

LANSOPRAZOLE FOR THE PREVENTION OF RECURRENCES OF ULCER COMPLICATIONS FROM LONG-TERM LOW-DOSE ASPIRIN USE

KAM CHUEN LAI, M.R.C.P., SHIU KUM LAM, M.D., KENT MAN CHU, F.R.C.S., BENJAMIN C.Y. WONG, M.D.,
WAI MO HUI, M.D., WAYNE H.C. HU, M.R.C.P., GEORGE K.K. LAU, M.D., WAI MAN WONG, M.R.C.P.,
MAN FUNG YUEN, M.R.C.P., ANNIE O.O. CHAN, M.R.C.P., CHING LUNG LAI, M.D., AND JOHN WONG, F.R.A.C.S.

ABSTRACT

Background The role of gastric acid suppression in preventing the recurrence of ulcer complications after the eradication of *Helicobacter pylori* infection in patients taking long-term low-dose aspirin is uncertain.

Methods We enrolled 123 patients who had ulcer complications after using low-dose aspirin continuously for more than one month and who had *H. pylori* infection. After the ulcers had healed and the *H. pylori* infection was eradicated, the patients were randomly assigned to treatment with 30 mg of lansoprazole daily or placebo, in addition to 100 mg of aspirin daily, for 12 months. The primary end point was the recurrence of ulcer complications.

Results During a median follow-up of 12 months, 9 of the 61 patients in the placebo group (14.8 percent), as compared with 1 of the 62 patients in the lansoprazole group (1.6 percent), had a recurrence of ulcer complications (adjusted hazard ratio, 9.6; 95 percent confidence interval, 1.2 to 76.1). Of these 10 patients, 4 had evidence of a recurrence of *H. pylori* infection and 2 had taken nonsteroidal antiinflammatory drugs before the onset of complications. Patients in the lansoprazole group were significantly less likely to have a recurrence of ulcer complications than patients in the placebo group ($P=0.008$). There was no significant difference in mortality between the two groups.

Conclusions In patients who had ulcer complications related to the long-term use of low-dose aspirin, treatment with lansoprazole in addition to the eradication of *H. pylori* infection significantly reduced the rate of recurrence of ulcer complications. (N Engl J Med 2002;346:2033-8.)

Copyright © 2002 Massachusetts Medical Society.

THE efficacy of low-dose aspirin (less than 325 mg daily) in the prevention of cardiovascular and cerebrovascular diseases is well established.¹ Patients who are taking low-dose aspirin, however, have an increased risk of ulcer complications,² and some of these patients should be given prophylactic treatment.

One of the available options for preventing these ulcer complications is the simultaneous use of proton-pump inhibitors, which reduce gastric acidity substantially. In a recent epidemiologic study, the use of

a proton-pump inhibitor was found to be associated with a decrease of 80 percent in the risk of gastrointestinal bleeding in subjects taking low-dose aspirin.³ Use of a proton-pump inhibitor was also shown to prevent the relapse of endoscopic ulcers in patients receiving long-term therapy with nonsteroidal antiinflammatory drugs (NSAIDs).^{4,5} Although no randomized study has examined the role of proton-pump inhibitors in subjects taking low-dose aspirin, it seems likely that the results of these studies of nonaspirin NSAIDs can be extrapolated to patients who are taking low-dose aspirin.

Since *Helicobacter pylori* infection is commonly found in patients with ulcer bleeding and is an important risk factor for peptic-ulcer bleeding, we compared the efficacy of eradication of *H. pylori* infection alone with that of the combination of such eradication with proton-pump inhibitor therapy in preventing the recurrence of ulcer complications in users of low-dose aspirin. Because ulcer bleeding occurring early in the course of aspirin treatment may be related to the hemorrhagic effect of aspirin on a preexisting ulcer or to its primary ulcerogenic effect, we limited our study to patients in whom ulcer bleeding developed after at least one month of low-dose aspirin therapy.

METHODS

Study Population

This prospective, randomized, controlled trial was conducted at the Queen Mary Hospital at the University of Hong Kong between January 1999 and July 2001, in accordance with the principles of good clinical practice and the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the University of Hong Kong, and all patients gave written informed consent.

We screened for eligibility patients who presented to our endoscopy unit with a history of bleeding or gastric-outlet obstruction due to gastroduodenal ulcer while receiving low-dose aspirin (defined as a daily dose of less than 325 mg). We enrolled patients in the study if they met the following criteria: endoscopy revealed a gastric ulcer, a duodenal ulcer, or a gastroduodenal ulcer, defined as a break in the mucosa at least 5 mm in diameter with unequivocal depth; they were receiving low-dose aspirin for at least one month before complications developed; they had a disease, such as stroke or ischemic heart disease, that required long-term,

From the Departments of Medicine (K.C.L., S.K.L., B.C.Y.W., W.M.H., W.H.C.H., G.K.K.L., W.M.W., M.E.Y., A.O.O.C., C.L.L.) and Surgery (K.M.C., J.W.), University of Hong Kong, Queen Mary Hospital, Hong Kong, China. Address reprint requests to Dr. K.C. Lai at the Department of Medicine, Queen Mary Hospital, Pokfulam, Hong Kong, China, or at kclai@hku.hk.

continuous treatment with low-dose aspirin; they were between 18 and 80 years of age; and the presence of *H. pylori* infection could be demonstrated by rapid urease testing, histologic analysis of an antral-biopsy specimen, or both. Patients were excluded if endoscopy revealed esophagitis; if they had a history of gastric or duodenal surgery other than oversewing of a perforation; if they were allergic to the study drugs; if they were receiving concomitant treatment with NSAIDs, corticosteroids, or anticoagulant agents; if they had active cancer; or if the *H. pylori* infection could not be eradicated after two attempts with eradication therapies.

Study Protocol

Detection of *H. pylori*

During endoscopy, two antral-biopsy specimens were obtained — one from the incisura and the other from the greater curve within 5 cm of the pylorus. The specimen from the greater curve was subjected to a standard rapid urease test (Campylobacter-Like Organism [CLO] test, Delta West). A negative CLO test was defined by the absence of a change in color after 24 hours. The specimen from the incisura was subjected to microscopical examination for *H. pylori* with the use of hematoxylin and eosin stain and Warthin–Starry stain, if necessary. Both tests have a sensitivity of 97.5 to 99.4 percent and a specificity of 100 percent in detecting *H. pylori*.⁶ *H. pylori* was considered to be present if either one of the two tests was positive; it was considered to be absent or successfully eradicated when both tests were negative. The microscopical detection of *H. pylori* is not affected by the continuous administration of a histamine H₂ antagonist.⁷

Treatment and Randomization

All patients who met the criteria for inclusion and did not meet the criteria for exclusion received a one-week course of anti-helicobacter therapy consisting of 30 mg of lansoprazole, 1 g of amoxicillin, and 500 mg of clarithromycin, all given twice daily. This course was followed by treatment with 20 mg of famotidine given twice daily for five weeks. Endoscopy was performed again at the end of treatment to check for healing of the ulcer and eradication of *H. pylori* infection. Patients in whom endoscopy revealed an unhealed ulcer were given 20 mg of famotidine twice daily for another eight weeks. Patients in whom *H. pylori* infection was not eradicated, as indicated by positive results on additional rapid urease tests or histologic examinations, received a one-week course of triple therapy consisting of 400 mg of ranitidine bismuth citrate, 1 g of amoxicillin, and 400 mg of metronidazole, all given twice daily. Patients with unhealed ulcers and two unsuccessful treatments for the eradication of *H. pylori* infection were withdrawn from the study. Patients with healed ulcers in whom *H. pylori* infection had been eradicated were randomly assigned to receive 100 mg of aspirin and 30 mg of lansoprazole or 100 mg of aspirin and matching placebo, all given once daily for 12 months. The treatment-group assignment had been determined previously by a list of random numbers generated by computer. The investigators who were responsible for treatment-group assignments and monitoring of the patients' progress were unaware of the treatment-group assignments until the analyses were completed, as were the members of the gastrointestinal-events review board.

Follow-up

Patients were followed as outpatients, with visits every two months. The administration of an antacid (Gelusil, Parke-Davis) was permitted for the control of mild symptoms of dyspepsia. Patients were advised to avoid taking NSAIDs other than the study drug if possible. Compliance with the regimen was assessed by counts of the pills that were returned. Upper gastrointestinal tract symptoms were assessed at each visit.

Patients were asked to report to the outpatient clinic if they had persistent ulcer symptoms (epigastric pain, dyspepsia, or recurrent

vomiting) that were not relieved by antacids and to report to the emergency room if they had evidence of gastrointestinal bleeding or ulcer complications (melena, hematemesis, or sudden onset of severe epigastric pain). Endoscopy was then repeated to document any recurrence of gastroduodenal ulcer. *H. pylori* was detected by carbon-13 urea breath testing and by additional rapid urease testing and microscopical examination of gastric mucosal-biopsy specimens. Blood counts were checked every six months. If the hemoglobin level had decreased by 2 g per deciliter or more, endoscopy was repeated to check for the presence of ulcers, and stool was checked for the presence of occult blood. No scheduled endoscopy was otherwise performed.

End Points

The primary end point was the recurrence of ulcer complications (bleeding, perforation, or obstruction). The secondary end point was the recurrence of gastroduodenal ulcer, including ulcer complications and symptomatic ulcers.

A gastrointestinal-events review board, whose members were unaware of the patients' treatment-group assignments, reviewed the data and determined whether the patients had reached the study end points according to prespecified criteria (Table 1). Events that were confirmed and that occurred during treatment or within 14 days after the discontinuation of treatment were included in the primary analysis. Patients with a recurrence of peptic ulcers were given standard antiulcer treatment, including histamine H₂ antagonists or proton-pump inhibitors for the healing of ulcers, and were cared for according to the standard practice at the hospital. Patients who withdrew from the study were followed until the end of the study for any recurrence of gastrointestinal complications.

Statistical Analysis

When we began the study, there were no data available about the rate of relapse of ulcer complications in aspirin users. We estimated that at one year, the primary end point (relapse of ulcer complications) after eradication of *H. pylori* infection would occur in 20 percent of patients in the placebo group and that the addition of lansoprazole would reduce the rate of relapse to 5 percent. It was estimated that we required a minimum of 90 patients in each treatment group to demonstrate an absolute difference of 15 percentage points with a type I error of 0.05 and a type II error of 0.2 (in two-sided tests).

We planned two interim analyses, to be conducted in April 2000 and April 2001. On the basis of the O'Brien–Fleming rules for early termination, we determined that we would stop the trial if the difference between the groups in the primary end point reached a significance level of 0.001 in the first analysis or 0.01 in the second analysis.⁸ The analyses were performed by independent investigators who were not involved in the treatment of the patients studied.

The homogeneity of the treatment groups at base line was analyzed by the chi-square test with Yates' correction or Fisher's exact test for categorical data and the Mann–Whitney U test for continuous variables. Statistical analysis of clinical events included the intention-to-treat population consisting of all patients who were enrolled in the study and underwent randomization. The probability of a recurrence of ulcer complications during follow-up was analyzed with the use of Kaplan–Meier survival estimates. The log-rank test was used to determine the differences between groups in the time to a recurrence of ulcer complications. The hazard ratio was adjusted by a Cox proportional-hazards model for the effects of potential confounding covariates, including the factors listed in Table 1, on the development of ulcers and ulcer complications.

SPSS software (SPSS), version 10.0 for Windows was used for all statistical calculations. All P values are two-sided.

TABLE 1. PRESPECIFIED CRITERIA FOR ULCER COMPLICATIONS.

TYPE OF EVENT	CONFIRMATORY CRITERIA
Upper gastrointestinal tract bleeding	Hematemesis, melena, or both, with a nonmalignant ulcer found on endoscopy or at surgery; decrease of ≥ 2 g per deciliter in the hemoglobin level with a nonmalignant ulcer found on endoscopy and occult-blood-positive stool
Gastric-outlet obstruction	Nausea and vomiting ≤ 24 hr after eating, with stenosis in the distal part of the stomach or duodenum, as a result of a nonmalignant ulcer found on endoscopy or at surgery
Gastric or duodenal perforation	Presence of perforation due to a nonmalignant ulcer that requires surgery

RESULTS

The first interim analysis was performed in April 2000 after 65 patients had been recruited. There were no recurrences of ulcer complications in the lansoprazole group (0 percent), and there were four in the placebo group (12.1 percent) ($P=0.05$).⁹ The second interim analysis was performed in April 2001, when 123 patients had been recruited, and because we found a significant difference between the two groups ($P=0.006$) in the occurrence of the primary end point, we stopped the recruitment and randomization of patients. Data analysis was completed in July 2001, when the median duration of follow-up was 12 months (range, 3 to 12). The results we report here are based on all 123 randomized patients with follow-up until July 2001.

Characteristics of the Patients

Of the 245 patients who underwent endoscopy because they had peptic-ulcer complications while taking low-dose aspirin (2 with gastric-outlet obstruction and 243 with upper gastrointestinal bleeding), 171 were found to be infected with *H. pylori*. Endoscopic hemostasis was unsuccessful in three patients, and surgery was performed immediately. Forty-one patients were not enrolled in the study: 28 had used aspirin for less than a month, 3 were using corticosteroids or anticoagulant agents in addition to aspirin, 2 had active cancer, and 8 declined to participate in the study.

Anti-helicobacter therapy was given to the remaining 127 patients. In four patients, the ulcer did not heal, *H. pylori* infection was not eradicated despite two attempts with anti-helicobacter therapy, or both. A total of 123 patients were randomly assigned to receive 100 mg of aspirin and either 30 mg of lansoprazole or matching placebo, all given once daily. The two treatment groups were similar with respect to base-line demographic characteristics, the clinical se-

verity of bleeding (as categorized on the basis of the vital signs and hemoglobin level on admission, and the need or lack of need for blood transfusion and endoscopic treatment), history or lack of history of previous ulcer bleeding, the location and size of ulcers, and the presence or absence of coexisting illnesses (Table 2).

Follow-up

The median duration of follow-up was 12 months in both treatment groups (range, 3 to 12). According to self-reports, four patients in the lansoprazole group (6.5 percent) and six patients in the placebo group (9.8 percent) did not comply with the protocol. In the lansoprazole group, one patient had an intolerance of the study medications, one stopped taking aspirin, and two were lost to follow-up. In the placebo group, two patients stopped taking aspirin, two were lost to follow-up, and two used other NSAIDs during the study. Pill counts indicated that all other patients took their medication on at least 75 percent of the days of the study.

Recurrence of Gastrointestinal Ulcers and Ulcer Complications

During the study period, 14 upper gastrointestinal tract events were adjudicated by the end-points committee. Of these, 10 events were confirmed.

Four patients had dyspepsia while taking low-dose aspirin and placebo, but endoscopy did not reveal any peptic ulcers. In these four patients, dyspepsia subsided after a short course of antacids, and aspirin therapy was continued. Two patients were found to have a decrease in the hemoglobin level of more than 2 g per deciliter from the base-line level after the ulcer had healed; in both these patients, stool was positive for occult blood. Endoscopy showed the presence of a gastric ulcer in one patient and a duodenal ulcer in the other patient. Eight patients presented with clinical evidence of upper gastrointestinal tract bleeding. Gastric ulcers were detected by endoscopy in all of these patients. One patient in the lansoprazole group died during the study period because of aspiration pneumonia secondary to a recurrence of stroke.

One episode of gastrointestinal bleeding occurred in the lansoprazole group and nine events occurred in the placebo group. The estimated probability of recurrence of gastroduodenal ulcers and ulcer complications was 1.6 percent in the lansoprazole group (1 of 62; 95 percent confidence interval, 0 to 9 percent) and 14.8 percent in the placebo group (9 of 61; 95 percent confidence interval, 7 to 26 percent; $P=0.008$; hazard ratio, 10.6; 95 percent confidence interval, 1.3 to 86.1). The log-rank test showed a significant difference between the two groups in the time to recurrence ($P=0.008$). After adjustment for the

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

VARIABLE	LANSOPRAZOLE GROUP (N=62)	PLACEBO GROUP (N=61)
Continuous variables		
Age — yr	71.5±8.0	69.1±7.6
Duration of follow-up — mo		
Median	12	12
Range	3–12	3–12
Hemoglobin level on admission — g/dl	9.9±1.5	10.2±1.8
Transfusion required — units	1.03±1.16	0.97±1.21
Size of ulcer — mm	11.6±4.6	11.2±4.0
Categorical variables		
Female sex — no. (%)	16 (25.8)	19 (31.1)
Age ≥65 yr — no. (%)	48 (77.4)	43 (70.5)
Smoking — no. (%)	8 (12.9)	12 (19.7)
Alcohol use — no. (%)	9 (14.5)	10 (16.4)
Medical history — no. (%)		
Cerebrovascular accident	28 (45.2)	36 (59.0)
Ischemic heart disease	34 (54.8)	25 (41.0)
Other concomitant illness	11 (17.7)	15 (24.6)
History of ulcer	6 (9.7)	7 (11.5)
History of bleeding	4 (6.5)	3 (4.9)
Clinical and laboratory variables		
Pulse ≥100 beats/min on admission — no. (%)	11 (17.7)	7 (11.5)
Systolic blood pressure <100 mm Hg on admission — no. (%)	9 (14.5)	7 (11.5)
Shock at presentation — no. (%)†	8 (12.9)	6 (9.8)
Serum urea level >10 mmol/liter — no. (%)	43 (69.4)	46 (75.4)
Transfusion required — no. (%)		
None	22 (35.5)	28 (45.9)
1–2 units	32 (51.6)	25 (41.0)
3–4 units	6 (9.7)	7 (11.5)
>4 units	2 (3.2)	1 (1.6)
Location of ulcer — no. (%)		
Gastric	47 (75.8)	44 (72.1)
Duodenal	12 (19.4)	14 (23.0)
Gastroduodenal	3 (4.8)	3 (4.9)
Ulcer size >10 mm — no. (%)	27 (43.5)	34 (55.7)
Endoscopic hemostasis required — no. (%)	20 (32.3)	16 (26.2)

*Plus-minus values are means ±SD.

†Shock was defined as a systolic blood pressure of less than 100 mm Hg with a pulse of 100 beats per minute or more.

possible confounding covariates, including age, history or lack of history of ulcer, history or lack of history of bleeding, location of ulcers, size of ulcers, and the presence or absence of coexisting illness, the hazard ratio according to the Cox proportional-hazards model was 9.6 (95 percent confidence interval, 1.2 to 76.1).

The characteristics of the patients who had recurrent gastroduodenal-ulcer complications are shown in Table 3. Two patients in the placebo group required endoscopic treatment to stop the bleeding. Of the 10 patients who had gastrointestinal events during the study, 4 (all in the placebo group) had a relapse of *H. pylori* infection, as determined by carbon-13 urea breath testing, rapid urease testing, and histologic examination of an antral-biopsy specimen.

Two patients had taken NSAIDs within four weeks before the onset of ulcer complications.

DISCUSSION

This study demonstrates that in patients who had been infected with *H. pylori* and had gastrointestinal bleeding while taking low-dose aspirin, maintenance treatment with a proton-pump inhibitor and eradication of the *H. pylori* infection led to a significant reduction in the recurrence of ulcer complications as compared with the eradication of *H. pylori* infection alone.

Since the dose of aspirin used in the primary and secondary prevention of vascular diseases is much lower than the doses of conventional nonaspirin NSAIDs used in treating patients with osteoarthritis or rheu-

TABLE 3. CHARACTERISTICS OF PATIENTS WITH RECURRENCES OF ULCER COMPLICATIONS OR CLINICAL REBLEEDING.*

VARIABLE	LANSOPRAZOLE GROUP (N=62)	PLACEBO GROUP (N=61)
Patients with recurrences of complications		
Total — no. (%)	1 (1.6)	9 (14.8)
Site of relapse — no.		
Gastric ulcer	1	8
Duodenal ulcer	0	1
Time to relapse — no.		
<6 mo	0	2
≥6 mo	1	7
Recurrence of <i>H. pylori</i> infection — no.	0	4
Deaths — no.	1	0
Patients with clinical rebleeding†		
Total — no.	0	8
Age — yr	—	66.5±8.5
Female sex — no. (%)	—	4 (50.0)
Transfusion required — units	—	1.13±1.46
Range	—	0–4
Location of ulcer — no.		
Gastric	—	8
Duodenal	—	0
Range of ulcer size — mm	—	5–15
Hemoglobin level on admission — g/dl	—	10.34±2.09
Pulse ≥100 beats/min on admission — no. (%)	—	3 (37.5)
Systolic blood pressure <100 mm Hg on admission — no. (%)	—	2 (25.0)
Shock at presentation — no. (%)‡	—	2 (25.0)
Serum urea level >10 mmol/liter — no. (%)	—	5 (62.5)
Endoscopic hemostasis required — no. (%)	—	2 (25.0)

*Plus-minus values are means ±SD.

†Two patients are not included, because their rebleeding was identified only by a decrease in hemoglobin levels.

‡Shock was defined as a systolic blood pressure of less than 100 mm Hg with a pulse of 100 beats per minute or more.

matoid arthritis, the risk of complications associated with low-dose aspirin might be expected to be correspondingly lower than the risk associated with those treatments.¹⁰ However, the effects of proton-pump inhibitor treatment in this aspirin-treated population had not been known.

Our study population was uniform in that all patients had had *H. pylori* infection that was successfully treated before randomization. We did not study the effect of previous *H. pylori* infection on the risk of a recurrence of ulcer complications in patients taking low-dose aspirin. Nevertheless, in our study, 14.8 percent of the patients in the placebo group had recurrences of ulcer complications despite the initial eradication of *H. pylori* infection. This high rate of recurrence may be attributable in part to the presence of other risk factors for a relapse of ulcer, including the recurrence of *H. pylori* infection in four patients and the concomitant use of NSAIDs in two patients. Even if we exclude these 6 patients from the analysis, however, 5 percent of the other patients in the pla-

cebo group (3 of 55) had a recurrence of ulcer complications despite the absence of other potential risk factors for a relapse of ulcer. This finding implies that the ulcerogenic effect of low-dose aspirin cannot be completely abolished by the eradication of *H. pylori* infection alone. The persistent ulcerogenic effect of aspirin is probably related to the fact that, even at a very low dose, aspirin can inhibit the synthesis of a substantial proportion of protective gastric prostaglandins.¹¹

We found that the addition of the proton-pump inhibitor lansoprazole significantly reduced the rate of recurrence of ulcer complications. Our findings confirm those of an epidemiologic study that showed a reduced risk of ulcer bleeding in patients taking low-dose aspirin and a proton-pump inhibitor at the same time.³ The reduction in the recurrence of aspirin-related ulcer bleeding that occurs as a result of the acid suppression associated with proton-pump inhibitors is most likely related to the protective effect of these drugs against mucosal injury. Another possible mech-

anism is that through acid suppression, the proton-pump inhibitor reduces acute aspirin-induced microbleeding from erosions.¹²

Our study had several drawbacks. We did not include a control group in which *H. pylori* infection was not eradicated, which would have enabled us to identify more definitively the effects of *H. pylori* infection in users of low-dose aspirin. Our local ethics committee thought it would be unethical to resume aspirin therapy without adding any other treatment in patients with *H. pylori*-infected ulcers, especially in those with complications such as bleeding. Moreover, there is a consensus that *H. pylori* infection in bleeding ulcers should be eradicated.¹³ Second, although we showed that lansoprazole reduced the rate of relapse of ulcer complications significantly better than placebo, with a hazard ratio of 9.6, the 95 percent confidence interval around the ratio was wide, suggesting that one must be cautious when translating our findings into practice. The wide confidence interval is probably related to the low rate of events in the lansoprazole group. In conclusion, we have demonstrated that after the initial eradication of *H. pylori* infection, proton-pump inhibitor therapy significantly reduces the risk of recurrences of ulcer complications in patients who continue to take low-dose aspirin.

Supported by a grant (311/041/0372) from the Peptic Ulcer Research Fund of the University of Hong Kong.

We are indebted to Drs. C.K. Chan and C.K. Hui for recruiting the patients and performing the endoscopy; to endoscopy nurses M. Chong, A. Tang, K.W. Wong, S.Y. Tang, M.Y. Lee, K.K. Chang, M. Chow, W.M. Chan, F.K. Kwok, Y.K. Lam, Y.M. Lam, S.M. Yeung, and S.Y. Lo at the Queen Mary Hospital for their assistance; to Professor W.K. Li of the Department of Statistics at the University of

Hong Kong for statistical advice; to Ms. April Wong for data management; and to Mr. Stanley Yeung for statistical calculations.

REFERENCES

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81-106. [Erratum, *BMJ* 1994;308:1540.]
2. Weil J, Colin-Jones D, Langman M, et al. Prophylactic aspirin and risk of peptic ulcer bleeding. *BMJ* 1995;310:827-30.
3. Lanas A, Bajador E, Serrano P, et al. Nitrovasodilators, low-dose aspirin, other nonsteroidal antiinflammatory drugs, and the risk of upper gastrointestinal bleeding. *N Engl J Med* 2000;343:834-9.
4. Hawkey CJ, Karrasch JA, Szczepanski L, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. *N Engl J Med* 1998;338:727-34.
5. Lai K-C, Lam S-K, Hui W-M, et al. Lansoprazole reduces ulcer relapse after eradication of *Helicobacter pylori* in NSAIDs users. *Gastroenterology* 2000;118:Suppl:A251. abstract.
6. Wong BC, Wong WM, Wang WH, et al. An evaluation of invasive and non-invasive tests for the diagnosis of *Helicobacter pylori* infection in Chinese. *Aliment Pharmacol Ther* 2001;15:505-11.
7. Hui WM, Lam SK, Ho J, et al. Effect of omeprazole on duodenal ulcer-associated antral gastritis and *Helicobacter pylori*. *Dig Dis Sci* 1991;36:577-82.
8. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549-56.
9. Lai K-C, Lam S-K, Chu K-M, et al. *H. pylori* eradication vs combined proton pump inhibitor and *H. pylori* eradication in the prevention of recurrent peptic ulcer complications in high-risk patients receiving low-dose aspirin. *Gastroenterology* 2001;120:Suppl:A-104. abstract.
10. 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;312:1563-6.
11. Cryer B, Feldman M. Effects of very low dose daily, long-term aspirin therapy on gastric, duodenal, and rectal prostaglandin levels and on mucosal injury in healthy humans. *Gastroenterology* 1999;117:17-25.
12. Cole AT, Brundell S, Hudson N, Hawthorne AB, Mahida YR, Hawkey CJ. Ranitidine: differential effects on gastric bleeding and mucosal damage induced by aspirin. *Aliment Pharmacol Ther* 1992;6:707-15.
13. Lam SK, Talley NJ. Report of the 1997 Asia Pacific Consensus Conference on the management of *Helicobacter pylori* infection. *J Gastroenterol Hepatol* 1998;13:1-12.

Copyright © 2002 Massachusetts Medical Society.

POSTING PRESENTATIONS AT MEDICAL MEETINGS ON THE INTERNET

Posting an audio recording of an oral presentation at a medical meeting on the Internet, with selected slides from the presentation, will not be considered prior publication. This will allow students and physicians who are unable to attend the meeting to hear the presentation and view the slides. If there are any questions about this policy, authors should feel free to call the *Journal's* Editorial Offices.