

# Cost Savings in Duodenal Ulcer Therapy Through *Helicobacter pylori* Eradication Compared With Conventional Therapies

## Results of a Randomized, Double-blind, Multicenter Trial

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**Background:** We hypothesized that treatment of duodenal ulcer disease with antibiotic therapy directed toward *Helicobacter pylori* infection is more cost-effective than therapy with antisecretory agents.

**Methods:** A randomized, double-blind, multicenter clinical trial of adult patients with active duodenal ulcer and *H pylori* infection was conducted. Patients were randomized to receive 500 mg of clarithromycin 3 times a day plus 40 mg of omeprazole daily for 14 days followed by 20 mg of omeprazole daily for an additional 14 days (group 1), 20 mg of omeprazole daily for 28 days (group 2), or 150 mg of ranitidine hydrochloride twice a day for 28 days (group 3). The use of ulcer-related health care resources was documented during monthly interviews for 1 year after the initial therapy. Clinical success was evaluated 4 to 6 weeks and 1 year after the end of therapy.

**Results:** Of the 819 patients enrolled, 727 completed the study. Group 1 included 243 patients; group 2, 248 patients; and group 3, 236 patients. Patients in group 1 used fewer ulcer-related health care resources during the 1 year after therapy compared with groups 2 and 3 (comparisons are given as group 1 vs group 2 and group 1 vs group 3, respectively): the number of endoscopies performed, 28 vs 76 ( $P < .001$ ) and vs 71 ( $P < .001$ ); patients receiving drugs to treat an ulcer, 118 vs 180 ( $P < .001$ ) and vs 168 ( $P < .001$ ); clinic visits, 83 vs 135 ( $P = .05$ ) and vs 161 ( $P < .001$ ); hos-

pitalizations, 0 vs 5 ( $P = .045$ ) and vs 6 ( $P = .02$ ); and length of hospital stay, 0 vs 24 days ( $P = .04$ ) and vs 37 ( $P = .04$ ). When ulcer-related costs were defined as the outcome variable in a multivariate linear regression analysis, therapy was determined to have a significant influence on costs (group 1 vs group 2,  $P < .001$ ; group 1 vs group 3,  $P = .008$ ). Clinical success rates at the end of the study and cure of *H pylori* infection were significantly greater in group 1 compared with groups 2 and 3 ( $P < .001$ ). Therapy with clarithromycin plus omeprazole provided savings of \$1.94 and \$2.96 (compared with therapy with omeprazole and with ranitidine hydrochloride, respectively) per dollar spent within the first year after therapy. This incremental cost-benefit translates to savings of \$547 or \$835 per patient in group 1 (compared with patients in group 2 or group 3, respectively) during the first year after therapy.

**Conclusions:** Combination therapy with clarithromycin and omeprazole resulted in significantly fewer uses of ulcer-related health care resources than conventional antisecretory therapy during a 1-year follow-up and significant savings in associated costs during the same period. Patients who received clarithromycin plus omeprazole also showed a significantly improved clinical outcome compared with patients who received only omeprazole or ranitidine.

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**H**ELICOBACTER *PYLORI* infection is present in approximately 90% of patients with duodenal ulcer disease, and the causal relationship between *H pylori* infection and duodenal ulcers is supported by the observation that ulcer recurrence is significantly decreased after the cure of infection.<sup>1</sup> Based on these findings, a comprehensive economic analysis of the treatment of *H pylori* infection was recommended by the National Institutes of Health Consensus Development Conference.<sup>1</sup> Studies using simulated economic models to compare the cost-effectiveness of various therapies for the treatment of duo-

denal ulcer disease<sup>2-9</sup> suggest that eradication of *H pylori* infection is cost-effective compared with intermittent or maintenance therapy with antisecretory agents such as omeprazole or ranitidine hydrochloride. However, no prospective, randomized clinical trials have assessed this hypothesis.

In previous studies, the treatment of duodenal ulcer with clarithromycin plus

The affiliations of the authors are listed in the acknowledgment section on pages 859 and 860. A complete list of the investigators participating in the Gastrointestinal Utilization Trial Study Group appears on page 855.

This article is also available on our Web site: [www.ama-assn.org/internal](http://www.ama-assn.org/internal).

## PATIENTS AND METHODS

### STUDY DESIGN

This randomized, double-blind, multicenter clinical trial was conducted at 132 sites in the United States.

### PATIENTS

Patients 18 years or older with signs or symptoms of an active duodenal ulcer (including daytime abdominal pain, nighttime abdominal pain, epigastric pain or burning, bloody stools, and belching) within 10 days of administration of the first dose of study drug were evaluated for study eligibility. Inclusion criteria included endoscopic diagnosis of an ulcer and, if a biopsy was performed, evidence of an *H pylori* infection by a positive rapid urease test from biopsy tissue and confirmation of the *H pylori* infection by histological analysis of biopsy tissue and/or a positive <sup>13</sup>C-urea breath test before therapy was initiated. Exclusion criteria included hospitalization at time of enrollment; recent alcohol or drug abuse or illegal drug use; preexisting or concurrent long-term use of nonsteroidal anti-inflammatory drugs; clinically significant medical findings other than duodenal ulcer; hepatic or renal disease; concomitant gastrointestinal disease (eg, Zollinger-Ellison syndrome, Crohn disease, cholecystitis, symptomatic pancreatobiliary tract disease, erosive reflux esophagitis, esophageal stricture, and esophageal ulcer or varices); gastric ulcer or malignant gastric neoplasm, pyloric obstruction, fresh clot, active bleeding, or perforated ulcer; or history of gastric surgery, vagotomy, or both. The study was conducted in accordance with regulations of the US Food and Drug Administration and all applicable local regulations governing clinical study conduct. Institutional review board approval was obtained by the investigator as required locally, and all patients gave written informed consent before inclusion in the study.

### DRUG ASSIGNMENT

Patients were randomized at each site in a 1:1:1 ratio to receive clarithromycin plus omeprazole, omeprazole only, or ranitidine only using computer-generated random assignment developed before study initiation by the Abbott Laboratories Department of Clinical Statistics, Abbott Park, Ill. The first patient was enrolled on July 7, 1994, and the last interview was completed on March 27, 1996.

### THERAPEUTIC REGIMENS

Enrolled patients were randomized to 1 of 3 regimens: group 1, 500 mg of clarithromycin 3 times a day plus 40 mg of omeprazole daily for 14 days followed by 20 mg of omeprazole daily for an additional 14 days; group 2, 20 mg of omeprazole daily for 28 days; or group 3, 150 mg of ranitidine twice a day for 28 days. Packages of randomized study drugs were distributed to each investigational site in blocks of 6, where they were dispensed to the patients. Study drugs and placebos were similar in appearance (tablets and capsules) and were dispensed in identical blister packs

(containing the same number of tablets and capsules, regardless of study group) within 1 box, which was individually labeled with a preprinted patient number, instructions for study drug administration, and space for recording the patient's initials and the date dispensed. Adherence to the regimen was determined by counting returned capsules and tablets at the end of therapy. Physicians, patients, laboratory personnel, and all study investigators were blinded to study drug randomization and the results of all diagnostic tests for *H pylori* infection for the full duration of the study.

### PROTOCOL

Protocol-directed procedures were performed at the investigational sites during scheduled clinic visits. At the pretherapy visit (within 3 days before therapy), a medical history, urea breath test, and endoscopic assessment of ulcer disease (with histological analysis for the presence of *H pylori* and analysis of *H pylori* infection using a rapid urease test in biopsy samples) were performed. No protocol-directed endoscopies were performed after the pretherapy visit; all subsequent procedures and therapy were to be prescribed according to the standard of care for each participating site. At the posttherapy visit on days 27 to 31, assessment of the clinical response to therapy, interim medical history, and evaluation of adherence to the therapeutic regimen were obtained. At the visit 4 to 6 weeks after therapy (4 to 6 weeks after the last dose of study drug), further assessment of the clinical response to therapy and a urea breath test to determine the status for *H pylori* infection were performed. Unscheduled visits because of recurrence of ulcer symptoms or lack of clinical improvement were performed at the clinical discretion of each physician. Monthly follow-up telephone interviews with the patients were conducted to determine the use of health care resources and clinical outcome variables. Health care resources included use of prescription drugs, clinic and emergency room visits, outpatient surgical procedures, and hospitalizations, as well as all diagnostic and therapeutic procedures performed at these visits.

### EVALUATION OF END POINTS

Clinical success and failure were assessed after the end of therapy (45 days after the last dose of the study drug) and at the end of the study (12 months after the last dose of the study drug). Clinical response was objectively defined as follows: *success*, the patient required less than 12 days of continuous antiulcer therapy during the 45 days after the last dose of the study drug (for the end of therapy) or before the last study interview (for the end of the study); and *failure*, the patient required 12 days or more of continuous antiulcer therapy or therapy for *H pylori* infection, which was initiated during the 45 days after the last dose of study drug (for the end of therapy) or before the last study interview (for the end of the study).

The eradication rate for *H pylori* infection was determined at a visit 4 to 6 weeks after therapy. Patients who were randomized to a study group and took the drug as directed at least 70% of the time, who had taken no other anti-infective drug or proton pump inhibitor between the posttherapy and 4- to 6-week posttherapy visits, and who

Continued on next page

had undergone assessment of *H pylori* infection were included in the per-protocol analysis. *Helicobacter pylori* infection was assessed by the <sup>13</sup>C-urea breath test and histological analysis of biopsy tissue (if a biopsy was performed). For the <sup>13</sup>C-urea breath test, a negative result was defined as an increase in <sup>13</sup>C-labeled carbon dioxide concentration of less than 4.0 over the concentration in the baseline sample.<sup>14</sup> The histological analysis was considered negative if no *H pylori* was visualized after staining of the gastric biopsy specimens.<sup>15</sup> The <sup>13</sup>C-urea breath test and histological assessments were performed by central laboratories. If results of the <sup>13</sup>C-urea breath test and the histological analysis were available, both were required to be negative to consider the response to therapy successful (eradication); if any test was positive, infection was considered persistent. If 1 or more analyses were performed but no result could be obtained, the response was considered indeterminate.

There were no protocol-directed restrictions about the medical care of patients after randomization to a study group; investigators were instructed to provide the standard of care for that site. Data about the use of health care resources were collected from each patient during monthly telephone interviews. All information about hospitalizations was verified by the investigator, and verification of other health care visits for each patient was attempted by requesting medical records, directly contacting the provider, or both. Investigators blinded to the patient's group identified each resource used during the course of the study as ulcer-related or not ulcer-related.

Medical, surgical, and diagnostic services performed or directed by physicians in the office, emergency room, or hospital were assigned code numbers using (as appropriate) the *Physicians' Current Procedural Terminology*,<sup>16</sup> the diagnosis related group,<sup>16</sup> or the *International Classification of Diseases, Ninth Revision (ICD-9)*.<sup>17</sup> These code numbers were converted to costs for each health care resource based on the actual average payments made for each coded procedure (including facility costs) by the US Health Care Finance Administration during 1995. The physicians' costs associated with endoscopy included the costs of the endoscopy and the histological analysis. The costs of days lost from work were calculated based on national survey data, reported as average annual pay by the US Bureau of the Census in 1993 [(\$26 382/230 Work Days) × ("Ulcer Days" Lost From Work)]. The costs of prescription drugs (taken during protocol-directed therapy and the posttherapy follow-up period) were based on the 1995 average wholesale price (Red Book).<sup>18</sup>

## STATISTICAL METHODS

The primary end points of the study were clinical success and the number of ulcer-related health care resources that were used during the study. The secondary end points were time to clinical failure, eradication of *H pylori* infection, and costs of ulcer-related health care resources (including the indirect cost of days lost from work and days lost from usual activity). The study was designed to enroll 750 patients (250 patients in each group) to obtain 600 evaluable patients (200 patients in each group), calculated to provide 85% power to detect a 15% difference in the clinical success rate

between groups at the .05 (2-tailed) significance level, assuming a 60% clinical success rate in the more successful group.

Patients who took at least 1 dose of study drug and participated in at least 1 economic interview were eligible for evaluation. The primary end point of clinical effectiveness was assessed by clinical responses at the end of therapy and the end of the study. Clinical success rates at the end of therapy and the end of the study were aggregated within groups and compared by using the Fisher exact test. Exact binomial 95% confidence intervals were computed for the 3 groups for clinical success rates. In addition, clinical effectiveness was evaluated by the time to failure (separately for end of therapy and the end of the study), defined as the number of days from the end of protocol-directed therapy until the therapy was designated a clinical failure. Censoring at the end of the study indicated that the therapy did not fail before the end of the study. Time-to-failure Kaplan-Meier curves were generated for each of the 3 groups and compared by using a log-rank test. Clinical effectiveness was also studied by the eradication rates of *H pylori* infection at 4 to 6 weeks after therapy; data were summarized by groups and compared by using the Fisher exact test combined with computation of the exact binomial 95% confidence intervals.

Values obtained for the use of health care resources depend on the length of time for which data are collected. Because the average follow-up was almost identical among groups, the use of health care resources among groups was compared without adjusting for the length of follow-up. The *P* values were obtained from 2-sample permutation tests with 10 000 random samples for all categories of health care resource use except prescription drugs. Based on the number of patients within each group who reported at least 1 use of a drug to treat an ulcer, the *P* value for drugs was calculated directly from the normal approximation for the binomial test. These analyses of significance depend on the differences in the number of events among the groups and the likelihood that the differences in numbers of events are the result of chance (ie, that a few patients in a selected group contributed disproportionately to the total). Therefore, the power of this statistical calculation depends on the distribution of events among the patients within a group; a large number of events associated with relatively few patients does not provide statistical significance.

There is no consensus on the most appropriate summarization method or statistical test for group differences in the costs associated with the use of health care resources.<sup>19,20</sup> For the present analysis, multivariate linear regression analyses with costs as the outcome variable and other variables (follow-up time, sex, race, age, and study group) as predictors were used. The statistical significance associated with each predictor variable was assessed by using a *t* test. The incremental cost-benefit (defined by cost savings) of clarithromycin plus omeprazole compared with only omeprazole or ranitidine was calculated by dividing the difference in total costs between 2 groups by the difference between the costs of therapy for the groups adjusted for the number of patients. Because the duration of the study was only 1 year beyond initial therapy, costs and events were not discounted for time effects.

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omeprazole resulted in decreased ulcer recurrence compared with omeprazole monotherapy.<sup>10-13</sup> We hypothesized that this improved clinical outcome would be associated with savings in the use of ulcer-related health care resources and associated health care costs. The present study was designed to assess the clinical effectiveness, the use of health care resources, and the economic costs of therapy with clarithromycin plus omeprazole compared with therapy with only omeprazole or ranitidine for 1 year in a setting that approximated usual clinical practice.

## RESULTS

### PATIENT POPULATIONS

**Figure 1** shows the disposition of the 819 patients enrolled in the clinical trial; 727 were eligible for evaluation. Of the patients ineligible for evaluation, 50 did not have *H pylori* infection confirmed before initiation of therapy, 2 had no active duodenal ulcer within 10 days before randomization, 19 did not meet inclusion criteria for medical reasons, 2 did not take their study medication, and 19 did not participate in any of the monthly economic surveys (**Table 1**). The

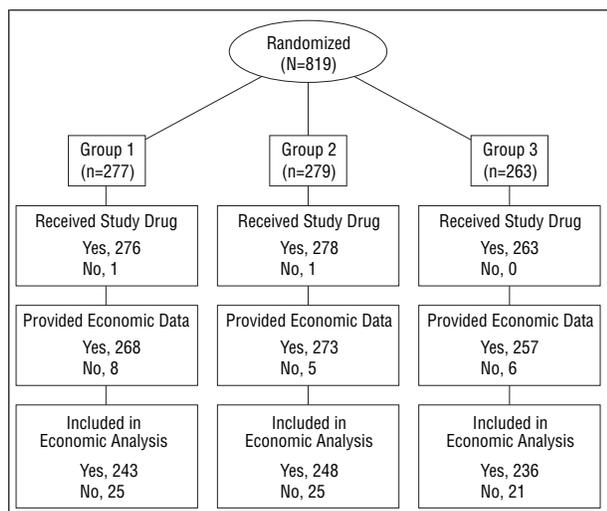
patients included in each of the groups were similar in sex, race, and age (**Table 2**). The mean length of follow-up for eligible patients was 11.3 months for group 1, 11.3 months for group 2, and 11.5 months for group 3. For groups 1, 2, and 3, respectively, alcohol was used by 47.7%, 41.1%, and 44.5%; tobacco was used by 44.0%, 42.7%, and 41.9%; and caffeine was used by 72.8%, 79.8%, and 76.3%. The differences in the use of alcohol, tobacco, and caffeine among groups were not statistically significant.

### STUDY SITES

**Table 3** summarizes the 132 sites in the United States that participated in the study. The sites were diverse, including Veterans Affairs medical centers, academic medical centers, managed care clinics, and fee-for-service clinics.

### ADHERENCE TO THE REGIMEN, PREMATURE DISCONTINUATION, AND ADVERSE EVENTS

Adherence to the regimen (return of less than 10% of the tablets or capsules) was 90% for capsules and 92% for tablets in group 1; 92% for capsules and 94% for tablets



**Figure 1.** Disposition of patients enrolled in the clinical trial. Patients in group 1 received 500 mg of clarithromycin 3 times a day plus 40 mg of omeprazole daily for 14 days followed by 20 mg of omeprazole daily for an additional 14 days; patients in group 2 received 20 mg of omeprazole daily for 28 days; and patients in group 3 received 150 mg of ranitidine hydrochloride twice a day for 28 days.

**Table 1. Patients Ineligible for the Study**

Reason	Group*			Total
	1	2	3	
No confirmation of <i>Helicobacter pylori</i> infection before therapy	15	18	17	50
No confirmation of duodenal ulcer	1	0	1	2
Confounding medical conditions or non-ulcer-related hospitalization	9	7	3	19
No study drug taken	1	1	0	2
No economic survey data	8	5	6	19
<b>Total</b>	<b>34</b>	<b>31</b>	<b>27</b>	<b>92</b>

\*Patients in group 1 received 500 mg of clarithromycin 3 times a day plus 40 mg of omeprazole daily for 14 days followed by 20 mg of omeprazole daily for an additional 14 days; patients in group 2 received 20 mg of omeprazole daily for 28 days; and patients in group 3 received 150 mg of ranitidine hydrochloride twice a day for 28 days.

in group 2; and 92% for capsules and 95% for tablets in group 3. Premature discontinuation of the study drug was reported for 7 (2.5%) of 277 patients in group 1, 7 (2.5%) of 279 patients in group 2, and 6 (2.3%) of 263 patients in group 3. Premature discontinuation of the study drug was insufficient reason for a patient to be considered ineligible for evaluation. No serious adverse events related to the study drug were noted in any of the groups.

## CLINICAL RESULTS

Clinical outcomes for each group were assessed on the basis of clinical success at the end of therapy and the end of the study and on the basis of eradication of *H pylori* infection (at 4-6 weeks after the last dose of study drug). Clinical success rates were higher for group 1 than for group 2 or group 3 (Table 4) at the end of therapy (group 1 vs group 2,  $P=.04$ ; group 1 vs group 3,  $P<.001$ ) and at the end of the study (group 1 vs groups 2 and 3,  $P<.001$ ). No specific prognostic factors for failure were identified

**Table 2. Characteristics of Enrolled Patients\***

Variable	Group			Total (N = 819)
	1 (n = 277)	2 (n = 279)	3 (n = 263)	
Sex				
M	193 (69.7)	196 (70.3)	194 (73.8)	583 (71.2)
F	84 (30.3)	83 (29.7)	69 (26.2)	236 (28.8)
Race				
Asian	11 (4.0)	8 (2.9)	12 (4.6)	31 (3.8)
Black	62 (22.4)	67 (24.0)	55 (20.9)	184 (22.5)
White	157 (56.7)	165 (59.1)	147 (55.9)	469 (57.3)
Hispanic	31 (11.2)	27 (9.7)	38 (14.4)	96 (11.7)
Other	16 (5.8)	12 (4.3)	11 (4.2)	39 (4.8)
Age, y				
Mean $\pm$ SD	48.3 $\pm$ 13.8	49.0 $\pm$ 14.5	48.6 $\pm$ 14.3	48.6 $\pm$ 14.2
Range	18-86	21-85	19-84	18-86

\*Data are given as number (percentage) unless otherwise indicated. For a description of the groups, see the footnote for Table 1.

**Table 3. Affiliations of Principal Investigators**

Affiliation	Sites	Patients Enrolled	Eligible Patients
Private	61	466	416
University	23	99	82
Veterans Affairs	12	74	69
Nonprofit	11	72	60
For profit	14	56	52
Health maintenance organization	7	37	33
Military	4	15	15
<b>Total</b>	<b>132</b>	<b>819</b>	<b>727</b>

when clinical success rates were stratified by pretherapy demographic and medical history variables. The time to failure was longer for group 1 than for groups 2 and 3 ( $P<.01$  based on log-rank calculations; Figure 2). In a per-protocol analysis, the eradication of *H pylori* infection was 67.5% for patients in group 1 compared with 6.9% for patients in group 2 and 4.3% for patients in group 3 (Table 4).

At some time during the follow-up period (after the 4- to 6-week posttherapy visit), 35 patients in group 1, 90 patients in group 2, and 97 patients in group 3 were prescribed non-study-directed eradication therapy. The results of this subsequent therapy are not reflected in the eradication rates of *H pylori* infection, but are discussed in the context of their effects on the use of health care resources.

## USE OF HEALTH CARE RESOURCES

Fewer ulcer-related health care resources were used by patients in group 1 compared with groups 2 and 3 (Table 5). Compared with group 2, group 1 underwent fewer endoscopies ( $P<.001$ ), fewer patients received drugs to treat an ulcer ( $P<.001$ ), fewer clinic visits were made ( $P=.005$ ), fewer patients were hospitalized ( $P=.045$ ), and the number of hospital days was lower ( $P=.04$ ). Differences in the number of emergency room visits ( $P=.49$ ), the number of work days lost ( $P=.3$ ), and

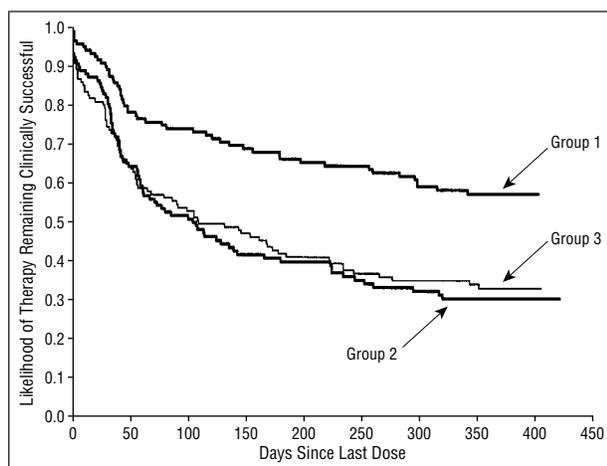
**Table 4. Clinical Outcomes\***

Measurement	Group		
	1	2	3
End of treatment (4-6 wk after therapy)			
Clinical success rate†	78.6 (191/243)	70.2 (174/248)	64.0 (151/236)
Exact binomial 95% CI	72.9-83.6	64.0-75.8	57.5-70.1
Eradication rate‡	67.5 (131/194)	6.9 (14/202)	4.3 (9/208)
Exact binomial 95% CI	60.4-70.1	3.8-11.4	2.0-8.1
End of the study (1 y after therapy)			
Clinical success rate‡	59.2 (144/243)	35.5 (88/248)	35.2 (83/236)
Exact binomial 95% CI	52.8-65.5	29.5-41.8	29.1-41.6

\*Data are given as percentage (number of patients in whom therapy was successful/number enrolled) unless otherwise indicated. For a description of the groups, see the footnote for Table 1. CI indicates confidence interval. All P values were determined by using the Fisher exact test.

†Group 1 vs group 2, P = .04; group 1 vs group 3, P < .001.

‡Group 1 vs groups 2 and 3, P < .001.



**Figure 2.** Kaplan-Meier curves depicting time to clinical failure. For a description of the groups, see the legend for Figure 1.

the number of days lost from usual activity ( $P = .89$ ) were not statistically significant. Compared with group 3, group 1 underwent fewer endoscopies ( $P < .001$ ), fewer patients received drugs to treat an ulcer ( $P < .001$ ), fewer clinic visits were made ( $P < .001$ ), fewer patients were hospitalized ( $P = .02$ ), and the number of hospital days was lower ( $P = .04$ ). Differences in the number of emergency room visits ( $P = .18$ ), the number of work days lost ( $P = .14$ ), and the number of days lost from usual activity ( $P = .41$ ) were not statistically significant. The calculation of statistical significance of events depends on the number of events and the distribution of events among patients in each study group. Therefore, the apparently large differences in the number of work days lost and the number of days of usual activity lost (Table 5) were not statistically significant because the contributions of only a few patients were responsible for much of the observed difference. The difference in the overall use of health care resources (ulcer-related and non-ulcer-related use) was not statistically significant between groups, except for hospitalizations (Table 6); the total number of hospitalizations for group 1 was significantly lower than that for group 2 ( $P = .02$ ), and the lower number of hospitalizations for group 1 compared with group 3 approached statistical significance ( $P = .07$ ). These results confirm that treatment of *H pylori* infection with clarithromycin plus

omeprazole has no negative effect on the overall use of health care resources by patients with duodenal ulcer and that cure of the infection may significantly reduce the number of hospitalizations compared with therapy with antisecretory agents.

#### COSTS ASSOCIATED WITH THE ULCER-RELATED USE OF HEALTH CARE RESOURCES

The associated costs of the ulcer-related health care resources used were less in group 1 than in groups 2 and 3. When the ulcer-related costs (Table 5) were designated as the outcome (dependent) variable in a multivariate linear regression analysis using the therapy group as a predictor variable, the therapy group was determined to be a significant influence in ulcer-related costs (group 1 vs group 2,  $P < .001$ ; group 1 vs group 3,  $P = .008$ ). When specific categories of ulcer-related costs were considered, therapy with clarithromycin plus omeprazole vs therapy with only omeprazole or ranitidine significantly predicted endoscopy costs ( $P < .001$ ), clinic visits costs ( $P = .002$ ), drug costs (vs omeprazole,  $P = .002$ ; vs ranitidine,  $P < .001$ ), and hospitalization costs (vs omeprazole,  $P = .04$ ; vs ranitidine,  $P = .06$ ); the therapy group was not a significant predictor of the costs of emergency room visits or work days lost (Table 5). In contrast, follow-up time, sex, race, and age had no statistically consistent effect for total or category-specific ulcer-related costs. The total direct costs (excluding the costs attributed to work days lost) per patient were \$332, \$647, and \$725 for groups 1, 2, and 3, respectively (Table 5).

The initial therapy for group 1 was more expensive (Table 7). However, the increased cost of initial eradication therapy was more than offset by the increased costs of subsequent treatment owing to reduced cure rates among patients initially receiving conventional antisecretory therapy. The incremental cost-benefit (defined by cost savings) of therapy with clarithromycin plus omeprazole compared with therapy with only omeprazole or ranitidine was calculated by dividing the difference in total costs between 2 groups by the difference between the costs of therapy, adjusted for the number of patients. Based on this calculation, for every dollar spent for therapy with clarithromycin plus omeprazole, \$1.94

**Table 5. Ulcer-Related Use of Health Care Resources and Associated Costs\***

Resource	Group					
	1 (n = 243)		2 (n = 248)		3 (n = 236)	
	No. of Events	Cost, \$	No. of Events	Cost, \$	No. of Events	Cost, \$
Endoscopy	31	...	76	...	71	...
Physician Facility	...	8772	...	20 994†	...	19 524†
	...	9548	...	23 408†	...	21 868†
Clinic visits	83	11 581	135	22 086‡	161	21 624‡
Emergency room visits	3	241	6	683	8	1035
Drugs§	118	50 512	180	78 983‡	168	79 969†
Hospitalization	0	0	5	14 300	6	26 970¶
Hospital days	0	...	24	...	37	...
Work days lost	104	11 929	183	20 991	467	53 567
Days of usual activity lost	302	...	329	...	572	...
Total direct costs per patient	...	332	...	647	...	725

\*For a description of the groups, see the footnote for Table 1. P values were calculated by using multivariate linear regression analyses; all are vs group 1. Ellipses indicate not applicable.

†P < .001.

‡P = .002.

§Number of patients who received any drug for the treatment of an ulcer.

||P = .04.

¶P = .06.

**Table 6. Ulcer-Related and Non-Ulcer-Related Use of Health Care Resources\***

Resource	Group		
	1 (n = 243)	2 (n = 248)	3 (n = 236)
Endoscopy	31	76	71
Clinic visits	740	755	695
Emergency room visits	45	42	67
Drugs	193	217	207
Hospitalization†	23	45	40
Hospital days	182	314	194

\*For a description of the groups, see the footnote for Table 1. P values were calculated from 2-sample permutation tests with 10 000 random samples.

†Group 1 vs group 2, P = .02; group 1 vs group 3, P = .07.

**Table 7. Ulcer-Related Health Care Costs\***

	Group		
	1 (n = 243)	2 (n = 248)	3 (n = 236)
Initial therapy	68 560	25 207	21 072
Ulcer-related			
Direct medical	80 654	160 454	170 990
Work loss-related	11 929	20 991	53 567
Total†	92 583	181 445	224 557
<b>Total</b>	<b>161 143</b>	<b>206 652</b>	<b>245 629</b>

\*For a description of the groups, see footnote for Table 1. Costs are given in dollars.

†Calculated from the costs itemized in Table 5, excluding the cost of initial therapy.

was saved within the first year after therapy compared with therapy with omeprazole (\$547 per patient). Compared with initial therapy with ranitidine, the savings after therapy with clarithromycin plus omeprazole were \$2.96 (\$835 per patient) for the first year after therapy. Thus, clarithromycin plus omeprazole was a dominant strategy (superior clinical outcome and reduced cost) compared with therapy with only omeprazole or ranitidine.

### COMMENT

Previous reports have suggested that therapy for the eradication of *H pylori* infection is cost-effective compared with intermittent or maintenance therapy with conventional antisecretory drugs for duodenal ulcer disease.<sup>2-9</sup> However, these studies were based on simulated models that included probabilities of clinical outcomes (derived from the medical literature) and estimated use of health care resources. Models can only approximate actual clinical practice and must be validated by data from prospective

clinical trials. By minimizing protocol-directed costs, the present clinical trial was designed to assess the actual use of health care resources by patients with duodenal ulcer for 1 year under conditions approximating routine clinical practice. The study demonstrated that patients treated with clarithromycin plus omeprazole experienced better clinical outcomes (increased clinical success and decreased time to clinical failure) and used fewer ulcer-related health care resources (and incurred fewer associated costs) compared with patients treated with only omeprazole or ranitidine.

The design of the study closely approximated actual clinical practice; no restrictions were placed on the health care given to patients in any study group after randomization. One shortcoming of modeling is the inability to incorporate the treatment of concomitant diseases or unexpected secondary effects of treatment. For instance, some researchers have suggested that the incidence of gastroesophageal reflux disease and obesity may be greater in persons who have undergone successful treat-

ment of duodenal ulcer disease.<sup>21,22</sup> Although no specific analysis of these secondary effects was made in the present study, any costs associated with the subsequent treatment of dyspeptic or reflux symptoms were considered in the total use of health care resources. All costs associated with any type of upper gastrointestinal symptoms were included in the ulcer-related costs. In addition, the inclusion of a broad spectrum of patients in each group should provide a valid representation of the costs associated with the care of clinically significant diseases that might affect ulcer-related use of health care resources. Although patients with certain existing concomitant diseases were excluded from randomization into the study, there was no further exclusion of patients with concomitant diseases during the 1 year follow-up period. The study also incorporated certain shortcomings of actual clinical practice, such as the repetition of diagnostic procedures or the liberal use of therapeutic interventions, which cannot be adequately accounted for in modeling. For example, several patients whose *H pylori* infection was cured (as judged by evaluation at the 4- to 6-week posttherapy visit) underwent subsequent additional and unnecessary courses of antibiotic therapy during the 1-year follow-up period, and these costs were included in the analysis. Because the setting of the present trial closely approximated actual clinical practice, the clinical and economic benefit of therapy with clarithromycin plus omeprazole should apply to patients outside the rigid confinement of prospective clinical trials designed to assess efficacy.

Other factors could have contributed to understating the economic benefits of therapy with clarithromycin plus omeprazole compared with therapy with only omeprazole or ranitidine. As an ethical consideration, the use of therapy for *H pylori* infection during the follow-up period was not restricted, and patients were prescribed eradication therapy if this was the standard of care for the site. Because 90 patients in group 2 and 97 patients in group 3 underwent non-protocol-directed eradication therapy after randomization to the study group (after the 4- to 6-week posttherapy visit), it might be expected that as many as 70 patients in each of these groups were cured of *H pylori* infection during the study. To the extent that this occurred, the costs of the use of health care resources for groups 2 and 3 were understated, and the clinical benefits for these groups were overstated.

Although the eradication rate for *H pylori* infection observed in group 1 compared favorably with the rates observed in previous well-controlled clinical trials,<sup>10-13</sup> it is possible that the design of the study (which more closely reflects clinical practice than most clinical trials) could have produced lower eradication rates than a trial specifically designed to assess the efficacy of therapy. Because the primary focus of the study was the use of health care resources, nonadherence to the therapeutic regimen was insufficient grounds for exclusion from the study; the per-protocol analysis of eradication used a minimum adherence rate of 70% for inclusion in the calculations. Moreover, adherence was assessed only by a count of returned tablets or capsules, and no protocol-defined assessment was made of adherence to the dosing schedule. The approaches to the treatment of *H pylori* infec-

tion have rapidly evolved during the past 3 years. When the present study was initiated, clarithromycin plus omeprazole was considered state-of-the-art therapy. However, a 1994 report suggested that therapy with clarithromycin plus amoxicillin (or a nitroimidazole) plus a proton pump inhibitor can provide efficacious eradication of *H pylori* infection (>90% efficacy).<sup>23</sup> The efficacy of some of these therapies has not been confirmed with patients in the United States in well-controlled clinical trials, and it remains to be determined how the results of these trials may translate to effectiveness in clinical practice. It seems likely that therapeutic regimens yielding higher rates of eradication of *H pylori* infection would provide correspondingly greater economic benefit compared with therapy with only omeprazole or ranitidine.

The actual economic benefits of therapy to eradicate *H pylori* infection as part of the treatment of duodenal ulcer disease may be greater than the benefits we report. The data for the use of health care resources were obtained from each patient during the study, and the accuracy of the information obtained was subsequently verified by inspection of relevant medical records. However, it was impossible to obtain and verify actual costs from all study sites. Therefore, the costs associated with the use of health care resources were determined by using payments made by the US Health Care Finance Administration during fiscal year 1995. These data are readily available, but they are likely to underestimate the actual reimbursement that a particular physician might have received for other privately insured patients. Costs associated with hospitalizations reflect actual costs, as they were based on *Physicians' Current Procedural Terminology* and diagnosis related group codes, with a minimum number of procedures coded. Finally, no costs were attributed to the days of usual activity lost.

This randomized, double-blind, multicenter clinical trial demonstrated that the implementation of therapy for the eradication of *H pylori* infection in patients with duodenal ulcer disease results in improved clinical outcome and decreased use of health care resources compared with conventional antisecretory monotherapy with omeprazole or ranitidine. Because the rate of ulcer recurrence after eradication therapy is much less frequent than recurrence after conventional therapy,<sup>10-13</sup> additional economic benefits could be expected to accrue by extending the analysis over a period longer than 1 year. The reduction in number of days of work and usual activity lost owing to ulcer disease suggests that quality of life also might improve after cure of *H pylori* infection compared with conventional antiulcer therapy. Thus, therapy to eradicate *H pylori* infection provides clinical benefit to patients and economic benefit to patients and society within the first year after therapy, and these benefits are likely to continue to accrue over the lifetime of the patient.

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