ibuprofen. Sample size calculations were based on assumptions of expected ulcer rates for ibuprofen of 20%, for aspirin or aspirin plus rofecoxib of 10%, and for placebo of 2.5%. With 350 evaluable patients in each treatment group there was 95% power to detect a difference in the proportion of patients who developed ulcers between ibuprofen and aspirin or rofecoxib plus aspirin, and 98% power to detect a difference between placebo and aspirin. Secondary hypotheses were that patients taking placebo and aspirin would have fewer ulcers than those taking ibuprofen, and that patients taking rofecoxib plus aspirin would have fewer ulcers ≥ 5 mm than patients taking ibuprofen. Exploratory evaluations included the change in number of gastric and duodenal erosions with treatment compared with baseline and the effect of antacid consumption on ulcer formation.

A life-table approach was used to analyze time-to-event data for ulcer incidences. A log-rank test was the primary statistical test used to compare cumulative incidence rates between treatment groups. Estimations of 12-week cumulative life-table rates were based on Kaplan-Meier methods. The change from baseline in number of erosions at both 6 and 12 weeks was analyzed using an analysis of covariance model with factors including treatment, baseline number of erosions, GI history, and study site. In addition, the proportion of patients in each treatment group who had an increase in erosions at 12 weeks compared with baseline was calculated. Time-weighted change from baseline in patient global assessment of disease activity was analyzed using an analysis of covariance model with factors including treatment, baseline assessment, and GI history. An analysis of covariance model also was used to analyze average daily use of acetaminophen as well as antacids. A modified intention-to-treat approach, in which all patients who had at least one treatment-phase measurement were included, was the primary analysis.

An assessment of treatment effect on ulcer incidence was prespecified for relevant patient subgroups to explore consistency of effects across subgroups. A Cox proportional hazard model with treatment, subgroup, and treatment-by-subgroup

Table 1. Selected Characteristics of the Osteoarthritis Patients at Randomization

	Placebo (N = 410)	Aspirin (N = 406)	Aspirin and rofecoxib (N = 399)	Ibuprofen (N = 400)
Female	301 (73%)	297 (73%)	300 (75%)	305 (76%)
Mean age (yr)	61 ± 8	61 ± 8	61 ± 8	61 ± 8
Mean weight (kg)	78 ± 18	77 ± 18	76 ± 18	78 ± 18
Alcohol use (>7 per wk)	11 (3%)	17 (4%)	14 (4%)	16 (4%)
Tobacco use	140 (34%)	144 (35%)	125 (31%)	129 (32%)
Prior GI event	33 (8%)	33 (8%)	41 (10%)	36 (9%)
<i>H. pylori</i> positive ^a	209 (51%)	187 (46%)	194 (49%)	193 (48%)
Baseline erosions	65 (16%)	71 (17%)	50 (13%)	46 (12%)
Mean patient global disease assessment (0-4)	2.2 ± 0.9	2.2 ± 0.9	2.2 ± 0.9	2.1 ± 0.9
Prior NSAID use	303 (74%)	285 (70%)	278 (70%)	291 (73%)

NOTE. Means ± SD.

^a*H. pylori* positivity based on positive histologic identification of organisms, positive rapid urease testing, or both.

interaction in the model was used to test treatment-by-subgroup interaction at the $\alpha = 0.05$ level. The study site was not prespecified as a variable in the analysis owing to the small treatment group sample sizes anticipated for many centers; however, an uneven distribution of ulcers across study sites was not evident in a review of the study results. Prespecified assessments of adverse events for the active treatments vs. placebo included the following: all clinical adverse experiences, edema, hypertension, heart failure, and predefined changes in hemoglobin and hematocrit, aspartate transaminase, alanine transaminase, and serum creatinine levels. Assessments of discontinuations caused by clinical adverse experiences, GI adverse experiences (including abdominal pain), edema, and hypertension also were prespecified.

A *P* value <0.05 was specified as significant in the analyses. The institutional review board at each center approved the protocols and all subjects gave written informed consent.

Results

A total of 2220 patients were screened for the 12-week study; 605 were excluded and 1615 patients were enrolled. The most common reasons for exclusion during screening were abnormal endoscopy at baseline (27%), patient withdrew consent (27%), and other medical problems (13%). A range of 3-80 patients were enrolled at 82 U.S. sites. Of the 1615 patients enrolled, 1223 (76%) completed 12 weeks of study therapy and 392 (24%) discontinued earlier. The most common reasons for discontinuation were study end point (41%), adverse experiences (27%), withdrawal of consent (14%), and lack of efficacy (10%). The overall rates of discontinuation were significantly higher in the ibuprofen (29%) and rofecoxib plus aspirin (28%) groups than in the placebo (21%) and aspirin (19%) groups, owing to the differences in study end point rates discussed later.

Of the 1615 randomized patients, 1519 had at least one endoscopy while on treatment and were included in the modified intention-to-treat analysis for the primary

end point. Baseline characteristics were similar in the 4 study groups (Table 1). The baseline characteristics in those randomized were comparable with those screened and with those in the primary intention-to-treat analysis. Compliance was $\geq 90\%$ in 90%, 89%, 89%, and 91% of the placebo, aspirin, rofecoxib plus aspirin, and ibuprofen arms, respectively.

The cumulative incidences by 12 weeks of ulcers that were ≥ 3 mm and ≥ 5 mm are shown in Table 2. For the primary analysis of ulcers ≥ 3 mm, the rate for ibuprofen was not significantly higher than the rate for rofecoxib plus aspirin (difference = 1.0%; 95% confidence interval [CI], -4.4% to 6.4%; *P* = 0.62) and the rate for aspirin was not significantly higher than the rate for placebo (difference = 1.4%; 95% CI, -2.2% to 5.0%; *P* = 0.39). The ibuprofen ulcer rate was significantly greater than the rates for placebo or aspirin. The rates for rofecoxib plus aspirin also were significantly greater than the rates for placebo (difference = 10.3%; 95% CI, 5.8%-14.8%; *P* < 0.001) or aspirin (difference = 8.9%; 95% CI, 4.2%-13.5%; *P* < 0.001). Similar differences were seen in the analysis of ulcers ≥ 5 mm. A proportion of the 12-week cumulative incidence of ulcers was made up of subjects who reached the study end point of ulcer at the 6-week endoscopy. The cumulative incidence rates of ulcers ≥ 3 mm at 6 weeks as compared with the 12-week cumulative incidence rates (which include subjects with ulcers at 6 weeks and those developing ulcers between 6 and 12 weeks) were 1.6% vs. 5.8% for placebo, 3.4% vs. 7.3% for aspirin, 7.5% vs. 16.1% for rofecoxib plus aspirin, and 11.1% vs. 17.1% for ibuprofen.

Separate analyses of gastric and duodenal ulcers are presented in Table 3. Results for gastric ulcers mirrored those for gastroduodenal ulcers as a whole. Duodenal ulcers were less common than gastric ulcers in all study groups, and the only significant difference between groups was for ibuprofen vs. placebo (*P* = 0.013). The

Table 2. 12-Week Cumulative Incidences of Gastroduodenal Ulcers in Osteoarthritis Patients

	Placebo (N = 381)	Aspirin (N = 387)	Aspirin and rofecoxib (N = 377)	Ibuprofen (N = 374)
Ulcer ≥ 3 mm				
Patients with ulcers	21	27	58	62
Life-table cumulative Incidence (95% CI)	5.8% (3.4%–8.3%)	7.3% (4.6%–9.9%)	16.1% ^a (12.3%–19.9%)	17.1% ^a (13.2%–21.0%)
Ulcer ≥ 5 mm				
Patients with ulcers	15	18	44	51
Life-table cumulative Incidence (95% CI)	4.2% (2.1%–6.3%)	4.9% (2.7%–7.1%)	12.4% ^a (9.0%–15.9%)	14.3% ^a (10.6%–17.9%)

^a $P < 0.001$ vs. placebo and vs. aspirin.

mean changes in total number of gastroduodenal erosions from baseline to week 12 adjusted for significant covariates such as baseline erosions and GI history (least-squares mean changes) are shown in Table 4. Both ibuprofen (mean change = 1.91) and rofecoxib plus aspirin (mean change = 1.67) caused a greater increase in erosions than did placebo (mean change = 0.17) or aspirin (mean change = 0.85). Enteric-coated 81-mg aspirin did lead to the development of significantly more erosions than placebo ($P = 0.002$). Most of the increase in number of erosions occurred by 6 weeks, with 6-week mean changes from baseline of 0.15 for placebo (vs. 0.17 at 12 wk), 0.77 for aspirin (vs. 0.85 at 12 wk), 1.56 for rofecoxib plus aspirin (vs. 1.67 at 12 wk), and 2.09 for ibuprofen (vs. 1.91 at 12 wk). At 12 weeks, an increase in erosions from baseline was seen in 20% of patients taking placebo, 32% of those taking aspirin ($P < 0.001$ vs. placebo), and 52% of those taking rofecoxib plus aspirin or ibuprofen ($P < 0.001$ vs. placebo and aspirin). Erosions were seen at 6 weeks but not at 12 weeks in 12.5% of the 1253 patients for whom data were available at both time points.

No significant treatment-by-subgroup interaction was seen for ulcer risk factors, including age ≥ 65 years, prior history of upper GI clinical events (perforation, bleeding, uncomplicated symptomatic ulcers), *Helicobacter pylori* status, baseline erosions, or prior NSAID use (Table 5).

The mean number of antacid tablets used per day was similar among the treatment groups, with the only significant difference seen on comparison of ibuprofen vs. aspirin (difference = 0.18 tablets/day; 95% CI, 0.03–0.32; $P = 0.021$). Patients were divided into 3 tertiles based on increasing antacid consumption. There was no significant difference in the ulcer rate by tertile of antacid use in any treatment group: overall, 11% of patients in the lowest- and highest-consuming tertile had ulcers identified.

A significantly greater improvement from baseline in patient global assessment of disease was seen with rofecoxib plus aspirin (–0.67) and with ibuprofen (–0.67) than with aspirin (–0.38) or placebo (–0.36). Furthermore, patients in the placebo and aspirin groups used significantly more acetaminophen than those in the rofecoxib plus aspirin or ibuprofen groups.

A summary of predefined clinical adverse experiences is listed in Table 6. Only 1 patient exceeded the predefined limit of changes in aspartate transaminase, alanine transaminase, or creatinine levels (a patient in the aspirin arm with alanine transaminase level >3 times upper limit of normal). A decrease in hemoglobin level greater than 2 g/dL or hematocrit level greater than 10% occurred in 0.8%, 1.6%, 0.8%, and 5.4% of patients taking placebo, aspirin, rofecoxib plus aspirin, or ibuprofen, respectively ($P < 0.005$ for ibuprofen vs. other

Table 3. 12-Week Cumulative Incidences of Gastric and Duodenal Ulcers ≥ 3 mm in Osteoarthritis Patients

	Placebo (N = 381)	Aspirin (N = 387)	Aspirin and rofecoxib (N = 377)	Ibuprofen (N = 374)
Gastric ulcer				
Patients with ulcers	17	22	50	51
Life-table cumulative Incidence (95% CI)	4.7% (2.5%–6.9%)	5.9% (3.5%–8.4%)	14.1% ^a (10.5%–17.8%)	14.3% ^a (10.7%–18.0%)
Duodenal ulcer				
Patients with ulcers	4	7	11	14
Life-table cumulative Incidence (95% CI)	1.1% (0.0%–2.2%)	1.9% (0.5%–3.3%)	3.1% (1.3%–4.9%)	3.9% ^b (1.9%–5.8%)

^a $P < 0.001$ vs. placebo and aspirin.

^b $P = 0.013$ vs. placebo.

Table 4. Least-Squares Mean Changes^a in Number of Gastroduodenal Erosions From Baseline to Week 12 in Osteoarthritis Patients

	Placebo (N = 381)	Aspirin (N = 387)	Aspirin and rofecoxib (N = 377)	Ibuprofen (N = 374)
Baseline mean ± SD	0.54 ± 1.82	0.68 ± 2.02	0.44 ± 1.57	0.39 ± 1.44
12-wk mean ± SD	0.71 ± 2.42	1.44 ± 3.21	2.15 ± 3.50	2.35 ± 3.83
Least-squares mean change (95% CI)	0.17 (-0.14 to 0.48)	0.85 ^b (0.55–1.16)	1.67 ^c (1.36–1.98)	1.91 ^b (1.59–2.22)

^aMean change adjusted for covariates including baseline erosions, GI history, treatment, and study site.

^b*P* = 0.002 vs. placebo.

^c*P* < 0.001 vs. placebo and aspirin.

groups). Although there were significantly higher rates compared with placebo (*P* < 0.05) of edema and hypertension in both the rofecoxib plus aspirin and ibuprofen treatment groups, only the ibuprofen group also had significantly higher rates compared with placebo (*P* < 0.05) of total clinical adverse experiences, discontinuations owing to any clinical adverse experiences, or discontinuations owing to GI organ system adverse experiences.

Discussion

This large, randomized, double-blind trial in osteoarthritis patients showed that 81 mg of enteric-coated aspirin daily did not significantly increase the rate of ulcer formation at 12 weeks as compared with placebo. When the maximum chronic dose of the selective COX-2 inhibitor rofecoxib (25 mg/day) was added, the ulcer rate was significantly greater than the rate with low-dose aspirin alone but was not significantly lower than the rate with a traditional nonselective NSAID alone (ibuprofen 800 mg 3 times/day). Low-dose aspirin caused a significantly greater increase in erosions from baseline than did placebo, although the increase was significantly less than that caused by rofecoxib plus

aspirin or by ibuprofen alone. Finally, as compared with placebo, discontinuations owing to GI adverse events were significantly more frequent with ibuprofen but not with aspirin or aspirin plus rofecoxib.

The lack of a significant increase in ulcers with low-dose aspirin at 12 weeks appears contradictory to the well-documented increase in GI bleeding with low-dose aspirin. Several potential explanations may be considered. Aspirin causes a topical injury that can be decreased with enteric coating.⁶ However, the clinically important ulcers caused by NSAIDs and aspirin are widely thought to result primarily from absorption and systemic activity of these agents rather than the topical injury, and the risk for GI bleeding is not decreased with the use of enteric-coated rather than plain aspirin.^{7,8} It seems very unlikely that low-dose aspirin would fail to produce ulcers via systemic action after 12 weeks but would cause them after longer periods of use. Thus, we conclude that the development of endoscopic ulcers may not predict clinical GI bleeding in patients taking low-dose aspirin. This contrasts with the situation for nonaspirin NSAIDs and COX-2 selective inhibitors, in which results of endoscopic studies do appear to predict rates of clinical events in outcome studies.^{10,11,13–16}

Table 5. Selected Subgroup Analyses of 12-Week Incidences of Gastroduodenal Ulcers

	Placebo	Aspirin	Aspirin and rofecoxib	Ibuprofen
Age <65 yr	14/248 (5.6%)	18/275 (6.6%)	32/267 (12.0%)	39/262 (14.9%)
Age ≥65 yr	7/133 (5.3%)	9/112 (8.0%)	26/110 (23.6%)	23/112 (20.5%)
Treatment-by-subgroup interaction for age, <i>P</i> = 0.38				
No prior GI event ^a	19/349 (5.4%)	19/357 (5.3%)	49/342 (14.3%)	54/341 (15.8%)
Prior GI event	2/32 (6.3%)	8/30 (26.7%)	9/35 (25.7%)	8/33 (24.2%)
Treatment-by-subgroup interaction for prior GI event, <i>P</i> = 0.14				
<i>H. pylori</i> negative	10/184 (5.4%)	15/206 (7.3%)	28/193 (14.5%)	28/197 (14.2%)
<i>H. pylori</i> positive	10/196 (5.1%)	12/181 (6.6%)	30/184 (16.3%)	34/177 (19.2%)
Treatment-by-subgroup interaction for <i>H. pylori</i> status, <i>P</i> = 0.76				
No baseline erosions	15/323 (4.6%)	18/319 (5.6%)	45/329 (13.7%)	47/331 (14.2%)
Baseline erosions	6/58 (10.3%)	9/68 (13.2%)	13/48 (27.1%)	15/43 (34.9%)
Treatment-by-subgroup interaction for baseline erosions, <i>P</i> = 0.98				
Prior NSAID use	14/283 (4.9%)	20/271 (7.4%)	37/263 (14.1%)	44/271 (16.2%)
No prior NSAID use	7/98 (7.1%)	7/116 (6.0%)	21/114 (18.4%)	18/103 (17.5%)
Treatment-by-subgroup interaction for prior NSAID use, <i>P</i> = 0.78				

^aUpper GI perforation, bleeding episode, or symptomatic ulcer.

Table 6. Prespecified Assessments of Clinical Adverse Experiences in Osteoarthritis Patients

	Placebo (N = 410)	Aspirin (N = 406)	Aspirin and rofecoxib (N = 399)	Ibuprofen (N = 400)
Clinical AE	225 (55%)	229 (56%)	235 (59%)	254 (64%) ^a
Discontinued because of clinical AE	16 (3.9%)	23 (5.7%)	20 (5.0%)	31 (7.8%) ^a
Discontinued because of GI AE	8 (2.0%)	13 (3.2%)	13 (3.3%)	23 (5.8%) ^a
Edema	3 (0.7%)	6 (1.5%)	17 (4.3%) ^a	14 (3.5%) ^a
Discontinued because of edema	0	1 (0.2%)	1 (0.3%)	1 (0.3%)
Hypertension	9 (2.2%)	16 (3.9%)	27 (6.8%) ^a	29 (7.3%) ^a
Discontinued because of hypertension	0	1 (0.2%)	2 (0.5%)	1 (0.3%)
Congestive heart failure	0	0	0	0

AE, adverse experience.

^a*P* < 0.05 vs. placebo.

Low-dose aspirin did cause a significant increase in erosions from baseline, which indicates a more limited induction of injury than seen with standard NSAIDs or high-dose aspirin. The clinical relevance of an increase in erosions is uncertain. However, the fact that low-dose aspirin is documented to increase the risk for upper GI bleeding, coupled with the fact that only erosions but not ulcers were increased with low-dose aspirin, raises the possibility that the development of erosions may be a meaningful surrogate. Low-dose aspirin often may require underlying lesions for the development of GI bleeding: ulcers or erosions already present could be increased in size or depth even with the more limited mucosal injury of low-dose aspirin and/or these lesions could develop bleeding owing to the potent and long-lasting antiplatelet effects of low-dose aspirin. Alternatively, low-dose aspirin might cause ulcerations only infrequently, but its potent antiplatelet effect might cause a high proportion of these lesions to bleed.

The finding that a selective COX-2 inhibitor plus low-dose aspirin leads to an ulcer rate near that of a dual COX-1/COX-2 inhibitor alone also provides interesting clues to the pathogenesis of NSAID-induced GI injury. Aspirin is a potent inhibitor of COX-1 activity, but, in whole-blood assays, it is a weak inhibitor of COX-2.¹⁷ In an animal model, neither a selective COX-1 inhibitor nor a selective COX-2 inhibitor induces gastric damage, but the combination causes injury comparable with a nonselective NSAID.¹⁸ Thus, we may postulate that low-dose aspirin alone primarily inhibits COX-1 and causes limited gastric injury. However, when a selective COX-2 inhibitor is added, the combination may take on some characteristics of a dual inhibitor of COX-1 and COX-2, leading to rates of ulcer formation similar to that of an NSAID alone.

Alternatively, low-dose aspirin initially could cause small lesions such as erosions that are perpetuated or increased over time by concomitant therapy with a selective COX-2 inhibitor. Induction of gastric ulcers in

animal models is associated with a marked increase in local COX-2 expression, and selective COX-2 inhibitors delay healing of these experimental ulcers similarly to nonselective NSAIDs.^{19–21} Furthermore, high-dose aspirin in rats induces COX-2 expression and lipoxin A₄ production in the gastric mucosa,²² and low-dose aspirin increases urinary excretion of lipoxin A₄ in human volunteers.²³ Production of lipoxin A₄, which appears to reduce aspirin-induced gastric damage in rats, is inhibited by the COX-2 selective inhibitor celecoxib.^{22,23} Thus, use of a COX-2 selective inhibitor theoretically could increase the gastric damage induced by low-dose aspirin in humans. In this hypothesis of gastric injury, selective COX-2 inhibitors would first require underlying injury caused by low-dose aspirin or other cause.

A clinically meaningful decrease in hemoglobin (>2 g/dL) or hematocrit (>10%) level was seen in significantly more patients taking ibuprofen (5.4%) than in those taking placebo, aspirin, or aspirin plus rofecoxib (0.8%–1.6%). Because this difference did not parallel the difference in endoscopically observed upper GI tract mucosal injury, it could relate to GI blood loss beyond the duodenum. Fecal red blood cell loss, a marker of the mucosal integrity of the entire GI tract, is increased by nonselective NSAIDs, as compared with placebo and COX-2 selective inhibitors.²⁴ Furthermore, nonselective NSAIDs are reported to increase the risk for lower GI clinical events, and this risk is decreased with COX-2 selective inhibitors.²⁵ A decrease in hemoglobin or hematocrit level also was reported to occur less frequently with a COX-2 selective inhibitor than with nonselective NSAIDs in the celecoxib long-term arthritis safety study (CLASS) GI outcome studies, and this difference remained in the subset of patients taking low-dose aspirin.^{26,27} Thus, we may speculate that ibuprofen might have caused mucosal injury beyond the upper GI tract that was not seen with low-dose aspirin or the combination of aspirin plus rofecoxib.

An important clinical question raised by our study is whether low-dose aspirin also increases GI tract damage when added to a nonselective NSAID—and secondarily whether the incidence of GI tract injury is higher with nonselective NSAIDs plus low-dose aspirin than with COX-2 selective inhibitors plus low-dose aspirin. Low-dose aspirin provides longer-lasting COX-1 inhibition than nonselective NSAIDs, and thus in combination with a nonselective NSAID might produce greater rates of ulcer formation and GI bleeding than a nonselective NSAID alone.

A recent presentation of preliminary data from a 1-week double-blind endoscopic trial comparing the incidence of gastroduodenal ulcers in healthy volunteers given 325 mg of aspirin plus placebo (N = 92), naproxen (N = 176), or celecoxib (N = 182) revealed that the COX-2 selective inhibitor plus aspirin induced significantly more ulcers at 1 week than aspirin alone (18.7% vs. 7.6%), but significantly fewer ulcers than the nonselective NSAID plus aspirin (18.7% vs. 27.3%).²⁸ We could not find any other randomized trials (either endoscopic studies or outcomes studies) designed to address this issue.

Post hoc subset analyses from randomized controlled trials provide the only other information on this issue. Pooled analysis of patients using low-dose aspirin (≤ 325 mg/day) in longer-term endoscopic studies revealed that the rate of ulcers with valdecoxib (13.3%) was lower than the rate with ibuprofen (32.3%) and diclofenac (31.8%) but not naproxen (11.4%).²⁹ In the CLASS outcomes study, the rates of upper GI clinical events among low-dose aspirin users for the celecoxib and ibuprofen/diclofenac groups were 4.3 and 4.9 events per 100 patient-years,²⁷ whereas in the 12-week SUCCESS-1 outcomes trial, rates of upper GI clinical events in low-dose aspirin users were 0.4% with celecoxib vs. 1.1% with diclofenac or naproxen.³⁰ None of these studies was designed or powered to address the effect of aspirin plus NSAID or COX-2 selective inhibitors. Furthermore, the earlier-described analyses are post hoc and do not compare randomized treatment arms, but rather nonrandomized subsets of the treatment arms. Definitive conclusions await studies of appropriate size and duration designed to assess ulcers or GI outcomes in low-dose aspirin users randomly assigned to NSAIDs or COX-2 selective inhibitors.

In summary, osteoarthritis patients taking 81 mg of enteric-coated aspirin for 12 weeks did not have a significantly greater rate of ulcers than patients given placebo. The addition of a COX-2 selective inhibitor to low-dose aspirin increased the ulcer incidence signifi-

cantly, to a rate not significantly less than that seen with a standard nonselective NSAID alone. Determining the relative impact of COX-2 selective inhibitors and nonselective NSAIDs on GI mucosal injury in patients taking low-dose aspirin for vascular prophylaxis will require further study.

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