# Ulcer Recurrence in High-Risk Patients Receiving Nonsteroidal Anti-Inflammatory Drugs Plus Low-Dose Aspirin: Results of a Post Hoc Subanalysis

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## ABSTRACT

**Background:** Concomitant aspirin use is a risk factor for nonsteroidal anti-inflammatory drug (NSAID)–associated upper gastrointestinal toxicity. In high-risk individuals, such as those with a history of NSAID-related gastric ulcer bleeding, gastroprotective therapy with a proton pump inhibitor has been reported to reduce the risk of recurrent aspirin-associated gastroduodenal ulcer bleeding.

**Objective:** This analysis compared the efficacy of misoprostol, lansoprazole, and placebo in reducing the risk of gastric or duodenal ulcer recurrence in patients taking NSAIDs and low-dose aspirin.

**Methods:** This post hoc subanalysis was based on a previous multicenter, prospective, randomized, double-blind, placebo-controlled, 12-week study in patients who had a history of gastric ulcer, were *Helicobacter pylori* negative, required chronic NSAID therapy, and were free of gastric or duodenal ulcer on baseline endoscopy. The study treatments were misoprostol 200 μg QID or lansoprazole 15 or 30 mg OD. The subanalysis included data from patients in the intent-to-treat cohort who took aspirin at an amount ≤325 mg/d. The end point was the cumulative rate of gastric ulcers, as assessed by serial endoscopy at 4, 8, and 12 weeks.

**Results:** Of 535 intent-to-treat patients from the primary study, 70 (40 men, 30 women; mean [SD] age, 64.7 [10.0] years; age range, 40–83 years) met the criteria for inclusion in the subanalysis. The proportions of patients who were free of gastric ulcers at the end of 12 weeks were 96% in the misoprostol group, 93% in the lansoprazole 15-mg group, 100% in the lansoprazole 30-mg group, and 35% in the placebo group ($P \leq 0.008$, each active treatment vs placebo). Adverse events considered possibly or probably related to treatment occurred in 5 (20.0%) misoprostol recipients (4 episodes of diarrhea, 1 episode of abdominal pain), 1 (14.3%) recipient of lansoprazole 30 mg (1 episode of pharyngitis), and 3 (13.6%) placebo recipients (1 episode each of abdominal pain, palpitations, and dyspepsia).

**Conclusions:** In this subgroup analysis in patients at high risk for recurrence of gastric ulcer, use of cotherapy with misoprostol 200 μg QID or lansoprazole 15 or 30 mg OD significantly lowered the risk for gastric ulcer recurrence. (*Clin Ther.* 2004;26:1637–1643) Copyright © 2004 Excerpta Medica, Inc.

**Key words:** lansoprazole, misoprostol, NSAIDs, gastroprotection, proton pump inhibitors.

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## INTRODUCTION

Approximately 70% of Americans aged >65 years use nonsteroidal anti-inflammatory drugs (NSAIDs) at least once weekly, and an estimated 34% take these drugs on a daily basis.[1] Use of NSAIDs increases the risk of serious ulcer complications by ~2.5- to 5-fold compared with nonuse,[2–4] resulting in significant morbidity and mortality and increased use of health care resources.[4–10] Use of cardioprotective low-dose aspirin is also common in the general population,[11] with recent studies suggesting that 25% of individuals aged >50 years[12] and ≥72% of those who have had an acute myocardial infarction[13,14] take aspirin at amounts ≤325 mg/d. Use of aspirin alone, even at low cardioprotective doses, increases the risk for gastrointestinal (GI) events by ~1.5- to 4-fold compared with placebo.[15–18]

Low-dose aspirin taken in combination with NSAIDs has been associated with an increased risk for complications of upper GI ulcer compared with NSAIDs alone; thus, concomitant aspirin use is a risk factor for NSAID-associated upper GI toxicity.[19] The association of combined NSAIDs and low-dose aspirin with increased upper GI risk was supported by the results of a cohort study from Denmark, in which patients taking low-dose aspirin (<150 mg/d) had a 2.6% incidence of GI bleeding, compared with a 5.6% incidence in those taking low-dose aspirin plus an NSAID.[18]

In high-risk individuals, such as those with a history of NSAID-related gastric ulcer bleeding, gastroprotective therapy with a proton pump inhibitor has been reported to significantly reduce the risk of recurrent aspirin-associated gastroduodenal ulcer bleeding ($P \leq 0.008$).[20,21] Furthermore, in 2 prospective, endoscopist-blinded trials,[22,23] proton pump inhibitors were found to be superior to histamine-2–receptor antagonists ($P \leq 0.04$) and of similar efficacy to misoprostol for the prevention of recurrent ulcers at the time of scheduled endoscopies. In the more recent prospective, double-blind study by Graham et al,[24] treatment with misoprostol 200 µg QID or lansoprazole 15 or 30 mg OD significantly reduced the risk of recurrent gastric ulcers in *Helicobacter pylori*–negative patients receiving NSAID therapy for 12 weeks ($P < 0.001$). However, these authors did not report results separately for the 13.1% (70/535) of patients who were taking aspirin at amounts ≤325 mg/d in addition to NSAID therapy.

To further understand the efficacy of misoprostol and lansoprazole in reducing the risk for gastric or duodenal ulcer recurrence in this population at high risk for recurrence due to the combined use of aspirin and NSAIDs, the present subanalysis used data from the study by Graham et al[24] to assess the rate of ulcer recurrence in patients taking NSAIDs plus aspirin.

## PATIENTS AND METHODS

### Primary Study

The primary study was a multicenter, prospective, double-blind, 12-week study in patients aged ≥18 years who had a history of endoscopically confirmed gastric ulcer with or without bleeding and required therapeutic doses of NSAIDs for the 12 weeks following enrollment.[24] Those who required therapy with nabumetone or aspirin (≥1300 mg/d) were excluded. All patients were *H pylori* negative (documented by urea breath test or histologic analysis) and, on prerandomization endoscopy, were negative for gastric or duodenal ulcer (defined as a lesion ≥5 mm in diameter with appreciable depth), severe erosive gastritis (defined as >25 erosions), or erosive esophagitis. Patients were excluded if they had used a proton pump inhibitor, a histamine-2–receptor antagonist, or misoprostol within 24 hours of starting the study.

Participants were randomized in blocks of 4 to receive 12 weeks of misoprostol 200 µg QID, lansoprazole 15 or 30 mg OD, or placebo. Antacids were provided for symptom relief as needed. Patients recorded episodes of daytime and nighttime abdominal pain in daily diaries. Endoscopy was performed after 4, 8, and 12 weeks of treatment to determine the presence of gastric and/or duodenal ulcers ≥5 mm in diameter. Endoscopists were blinded to treatment assignment.

After the exclusion of 2 patients who did not take any study medication (1 each in the lansoprazole 30 mg group and the placebo group), the intent-to-treat population consisted of 535 patients. Two hundred four (38.1%) of these patients entered the study after having documented healing of NSAID-associated gastric ulcer with lansoprazole or ranitidine in a separate study of ulcer healing[25,26]; these patients were allowed to enter the primary study within 7 days of the completion of previous study treatment.

Approval for the study was obtained from the institutional review board of each of the 63 participating

North American centers, and written informed consent was obtained from each patient before enrollment.

### Subanalysis

The subanalysis involved 70 patients from the intent-to-treat population (those who received ≥1 dose of study medication) in the primary study who were receiving aspirin at amounts ≤325 mg/d in addition to NSAID therapy. These patients were considered at high risk for gastric or duodenal ulcers. The end point of interest was the cumulative rate of gastric ulcers on endoscopy at 4, 8, and 12 weeks.

Pairwise comparisons were made between treatment groups for all efficacy and safety end points. The comparability of demographic characteristics between subanalysis groups at baseline was assessed using the chi-square test (F test for age), and medical and social characteristics were compared using the Fisher exact test. Life-table methods were used to estimate ulcer incidence rates. The life-table analysis of time to ulcer occurrence was performed using the Cochran-Mantel-Haenszel method to test for treatment differences between subgroups. The Fisher exact test was used to compare the between-subgroup incidence of adverse events possibly or probably related to treatment.

## RESULTS

Of the 70 patients receiving concomitant aspirin and NSAIDs in the primary study (40 men, 30 women; mean [SD] age, 64.7 [10.0] years; age range, 40–83 years), 25 (35.7%) were randomized to receive misoprostol, 16 (22.9%) lansoprazole 15 mg, 7 (10.0%) lansoprazole 30 mg, and 22 (31.4%) placebo. The treatment groups within the subanalysis population were predominantly white and were well matched at baseline in terms of demographic characteristics (**Table I**). The most frequently used nonaspirin NSAIDs were ibuprofen, naproxen, and diclofenac (**Table II**).

Of the 70 patients in the subanalysis population, 8 (11.4%) discontinued the study prematurely (3 misoprostol, 1 lansoprazole 15 mg, 1 lansoprazole 30 mg, 3 placebo). The reasons for discontinuation included adverse events (2 misoprostol [chest pain/dyspepsia, diarrhea], 1 lansoprazole 15 mg [atrial fibrillation], 3 placebo [palpitation, tendon disorder, chest pain]), personal reasons (1 lansoprazole 30 mg), and other (2 misoprostol).

Significantly greater proportions of patients taking NSAIDs plus aspirin remained free of gastric ulcers by 12 weeks in the misoprostol and lansoprazole 15- and 30-mg groups compared with the placebo group

Table I. Baseline demographic and clinical characteristics of intent-to-treat patients included in the subgroup analysis.

| Characteristic | Misoprostol 200 µg QID (n = 25) | Lansoprazole 15 mg OD (n = 16) | Lansoprazole 30 mg OD (n = 7) | Placebo (n = 22) | Total (N = 70) |
|---|---|---|---|---|---|
| Age, y | | | | | |
| Mean (SD) | 63.2 (9.9) | 66.3 (11.0) | 67.6 (10.0) | 64.4 (9.7) | 64.7 (10.0) |
| Range | 40–77 | 48–80 | 52–83 | 44–81 | 40–83 |
| Sex, no. (%) | | | | | |
| Male | 14 (56.0) | 10.0 (62.5) | 5 (71.4) | 11 (50.0) | 40 (57.1) |
| Female | 11 (44.0) | 6 (37.5) | 2 (28.6) | 11 (50.0) | 30 (42.9) |
| Race, no. (%) | | | | | |
| White | 24 (96.0) | 16 (100.0) | 6 (85.7) | 21 (95.5) | 67 (95.7) |
| Black | 0 (0.0) | 0 (0.0) | 1 (14.3) | 0 (0.0) | 1 (1.4) |
| Other | 1 (4.0) | 0 (0.0) | 0 (0.0) | 1 (4.5) | 2 (2.9) |
| Caffeine use, no. (%) | 23 (92.0) | 13 (81.3) | 6 (85.7) | 18 (81.8) | 60 (85.7) |
| Smoking, no. (%) | 10 (40.0) | 3 (18.8) | 1 (14.3) | 7 (31.8) | 21 (30.0) |
| Alcohol use, no. (%) | 7 (28.0) | 8 (50.0) | 3 (42.9) | 7 (31.8) | 25 (35.7) |

Table II. Concomitant nonsteroidal anti-inflammatory drugs (NSAIDs) taken within 1 month of beginning study treatment and during the study (no. [%]).*

| NSAID | Misoprostol 200 μg QID (n = 25) | Lansoprazole 15 mg OD (n = 16) | Lansoprazole 30 mg OD (n = 7) | Placebo (n = 22) |
|---|---|---|---|---|
| Aspirin and aspirin combinations | 25 (100.0) | 16 (100.0) | 7 (100.0) | 22 (100.0) |
| Naproxen | 9 (36.0) | 6 (37.5) | 2 (28.6) | 9 (40.9) |
| Ibuprofen | 12 (48.0) | 3 (18.8) | 1 (14.3) | 8 (36.4) |
| Diclofenac | 8 (32.0) | 6 (37.5) | 2 (28.6) | 7 (31.8) |
| Piroxicam | 5 (20.0) | 1 (6.3) | 3 (42.9) | 2 (9.1) |
| Other† | 6 (24.0) | 5 (31.3) | 3 (42.9) | 9 (40.9) |

*Patients may have taken >1 NSAID.
†Including flurbiprofen, sulindac, diflunisal, indomethacin, etodolac, ketoprofen, tolmetin, salicylates, and phenylbutazone.

(all comparisons, $P \leq 0.008$). Of the 25 patients in the misoprostol group, only 1 had a recurrent gastric ulcer (detected at week 4); thus, the proportion of misoprostol recipients who remained free of gastric ulcers at the end of 12 weeks was 96%. Of the 16 patients receiving lansoprazole 15 mg, 1 had a recurrent gastric ulcer (detected at 12 weeks), with the result that the proportion of patients who received lansoprazole 15 mg and remained free of gastric ulcers over the duration of the study was 93%. There were no gastric ulcer recurrences in the lansoprazole 30-mg group. Of the 22 patients who received placebo, 56% remained free of gastric ulcers at week 4, 49% at week 8, and 35% at week 12 (**Figure**).

Adverse events judged possibly or probably related to treatment were reported by 20.0% (5/25) of misoprostol recipients, 14.3% (1/7) of lansoprazole 30-mg recipients, and 13.6% (3/22) of placebo recipients. In the misoprostol group, 4 (16.0%) patients reported treatment-related diarrhea and 1 (4.0%) reported abdominal pain. One episode of pharyngitis was reported by 1 (14.3%) patient who received lansoprazole 30 mg. No treatment-related adverse events were reported with lansoprazole 15 mg. One episode each of abdominal pain, palpitation, and dyspepsia were reported by 3 patients who received placebo.

## DISCUSSION

This post hoc subanalysis of a prospective, double-blind, controlled clinical trial that enrolled 535 predominantly white patients (484/535 [90.5%])[24] was conducted to examine whether the efficacy of gastroprotective therapy against ulcer recurrence extends to patients taking concomitant nonspecific NSAIDs and low-dose aspirin. In this subanalysis, placebo recipients had a gastric ulcer recurrence rate of 65% in the course of the 12-week trial; the rate of recurrence was significantly reduced in patients receiving gastroprotective therapy compared with those receiving placebo ($P < 0.008$). Consistent with the results of the primary study, this subanalysis found a high rate of gastric ulcer recurrence in patients who received placebo. Those randomized to receive placebo in the primary study were receiving only an NSAID plus aspirin, without gastroprotective therapy. The clinical implication is that patients with a history of ulcer who are taking dual therapy with aspirin and an NSAID are at increased risk for ulcer recurrence and upper GI ulcer bleeding, indicating a need for strategies that reduce this risk.

The use of low "cardioprotective" doses of aspirin is common in the general population, as well as in populations with heightened cardiovascular risk. For example, in the relatively healthy population of the Nurses' Health Studies,[12] ~25% of women aged >51 years reported using aspirin ≥6 days/wk and 42% reported using NSAIDs ≥1 day/wk. In other studies, as would be expected, aspirin use was greater in patients who had been recently hospitalized for a myocardial infarction compared with the general population, with ≥72% taking low-dose aspirin at the time of hospital discharge.[13,14] Use of traditional NSAIDs is also common, particularly in the elderly.[1]

In patients requiring low-dose aspirin along with anti-inflammatory therapy, selection of a

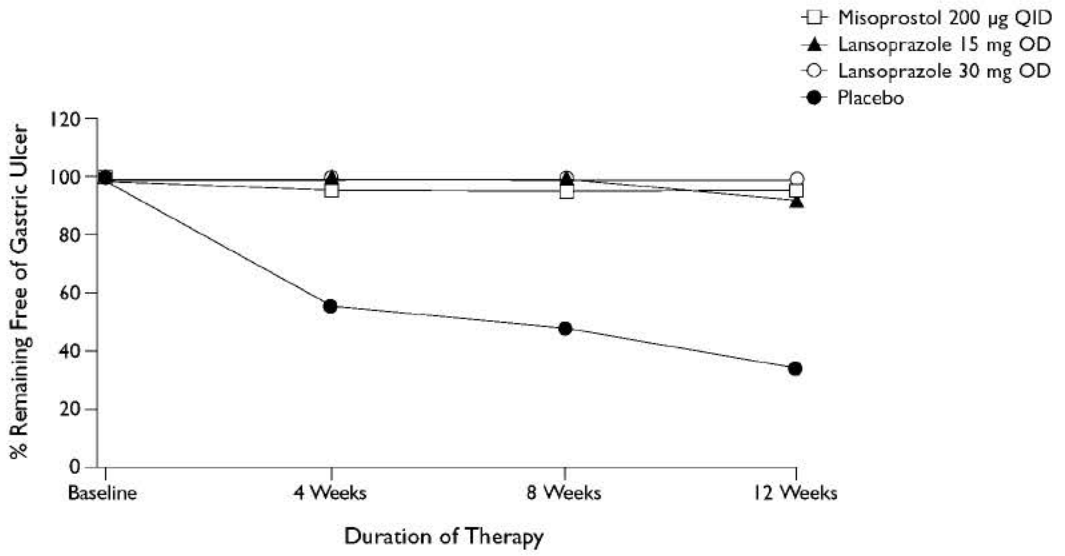


Figure. Proportion of the intent-to-treat population remaining free of gastric ulcer disease during 12 weeks of therapy, calculated by life-table methods. All active treatments were significant versus placebo at each treatment visit ($P \leq 0.008$).

cyclooxygenase-2 (COX-2)–selective inhibitor rather than a nonselective NSAID may be a useful therapeutic approach. Although it has been suggested that the COX-2–selective inhibitors have less GI toxicity than nonselective NSAIDs,[19,27] the safety of low-dose aspirin coadministered with COX-2–selective inhibitors has not been well studied. As reported by Silverstein et al,[19] the underpowered analysis in patients taking aspirin in the Celecoxib Long-Term Arthritis Safety Study suggested no benefit for COX-2–selective inhibitors compared with ibuprofen or diclofenac. However, this conclusion has not been supported by the results of endoscopic trials. In 2 ad hoc analyses involving patients taking aspirin who were given either a COX-2–selective inhibitor, a nonselective NSAID, or placebo,[28,29] the rate of endoscopically documented ulcers in those taking aspirin plus a COX-2–selective inhibitor was ~50% lower than that in patients taking aspirin and a nonselective NSAID. In the first of these studies,[28] the proportion of patients who developed an ulcer while receiving celecoxib plus aspirin was 10.4% (11/106), compared with 22.2% (24/108) of those who received a nonselective NSAID plus aspirin. Similar results were observed in the second analysis[29]: gastroduodenal ulcers (defined as lesions >3 mm in depth) were documented in 11.7% (27/231) of those who received valdecoxib and aspirin and 21.4% (33/154) of those who received a nonselective NSAID and aspirin (relative risk, 1.8). In a prospective trial, Goldstein et al[30] found that concomitant use of celecoxib and aspirin was associated with a 37% risk reduction in 7-day rates of endoscopically documented gastroduodenal ulcers compared with use of naproxen and aspirin. However, whether there is an additive effect to aspirin plus a COX-2–selective inhibitor remains unclear, as these investigators also found that celecoxib added to aspirin was associated with an increased incidence of gastroduodenal ulcers compared with aspirin alone.

## CONCLUSIONS

In this post hoc analysis, patients with a history of gastric ulcer who used aspirin and continued NSAID therapy were at high risk for ulcer recurrence. Cotherapy with misoprostol or lansoprazole lowered the risk of ulcer recurrence in these high-risk individuals.

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