

PREVENTING RECURRENT UPPER GASTROINTESTINAL BLEEDING
IN PATIENTS WITH *HELICOBACTER PYLORI* INFECTION WHO ARE TAKING
LOW-DOSE ASPIRIN OR NAPROXEN

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ABSTRACT

Background Many patients who have had upper gastrointestinal bleeding continue to take low-dose aspirin for cardiovascular prophylaxis or other nonsteroidal antiinflammatory drugs (NSAIDs) for musculoskeletal pain. It is uncertain whether infection with *Helicobacter pylori* is a risk factor for bleeding in such patients.

Methods We studied patients with a history of upper gastrointestinal bleeding who were infected with *H. pylori* and who were taking low-dose aspirin or other NSAIDs. We evaluated whether eradication of the infection or omeprazole treatment was more effective in preventing recurrent bleeding. We recruited patients who presented with upper gastrointestinal bleeding that was confirmed by endoscopy. Their ulcers were healed by daily treatment with 20 mg of omeprazole for eight weeks or longer. Then, those who had been taking aspirin were given 80 mg of aspirin daily, and those who had been taking other NSAIDs were given 500 mg of naproxen twice daily for six months. The patients in each group were then randomly assigned separately to receive 20 mg of omeprazole daily for six months or one week of eradication therapy, consisting of 120 mg of bismuth subcitrate, 500 mg of tetracycline, and 400 mg of metronidazole, all given four times daily, followed by placebo for six months.

Results We enrolled 400 patients (250 of whom were taking aspirin and 150 of whom were taking other NSAIDs). Among those taking aspirin, the probability of recurrent bleeding during the six-month period was 1.9 percent for patients who received eradication therapy and 0.9 percent for patients who received omeprazole (absolute difference, 1.0 percent; 95 percent confidence interval for the difference, -1.9 to 3.9 percent). Among users of other NSAIDs, the probability of recurrent bleeding was 18.8 percent for patients receiving eradication therapy and 4.4 percent for those treated with omeprazole (absolute difference, 14.4 percent; 95 percent confidence interval for the difference, 4.4 to 24.4 percent; $P=0.005$).

Conclusions Among patients with *H. pylori* infection and a history of upper gastrointestinal bleeding who are taking low-dose aspirin, the eradication of *H. pylori* is equivalent to treatment with omeprazole in preventing recurrent bleeding. Omeprazole is superior to the eradication of *H. pylori* in preventing recurrent bleeding in patients who are taking other NSAIDs, such as naproxen. (N Engl J Med 2001;344:967-73.)

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A SPIRIN at low doses and other nonsteroidal antiinflammatory drugs (NSAIDs) are major causes of upper gastrointestinal bleeding worldwide. Low-dose aspirin is increasingly used for cardiovascular prophylaxis, but it doubles the risk of bleeding ulcers, even at doses as low as 75 mg daily.¹ Other NSAIDs are commonly taken for musculoskeletal pain. Epidemiologic studies have shown that the use of NSAIDs increases the risk of ulcer complications by a factor of 4.² A history of upper gastrointestinal bleeding is a significant risk factor for recurrent bleeding in those taking low-dose aspirin³ or other NSAIDs.^{3,4} To date, there are few strategies that effectively prevent ulcers from bleeding in people who take aspirin or other NSAIDs and are at high risk for bleeding.

One approach is concurrent therapy with proton-pump inhibitors. Recent epidemiologic data suggest that this treatment reduces the risk of bleeding in patients taking low-dose aspirin³ or other NSAIDs.^{3,5} However, the long-term cost of this therapy would be substantial.

Another approach is the eradication of *Helicobacter pylori* infection.^{6,7} It is uncertain whether *H. pylori* infection is a risk factor for bleeding ulcers in people who are taking aspirin or other NSAIDs. There are data to suggest that *H. pylori* increases,⁸ has no effect on,^{9,10} or even decreases¹¹ the risk of bleeding among users of aspirin or other NSAIDs. It is not known whether eradicating the infection would substantially reduce the risk of bleeding ulcers in those taking low-dose aspirin or other NSAIDs and would thus obviate the need for acid-suppressive therapy.

We hypothesized that eradicating *H. pylori* infection was equivalent to maintenance therapy with omeprazole in terms of preventing recurrent upper gastrointestinal bleeding in people with *H. pylori* infection who were taking low-dose aspirin or other NSAIDs.

METHODS

Patients

This study was a randomized comparison of the eradication of *H. pylori* and treatment with omeprazole for the prevention of re-

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current upper gastrointestinal bleeding in patients with *H. pylori* infection who were taking low-dose aspirin for coronary heart disease or stroke and patients who were infected with *H. pylori* who were taking NSAIDs other than aspirin for arthritis. The protocol was approved by the ethics committee at the Chinese University of Hong Kong, and all participants provided written informed consent.

From May 1995 to January 2000, we screened users of low-dose aspirin (≤ 325 mg per day) or other NSAIDs who presented with upper gastrointestinal bleeding at the Prince of Wales Hospital. The patients underwent endoscopy within 24 hours after presentation to identify the site of bleeding and determine their *H. pylori* status. The inclusion criteria were endoscopically confirmed ulcers or bleeding erosions, histologically documented *H. pylori* infection, and long-term use or anticipated long-term use (i.e., use for at least six months) of low-dose aspirin or other NSAIDs. The exclusion criteria were concomitant use of nonaspirin NSAIDs and low-dose aspirin, corticosteroids, or anticoagulants; a history of gastric surgery; or the presence of erosive esophagitis, gastroesophageal varices, gastric-outlet obstruction, renal failure (defined by a serum creatinine level of more than 2.26 mg per deciliter [200 μ mol per liter]), terminal illness, or cancer.

All patients were given 20 mg of omeprazole daily for eight weeks to promote ulcer healing. Aspirin and other NSAIDs were withheld during this period. Follow-up endoscopy was performed by one investigator to determine whether the ulcer had healed. Unhealed ulcers were treated with additional courses of omeprazole until complete healing occurred, as determined endoscopically.

Randomization

Eligible patients underwent randomization once the healing of ulcers was confirmed. Patients with coronary heart disease or stroke were given 80 mg of aspirin daily for six months and patients with arthritis were given 500 mg of naproxen twice daily for six months. Randomization was carried out separately in these two groups. In each group, the patients were randomly assigned to receive 20 mg of omeprazole daily for six months or a one-week course of eradication therapy (consisting of 120 mg of bismuth subcitrate, 500 mg of tetracycline, and 400 mg of metronidazole, all of which were given four times daily), followed by an identical-appearing omeprazole placebo. Randomization was carried out through the use of computer-generated lists of random numbers in blocks of 10. Consecutively numbered, sealed packages of drugs were dispensed by a research nurse.

Monitoring

One investigator monitored the patients' hemoglobin levels, serum biochemical values, and symptoms of recurrent bleeding every eight weeks for six months. A research nurse evaluated drug compliance and adverse events. A direct telephone line was provided so that the patients could report any serious adverse events. The final *H. pylori* status was determined by a carbon-13 urea breath test four weeks after the study medications were stopped. Patients who withdrew early were reassessed at six months for recurrent bleeding.

End Point

The end point was recurrent upper gastrointestinal bleeding within six months, which was defined as hematemesis or melena 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 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 in the presence of blood in the stomach. Endoscopy was performed if hematemesis or melena was confirmed by the admitting medical officer. Undocumented hematemesis or melena or the presence of heme-positive stool was not an indication for endoscopy. Members of an independent adjudication committee who were not aware of the patients' treatment assignments performed endoscopy and determined the source of bleeding.

Statistical Analysis

We considered that the effect of the eradication of *H. pylori* would be equivalent to the effect of treatment with omeprazole if the upper limit of the 95 percent confidence interval of the difference in the probability of recurrent bleeding at six months did not exceed 5 percentage points. The power calculations were applied separately for the aspirin and the naproxen groups. On the assumption that omeprazole would reduce the six-month probability of recurrent bleeding to 1.5 percent, we calculated that 125 patients would be required in the eradication-therapy group and 125 patients in the omeprazole group to give the study a power of 80 percent at a 5 percent significance level with the use of a one-sided equivalence test of proportions (PASS software, version 2000, NCSS, Kaysville, Utah).

Because recurrent bleeding is a serious complication, two planned interim analyses were performed in July 1997 and July 1999 to compare the safety of the two treatments. To terminate the trial if one treatment was markedly inferior to the other, we used a pre-defined early stopping rule that specified a level of significance of 0.0005 for the first analysis and 0.01 for the second analysis.¹² The first interim results did not justify early termination.¹³ The second interim analysis included data for 150 patients in the naproxen group (median follow-up, 6 months; range, 10 days to 6 months) and 180 in the aspirin group (median follow-up, 6 months; range, 2 to 6 months). The results showed that in the aspirin group, the probability of recurrent bleeding was similar for patients receiving either treatment ($P=1.00$). In the naproxen group, however, there was a marked difference in the probability of recurrent bleeding: it was 18.8 percent among patients treated with eradication therapy and 4.4 percent among patients treated with omeprazole ($P=0.005$). Because this difference reached the criterion for early stopping, the assignment of patients to the naproxen group was terminated after the second interim analysis. The final analysis was performed in July 2000, after 250 patients in the aspirin group had completed the study. Data analyses were carried out exclusively by a data-review committee at these specified dates.

The Kaplan-Meier method was used to estimate the likelihood of reaching the end point of recurrent upper gastrointestinal bleeding within six months according to the intention-to-treat principle. The log-rank test was used for comparisons between treatment groups. The intention-to-treat analysis included all patients who had taken at least one dose of a study medication. Failure to take at least 70 percent of the study drugs or use of nonstudy drugs, including antiulcer agents, corticosteroids, anticoagulants, NSAIDs other than aspirin or naproxen, or antiplatelet agents, was considered a protocol violation. In the naproxen group, a Cox proportional-hazards model was used to adjust for possibly confounding covariates, including age, the presence or absence of other illnesses, location of the ulcers (stomach, duodenum, or both), diameter of the ulcers (greater than 2 cm, or 2 cm or less), and the presence or absence of previous ulcer disease (symptomatic ulcer or bleeding ulcers).¹⁴ The patients' base-line characteristics were compared with use of Student's *t*-test for parametric data, the Mann-Whitney *U* test for nonparametric data, and Pearson's chi-square test for proportions (SPSS software, version 10.0, SPSS, Chicago). All *P* values are two-tailed.

RESULTS

Study Groups

We screened 896 users of low-dose aspirin (from May 1995 through January 2000) or other NSAIDs (from May 1995 through July 1999) who presented with upper gastrointestinal bleeding. A total of 58 percent of aspirin users and 49 percent of users of other NSAIDs were positive for *H. pylori* infection. We enrolled 400 patients with *H. pylori* infection: 250 in the aspirin group and 150 in the naproxen group (Fig. 1). The study groups were similar with re-

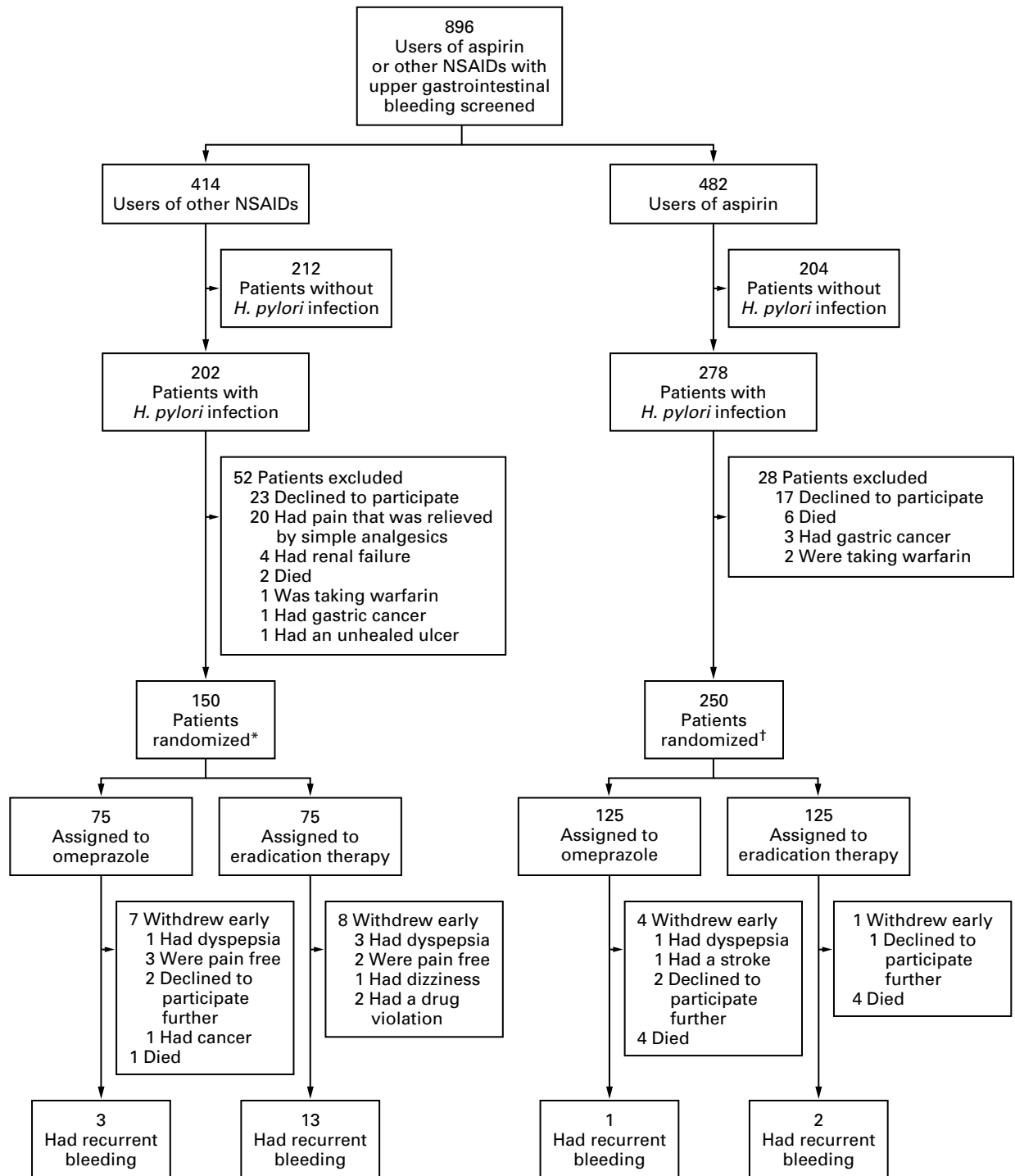


Figure 1. Design of and Outcome of the Study. NSAID denotes nonsteroidal antiinflammatory drug. Early withdrawal refers to the discontinuation of the randomized treatment, but with continued follow-up for recurrent bleeding. *Patients in this group received naproxen. †Patients in this group received low-dose aspirin.

spect to demographic characteristics, the prevalence of coexisting conditions, the location and size of the ulcers, the severity of bleeding at presentation, and the prevalence of previous ulcer disease (Tables 1 and 2).

Aspirin Group

We enrolled 250 patients in the aspirin group (median follow-up, 6 months; range, 2 to 6 months). A predefined level of drug compliance was achieved in 98 percent of the patients who received eradication therapy or omeprazole. Eradication therapy was effective in 93 percent of the patients who received it. Seven percent of the patients in the omeprazole group had a negative urea breath test.

Five patients met the criteria for repeated endoscopy: three had hematemesis or melena, and two had only a drop in the hemoglobin level of at least 2 g per deciliter. All five patients underwent endoscopy. Three of them were confirmed to have recurrent bleeding: two had been assigned to eradication therapy, and one to omeprazole (Table 3). Of the two patients who had recurrent bleeding after the eradication of *H. pylori*, one took a concomitant nonaspirin NSAID for musculoskeletal pain. The two patients with a drop in hemoglobin of at least 2 g per deciliter had normal findings on endoscopy (one received eradication therapy, and one received omeprazole). The estimated probability of recurrent bleeding during the six-month study was 1.9 percent for patients who received eradication therapy and 0.9 percent for patients who received omeprazole (absolute difference, 1.0 percent; 95 percent confidence interval for the difference, -1.9 to 3.9 percent) (Table 4).

The number of early withdrawals was similar in the two subgroups (Fig. 1). Four patients who received eradication therapy died (one from myocardial infarction, one from heart failure, one from acute renal failure, and one from aspiration pneumonia), and four patients who received omeprazole died (two from heart failure, one from aspiration pneumonia, and one from cholangitis).

Naproxen Group

We enrolled 150 patients in the naproxen group (median follow-up, 6 months; range, 10 days to 6 months). Predefined drug compliance was achieved in 88 percent of the patients who received eradication therapy and 87 percent of those who received omeprazole. Eradication therapy was effective in 91 percent of the patients who received it. Ten percent of the patients in the omeprazole group had a negative urea breath test.

Eighteen patients met the criteria for repeated endoscopy: 16 had hematemesis or melena, and 2 had only a drop in hemoglobin of at least 2 g per deciliter. All 18 patients underwent endoscopy, and 16 were confirmed to have recurrent bleeding (13 had received eradication therapy and 3 had received omeprazole) (Table 3). The two patients with a drop in hemoglobin of at least 2 g per deciliter had normal findings on endoscopy (one had received eradication therapy and one had received omeprazole). The estimated probability of recurrent bleeding during the six-month study was 18.8 percent for patients who received eradication therapy and 4.4 percent for patients who received omeprazole (absolute difference, 14.4 percent; 95 percent confidence interval for the difference, 4.4 to 24.4 percent; $P=0.005$) (Table 4 and Fig. 2). In the Cox proportional-hazards model, only a history of ulcer disease was significantly associated with an increased risk of recurrent bleeding (hazard ratio, 5.4; 95 percent confidence interval, 1.9 to 15.5). After adjustment for the covariates of age, the presence or absence of other illnesses, the size and location of the ulcers, and the presence or absence of a history of ulcer disease, the adjusted hazard ratio was 7.1 (95 percent confidence interval, 1.9 to 27.6).

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS IN THE ASPIRIN GROUP.*

CHARACTERISTIC	OMEPRAZOLE THERAPY (N=125)	ERADICATION THERAPY (N=125)
Male sex — no. (%)	79 (63)	92 (74)
Age — yr	69±10	69±10
Current smoking — no. (%)	15 (12)	17 (14)
Current drinking — no. (%)	9 (7)	11 (9)
Type and location of lesion — no. (%)		
Gastric ulcer	58 (46)	57 (46)
Duodenal ulcer	55 (44)	50 (40)
Gastric and duodenal ulcers	7 (6)	8 (6)
Bleeding erosion	5 (4)	10 (8)
Size of ulcer — cm	0.9±0.5	0.8±0.5
Ulcers with active bleeding or nonbleeding visible vessels — no. (%)	35 (28)	28 (22)
Units of blood transfused before randomization		
Median	1	1
Range	0–6	0–5
Coexisting condition — no. (%)		
Coronary heart disease	93 (74)	108 (86)
Ischemic stroke	32 (26)	17 (14)
Dose of aspirin used before the index event — no. (%)		
80 mg/day	88 (70)	107 (86)
160 mg/day	32 (26)	17 (14)
325 mg/day	5 (4)	1 (1)
Previous symptomatic ulcers — no. (%)	30 (24)	37 (30)
Previous upper gastrointestinal bleeding — no. (%)	23 (18)	33 (26)

*Plus-minus values are means ±SD. There were no significant differences between the groups.

razole) (Table 3). The two patients with a drop in hemoglobin of at least 2 g per deciliter had normal findings on endoscopy (one had received eradication therapy and one had received omeprazole). The estimated probability of recurrent bleeding during the six-month study was 18.8 percent for patients who received eradication therapy and 4.4 percent for patients who received omeprazole (absolute difference, 14.4 percent; 95 percent confidence interval for the difference, 4.4 to 24.4 percent; $P=0.005$) (Table 4 and Fig. 2). In the Cox proportional-hazards model, only a history of ulcer disease was significantly associated with an increased risk of recurrent bleeding (hazard ratio, 5.4; 95 percent confidence interval, 1.9 to 15.5). After adjustment for the covariates of age, the presence or absence of other illnesses, the size and location of the ulcers, and the presence or absence of a history of ulcer disease, the adjusted hazard ratio was 7.1 (95 percent confidence interval, 1.9 to 27.6).

The number of early withdrawals was similar in the two subgroups (Fig. 1). Patients who withdrew early did not have recurrent bleeding six months after the beginning of treatment. One patient in the omepra-

TABLE 2. BASE-LINE CHARACTERISTICS OF THE PATIENTS IN THE NAPROXEN GROUP.*

CHARACTERISTIC	OMEPRAZOLE THERAPY (N=75)	ERADICATION THERAPY (N=75)
Male sex — no. (%)	39 (52)	37 (49)
Age — yr	67±13	65±12
Current smoking — no. (%)	8 (11)	13 (17)
Current drinking — no. (%)	5 (7)	10 (13)
Type and location of lesion — no. (%)		
Gastric ulcer	38 (51)	31 (41)
Duodenal ulcer	29 (39)	38 (51)
Gastric and duodenal ulcers	8 (11)	5 (7)
Bleeding erosion	0	1 (1)
Size of ulcer — cm	1.1±0.8	0.9±0.6
Ulcers with active bleeding or nonbleeding visible vessels — no. (%)	20 (27)	19 (25)
Units of blood transfused before randomization		
Median	1	1
Range	0–9	0–5
Type of arthritis — no. (%)		
Osteoarthritis	57 (76)	55 (73)
Rheumatoid arthritis	2 (3)	5 (7)
Gouty arthritis	7 (9)	7 (9)
Other	9 (12)	8 (11)
Coexisting conditions — no. (%)†	32 (43)	32 (43)
Previous symptomatic ulcers — no. (%)	25 (33)	9 (12)
Previous upper gastrointestinal bleeding — no. (%)	18 (24)	16 (21)

*Plus-minus values are means ±SD. There were no significant differences between the groups.

†Coexisting conditions included congestive heart failure, hypertensive heart disease, cerebrovascular disease, chronic obstructive airway disease, and cirrhosis.

zole group died of nasopharyngeal carcinoma three months after the beginning of treatment.

DISCUSSION

We set out to test the hypothesis that eradication of *H. pylori* is equivalent to maintenance treatment with omeprazole for the secondary prevention of upper gastrointestinal bleeding in patients who are taking low-dose aspirin or other NSAIDs. The patients enrolled in this study were at risk for recurrent bleeding because they had a recent history of upper gastrointestinal bleeding.^{3,4} Our results show that in patients infected with *H. pylori* who are taking low-dose aspirin, the eradication of *H. pylori* alone is as effective as maintenance treatment with omeprazole in preventing recurrent upper gastrointestinal bleeding. The equivalence was demonstrated by the absence of a clinically important difference between the results of the two treatments. In contrast, we found that omeprazole is superior to the eradication of *H. pylori* in preventing recurrent bleeding in patients with *H. pylori* infection who are taking naproxen.

Among persons who are infected with *H. pylori*

TABLE 3. CHARACTERISTICS OF PATIENTS WITH RECURRENT UPPER GASTROINTESTINAL BLEEDING.

CHARACTERISTIC	ASPIRIN GROUP (N=3)	NAPROXEN GROUP (N=16)
History of symptomatic or bleeding ulcers — no. (%)	0	10 (62)
Type and location of lesions — no. (%)		
Gastric ulcer	3 (100)	1 (6)
Duodenal ulcer	0	13 (81)*
Gastric and duodenal ulcers	0	2 (12)
Bleeding erosion	0	0
Size of ulcer — cm	0.5–1.0	0.5–3.0
Endoscopic therapy required — no. (%)	1 (33)	5 (31)
Transfusion required — no. (%)†	2 (67)	11 (69)
No. of units transfused	1–9	1–7
Duration of hospital stay — days	5–28	2–8

*The ulcers were complicated by duodenal stenosis in two patients.

†One patient in the aspirin group and two in the naproxen group were in shock when they were admitted. None underwent a surgical intervention or died.

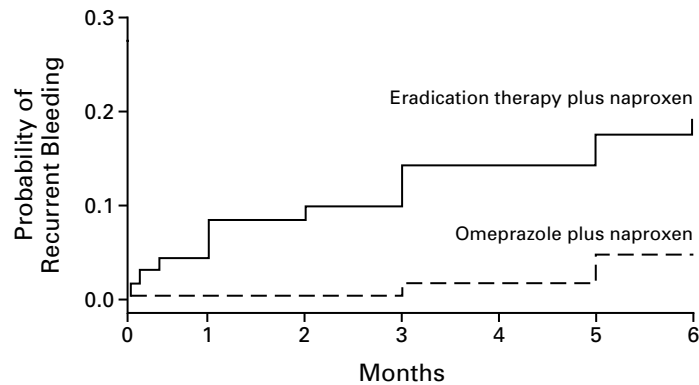
TABLE 4. KAPLAN-MEIER ESTIMATES OF THE LIKELIHOOD OF RECURRENT UPPER GASTROINTESTINAL BLEEDING AT SIX MONTHS IN THE ASPIRIN GROUP AND THE NAPROXEN GROUP.*

GROUP	PROBABILITY OF RECURRENT BLEEDING (95% CI)		ABSOLUTE DIFFERENCE IN THE PROBABILITY OF RECURRENT BLEEDING (95% CI)†
	OMEPRAZOLE THERAPY	ERADICATION THERAPY	
	percent		
Aspirin	0.9 (–0.8 to 2.6)	1.9 (–0.7 to 4.5)	1.0 (–1.9 to 3.9)
Naproxen	4.4 (–0.5 to 9.3)	18.8 (9.5 to 28.1)	14.4 (4.4 to 24.4)

*CI denotes confidence interval.

†The two treatments were considered equivalent if the upper limit of the 95 percent confidence interval for the difference in the probability of recurrent bleeding at six months did not exceed 5 percent.

and who take aspirin, bleeding ulcers could be attributed to *H. pylori*, aspirin, or both. It is impossible to distinguish ulcers related to *H. pylori* from ulcers related to aspirin.¹⁵ One might argue that the eradication of *H. pylori* may not prevent ulcers related to aspirin use. However, our findings suggest that the eradication of *H. pylori* prevents recurrent bleeding in patients who are taking low-dose aspirin irrespective of the location or cause of the ulcers. Thus, *H. pylori* and low-dose aspirin may have a synergistic



No. AT RISK	0	1	2	3	4	5	6
Omeprazole plus naproxen	75	75	75	74	65	64	62
Eradication therapy plus naproxen	75	71	68	61	55	53	50

Figure 2. Cumulative Probability of Recurrent Bleeding in Users of Nonaspirin NSAIDs Who Received Eradication Therapy for *Helicobacter pylori* plus Naproxen or Maintenance Omeprazole plus Naproxen. The difference between groups was significant ($P=0.005$ by the log-rank test).

effect that increases the risk of bleeding from ulcers, so that curing the infection would substantially lower the risk of recurrent bleeding.

In contrast to the case with recurrent bleeding associated with low-dose aspirin use, our results indicate that the eradication of *H. pylori* is inferior to omeprazole in preventing recurrent bleeding associated with nonaspirin NSAIDs. Whether the eradication of *H. pylori* can reduce the risk of ulcers appears to vary according to the group of patients using nonaspirin NSAIDs. For people who have never been treated with nonaspirin NSAIDs, we showed in an earlier study that eradicating *H. pylori* before NSAID treatment was initiated reduces the risk of ulcers.¹⁶ For long-term users of nonaspirin NSAIDs, however, the eradication of *H. pylori* has not been shown to prevent gastroduodenal injury.¹⁷ Our current findings indicate that the eradication of *H. pylori* alone is not sufficient to prevent recurrent bleeding in susceptible long-term users of nonaspirin NSAIDs.

The divergent outcomes in patients taking aspirin and those taking other NSAIDs suggest that *H. pylori* may have a more important role in ulcer bleeding associated with low-dose aspirin than in bleeding associated with other NSAIDs. One explanation is that low-dose aspirin may not be as ulcerogenic as other NSAIDs. Other factors, such as *H. pylori* infection, may need to be present for aspirin to induce substantial gastroduodenal bleeding. Infection with *H. pylori* has been shown to impair gastric adaptation to aspirin. The eradication of *H. pylori* restores this ability and increases the mucosal resistance to

aspirin.¹⁸ Alternatively, low-dose aspirin may provoke bleeding from preexisting *H. pylori*-induced ulcers through its antiplatelet effect. Eradication of *H. pylori* restores the mucosal barrier and thus the ability to withstand the damaging effects of aspirin. In contrast, other NSAIDs can induce peptic ulcers in the absence of *H. pylori*.¹⁹ It is possible that in *H. pylori*-infected long-term users of nonaspirin NSAIDs, many ulcers are induced by NSAIDs rather than by *H. pylori*.

Previous endoscopic studies found that among users of nonaspirin NSAIDs who were receiving omeprazole, those infected with *H. pylori* had less severe mucosal injury than those who were not infected with *H. pylori*.^{20,21} *H. pylori* augments the acid-suppressing effect of proton-pump inhibitors.^{22,23} It is unclear whether omeprazole can effectively prevent bleeding ulcers in users of nonaspirin NSAIDs who are not infected with *H. pylori*. Even so, augmentation of the acid-suppressing effect of proton-pump inhibitors by *H. pylori* cannot be used to justify the failure to treat *H. pylori* infection in users of nonaspirin NSAIDs who are receiving acid-suppressive therapy, since *H. pylori* is a risk factor both for peptic ulcer and for cancer of the stomach.

Our study had several limitations. First, the absolute reduction in the risk of recurrent bleeding that was attributable to the eradication of *H. pylori* cannot be determined, because a placebo group was not included. However, our objective was to investigate whether the eradication of *H. pylori* could substitute for omeprazole therapy in persons at high risk for

upper gastrointestinal bleeding. It would be unethical to withhold treatment to prevent recurrence of ulcer bleeding from such patients. Second, therapy with bismuth may have a slight protective effect on mucosa, although it is very unlikely that one week of bismuth could prevent complications of ulcers, such as bleeding. Third, we studied only naproxen and thus did not address the differences in the ulcerogenicity of other NSAIDs. Since epidemiologic studies do not suggest that naproxen is associated with a higher risk of ulcer bleeding than are other commonly used non-aspirin NSAIDs,²⁴ we believe it is reasonable to extend our findings to other nonaspirin NSAIDs.

In summary, we found that in patients who were infected with *H. pylori* and who were receiving low-dose aspirin, the eradication of *H. pylori* is as effective as maintenance therapy with omeprazole in preventing recurrent upper gastrointestinal bleeding. In the light of the increasing use of aspirin for cardiovascular prophylaxis, our findings suggest that patients who are at risk for bleeding from ulcers should be tested for *H. pylori* infection and treated for it if the infection is found. In contrast, we found that therapy with omeprazole is superior to the eradication of *H. pylori* for the secondary prevention of upper gastrointestinal bleeding in *H. pylori*-infected users of naproxen, and presumably other nonaspirin NSAIDs.

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REFERENCES

- Weil J, Colin-Jones D, Langman M, et al. Prophylactic aspirin and risk of peptic ulcer bleeding. *BMJ* 1995;310:827-30.
- Hernandez-Diaz S, Rodriguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. *Arch Intern Med* 2000;160:2093-9.
- Lanas A, Bajador E, Serrano P, et al. Nitrovasodilators, low-dose aspirin, other nonsteroidal anti-inflammatory drugs, and the risk of upper gastrointestinal bleeding. *N Engl J Med* 2000;343:834-9.
- Garcia Rodriguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994;343:769-72. [Erratum, *Lancet* 1994;343:1048.]
- Garcia Rodriguez LA, Ruigomez A. Secondary prevention of upper gastrointestinal bleeding associated with maintenance acid-suppressing treatment in patients with peptic ulcer bleed. *Epidemiology* 1999;10:228-32.
- Russell RI. *Helicobacter pylori* and non-steroidal anti-inflammatory drugs: ulcers and bleeding ulcers. *Ital J Gastroenterol Hepatol* 1999;31:116-8.
- McCarthy DM. *Helicobacter pylori* and non-steroidal anti-inflammatory drugs: does infection affect the outcome of NSAID therapy? *Yale J Biol Med* 1998;71:101-11.
- Aalykke C, Lauritsen JM, Hallas J, Reinholdt S, Krogfelt K, Lauritsen K. *Helicobacter pylori* and risk of ulcer bleeding among users of nonsteroidal anti-inflammatory drugs: a case-control study. *Gastroenterology* 1999;116:1305-9.
- Labenz J, Peitz U, Kohl H, et al. *Helicobacter pylori* increases the risk of peptic ulcer bleeding: a case-control study. *Ital J Gastroenterol Hepatol* 1999;31:110-5.
- Cullen DJ, Hawkey GM, Greenwood DC, et al. Peptic ulcer bleeding in the elderly: relative roles of *Helicobacter pylori* and non-steroidal anti-inflammatory drugs. *Gut* 1997;41:459-62.
- Santolaria S, Lanasa A, Benito R, Perez-Aisa MP, Montoro M, Sainz R. *Helicobacter pylori* infection is a protective factor for bleeding gastric ulcers but not for bleeding duodenal ulcers in NSAID users. *Aliment Pharmacol Ther* 1999;13:1511-8.
- O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549-56.
- Chan FKL, Sung JY, Suen R, et al. Eradication of *H. pylori* versus maintenance acid suppression to prevent recurrent ulcer hemorrhage in high risk NSAID users: a prospective randomized study. *Gastroenterology* 1998;114:A87. abstract.
- Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
- Graham DY. Nonsteroidal anti-inflammatory drugs, *Helicobacter pylori*, and ulcers: where we stand. *Am J Gastroenterol* 1996;91:2080-6.
- Chan FK, Sung JJ, Chung SC, et al. Randomised trial of eradication of *Helicobacter pylori* before non-steroidal anti-inflammatory drug therapy to prevent peptic ulcers. *Lancet* 1997;350:975-9.
- Hawkey CJ, Tulassay Z, Szczepanski L, et al. Randomised controlled trial of *Helicobacter pylori* eradication in patients on non-steroidal anti-inflammatory drugs: HELP NSAIDs study. *Lancet* 1998;352:1016-21. [Erratum, *Lancet* 1998;352:1634.]
- Konturek JW, Dembinski A, Konturek SJ, Stachura J, Domschke W. Infection of *Helicobacter pylori* in gastric adaptation to continued administration of aspirin in humans. *Gastroenterology* 1998;114:245-55.
- Laine L, Marin-Sorensen M, Weinstein WM. Nonsteroidal anti-inflammatory drug-associated gastric ulcers do not require *Helicobacter pylori* for their development. *Am J Gastroenterol* 1992;87:1398-402.
- Yeomans ND, Tulassay Z, Juhász L, et al. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal anti-inflammatory drugs. *N Engl J Med* 1998;338:719-26.
- Hawkey CJ, Karrasch JA, Szczepański L, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal anti-inflammatory drugs. *N Engl J Med* 1998;338:727-34.
- Labenz J, Tillenburg B, Peitz U, et al. *Helicobacter pylori* augments the pH-increasing effect of omeprazole in patients with duodenal ulcer. *Gastroenterology* 1996;110:725-32.
- Gillen D, Wirz AA, Neithercut WD, Ardill JES, McColl KEL. *Helicobacter pylori* infection potentiates the inhibition of gastric acid secretion by omeprazole. *Gut* 1999;44:468-75.
- Henry D, Lim LL, Garcia Rodriguez LA, et al. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *BMJ* 1996;312:563-6.

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