

Efficacy of Omeprazole for the Treatment of Symptomatic Acid Reflux Disease Without Esophagitis

Joel E. Richter, MD; David Peura, MD; Stanley B. Benjamin, MD; Bo Joelsson, MD, PhD; James Whipple, MS

Background: Up to three quarters of patients with gastroesophageal reflux disease (GERD) have symptoms, such as heartburn, but no macroscopic evidence of erosive esophagitis, making symptomatic GERD a common clinical problem in the primary care setting.

Objective: To compare the efficacy and safety of omeprazole, 20 mg once daily; omeprazole, 10 mg once daily; and placebo in the treatment of symptomatic GERD without erosive esophagitis.

Methods: Patients with a history of heartburn (≥ 12 months) and episodes of moderate to severe heartburn on 4 or more of the 7 days before endoscopy were eligible to participate in this 4-week, randomized, double-blind, placebo-controlled trial. The absence of erosive esophagitis was established through endoscopy. Eligible patients were randomized to 1 of 3 treatment groups: omeprazole, 20 mg once daily; omeprazole, 10 mg once daily; or placebo. Patients were assessed at weeks 2 and 4. The efficacy of omeprazole for the treatment of heartburn was determined mainly through the following diary card data: daily resolution of heartburn and complete resolution of heartburn every day during 1 week of treatment. The efficacy of omeprazole for the treatment of acid

regurgitation, dysphagia, epigastric pain, and nausea was also assessed.

Results: Of 359 randomized patients, 355 were included in the statistical analysis (intention-to-treat population). Daily proportions of patients with no heartburn were consistently greater in the 20-mg omeprazole group (62%, day 7; 74%, day 27) than in the 10-mg omeprazole group (41%, day 7; 49%, day 27) or the placebo group (14%, day 7; 23%, day 27). Complete resolution of heartburn every day during the last treatment week was significantly ($P \leq .002$) higher in the 20-mg omeprazole group (48%) than in the 10-mg omeprazole (27%) or placebo (5%) group. Omeprazole was significantly ($P \leq .003$) more effective than placebo for the treatment of acid regurgitation, dysphagia, epigastric pain, and nausea.

Conclusions: Patients with symptomatic GERD require profound acid suppression to achieve symptomatic relief. Omeprazole, 20 mg once daily, was superior to omeprazole, 10 mg once daily, and to placebo in providing early and sustained resolution of heartburn, as well as treatment of other troublesome GERD symptoms.

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From the Department of Gastroenterology, Cleveland Clinic Foundation, Cleveland, Ohio (Dr Richter); Department of Internal Medicine, University of Virginia School of Medicine, Charlottesville (Dr Peura); Division of Gastroenterology, Georgetown University Medical Center, Washington, DC (Dr Benjamin); and AstraZeneca LP (formerly Astra Pharmaceuticals LP, successor to Astra Merck Inc), Wayne, Pa (Dr Joelsson and Mr Whipple).

GASTROESOPHAGEAL reflux disease (GERD), which results from abnormal exposure of the esophagus to refluxed gastric acid, is a clinical problem that is commonly seen in primary care practices. Heartburn is the classic symptom of GERD, but other symptoms, such as acid regurgitation, dysphagia, and epigastric pain, are also common. Many patients with GERD who are troubled by heartburn have no macroscopic evidence of esophagitis, ie, they have no clear-cut breaks in the esophageal mucosa as determined by endoscopy; these patients are said to have symptomatic nonerosive GERD. It is estimated that one half to three quarters of patients with GERD do not have erosive esophagitis (ie, have normal endoscopy results),¹⁻³

making this a more widespread clinical problem than reflux esophagitis. Moreover, heartburn, even in the absence of demonstrable esophagitis, can seriously affect a patient's quality of life.⁴

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The interrelationship between GERD symptoms and esophagitis has not been clearly defined; symptoms do not necessarily predict the presence of esophageal inflammation, nor do patients with reflux esophagitis always suffer from heartburn. Paradoxically, patients with severe lesions (eg, those with Barrett esophagus) often have no symptoms.^{5,6}

Gastroesophageal reflux disease with or without esophagitis is a chronic recurring disease whose pathophysi-

PATIENTS AND METHODS

PATIENT INCLUSION AND EXCLUSION CRITERIA

Study inclusion criteria were chosen to identify patients with chronic symptomatic GERD without erosive esophagitis. Adults 18 years or older with a history of heartburn (≥ 12 months) as the predominant symptom of GERD and with current episodes of moderate to severe heartburn on at least 4 of the last 7 days prior to endoscopy were eligible to participate. A diagnosis of GERD was also established by a predefined threshold of acid reflux ($\text{pH} \leq 4.00$ for $\geq 5\%$ of the 24-hour period) based on intraesophageal pH monitoring as measured in the distal esophagus 5 cm above the lower esophageal sphincter.^{27,28} Each patient had to demonstrate an absence of erosive esophagitis or more advanced esophageal lesions (such as ulcer, stricture, or Barrett metaplasia) based on endoscopy performed within 7 days prior to study randomization. Patients with erythema, friability, or edema without breaks in the esophageal mucosa could, however, be included. Women were permitted to participate in the study if they were using an acceptable method of birth control, were surgically sterilized, or were postmenopausal. Women of child-bearing potential had to have a negative serum pregnancy test result prior to study enrollment.

Patients were excluded if they had any condition that could interfere with the assessment of heartburn or for any of the following conditions: evidence of esophageal, gastric, or duodenal ulcers; evidence of gastrointestinal bleeding at the time of screening or within 3 days of randomization; Zollinger-Ellison syndrome; or history or current evidence of pancreatitis, malabsorption, or inflammatory bowel disease. In addition, patients with a history of severe pulmonary or liver disease, renal disease, any active malignant neoplasm (except superficial skin disease), uncontrolled diabetes mellitus, cerebral vascular disease, any bleeding disorder, or any condition that might require surgery were not enrolled. Neither use of a proton pump inhibitor within 28 days of

the baseline visit nor use of an H2RA during the week prior to the screening endoscopy or in the interval between the screening endoscopy and baseline visit was permitted. Patients with an anticipated need for concomitant medication with anticholinergics, promotility agents, prostaglandin analogs, sucralfate, nonsteroidal anti-inflammatory drugs (NSAIDs), or salicylates other than low-dose aspirin (≤ 165 mg/d for cardiovascular prophylaxis) were not permitted to enroll.

Written informed consent was obtained from all patients. The protocol was approved by the institutional review board at each center prior to the start of the study.

STUDY DESIGN

This prospective, randomized, double-blind, placebo-controlled, parallel-group study was conducted at 36 centers in the United States. During the 1-week screening phase of the study, patients underwent endoscopy, 24-hour intraesophageal pH monitoring, and symptom assessment to qualify for the 4-week study (**Figure 1**). Baseline evaluation also included a general medical history (including GERD history) and assessment of alcohol and tobacco use. Routine laboratory studies (including hematologic, renal, and hepatic function tests) were conducted at baseline and at week 4 or at the time of study withdrawal.

Patients with moderate to severe heartburn but no evidence of erosive esophagitis were randomized to 1 of 3 treatment groups: omeprazole, 20 mg once daily; omeprazole, 10 mg once daily; or placebo. Patients were instructed to take their medication once daily, each morning before breakfast.

Patients received antacid tablets (Gelusil; Parke-Davis Pharmaceuticals, Morris Plains, NJ) as rescue medication for relief of heartburn, sour stomach, acid indigestion, or gas (up to a maximum of 6 tablets per day). Use of any other antacid during the treatment period was prohibited. Antacid use was monitored through tablet counts and patient diary card entries.

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ologic features are complex and multifactorial. Transient relaxation of the normal basal lower esophageal sphincter is generally associated with reflux episodes, although other factors, such as reduced esophageal clearance, impaired resistance of the esophageal mucosa to acid, and incompetence of the lower esophageal sphincter, may also contribute to this condition.⁷⁻¹⁰ Gastroesophageal reflux disease affects a substantial proportion of adults in Western countries¹⁰; in population-based studies, approximately 40% of all adults experience monthly heartburn, 10% to 20% have heartburn at least once per week, and 4% to 10% have daily heartburn episodes.^{1,11-13} However, precise epidemiologic data on the prevalence of GERD without esophagitis are equivocal because of a lack of uniformity in the definitions of outcomes throughout the literature. Treatment of GERD is important because of the considerable morbidity associated with the disease¹⁰; when not successfully managed, it may lead to complications, such as esophageal stricture, esophageal ulcer and bleeding, and Barrett esophagus.^{12,14-17}

A strong association between GERD symptoms and esophageal acid exposure has been demonstrated.^{8,18,19} The findings of numerous clinical trials have shown that increasing the level of suppression of gastric acid secretion is associated with improved symptom relief in GERD.^{20,21} Acid suppression agents, including histamine-2 receptor antagonists (H2RAs) and proton pump inhibitors, have become mainstays in the treatment of GERD, whether or not patients have erosive esophagitis. Treatment with an H2RA, such as ranitidine, however, is of limited value for this condition. Numerous clinical trials of patients with GERD with varying grades of esophagitis have demonstrated that ranitidine, 150 mg twice daily, is consistently less effective than omeprazole, 20 mg once daily,²²⁻²⁴ or lansoprazole, 30 mg once daily,^{25,26} for the resolution of GERD symptoms.

The goal of the present multicenter double-blind study was to assess the efficacy and safety of omeprazole, 20 and 10 mg once daily, in a US patient population with endoscopy-negative GERD manifested by chronic heartburn and evidence of excessive acid reflux

EVALUATION VARIABLES

The primary goal of this study was to determine the efficacy of omeprazole therapy for the complete resolution of heartburn in patients with GERD who do not have erosive esophagitis. Severity of heartburn was ranked as follows: none (no heartburn of any sort), mild (awareness, but easily tolerated), moderate (discomforting heartburn, causing interference with normal daily activities), or severe (incapacitating heartburn preventing performance of normal daily activities). All efficacy data related to heartburn were recorded by the patients on diary cards. Each patient maintained a diary to record occurrence and severity of heartburn symptoms, study medication use, and antacid use each day. The study was also designed to determine if omeprazole therapy effectively resolves other symptoms of GERD, ie, acid regurgitation, dysphagia, epigastric pain, and nausea; these other symptoms were assessed by investigators at baseline and at weeks 2 and 4.

The following parameters were analyzed to determine the efficacy of omeprazole, 20 and 10 mg, in the treatment of GERD: daily occurrence of heartburn (proportion of patients with no heartburn on each day of the study period) and complete resolution of heartburn (no heartburn of any sort for the 7 days prior to evaluation at weeks 2 and 4). In addition, average daily Gelusil use was calculated. The severity of acid regurgitation, dysphagia, epigastric pain, and nausea was classified by investigators as none (no symptoms); mild (awareness of sign or symptom, but easily tolerated); moderate (discomfort causing interference with normal daily activities); or severe (incapacitating symptoms preventing performance of normal daily activities). Investigators posed standardized questions to patients about these symptoms at baseline and during the week 2 and week 4 visits.

The safety analysis was based on clinical adverse events and laboratory test results. At each visit (week 2 and week 4), patients reported all adverse events that had occurred since the previous visit. Any change in the

patient's clinical status was reported on the case record forms regardless of whether it was determined by the investigator to be related to the test drug. Laboratory test results were summarized according to predefined limits of change from baseline as well as mean changes from baseline at the final visit.

STATISTICAL ANALYSES

The analyses of the data are based on an intent-to-treat population, ie, all patients who were randomized, took at least 1 dose of study medication, and had at least 1 observation. All significance tests were 2-tailed, and a significance level of $P \leq .05$ was used to determine differences between treatment groups.

Complete resolution of heartburn and severity of other GERD symptoms were evaluated using a Cochran-Mantel-Haenszel χ^2 test, stratified by investigational site. Differences between treatment groups for the mean number of heartburn episodes per day and mean number of Gelusil tablets consumed per day were determined through analysis of variance.

A longitudinal analysis of the odds of daily heartburn resolution over the 4-week treatment period was conducted using a generalized estimating equation model.²⁹ The model used a logit link for the mean and an exchangeable correlation for the repeated measures. Day and the logarithm of day were both included as time-varying covariates.

Differences between treatment groups for both clinical and laboratory adverse events were analyzed using the Fisher exact test. A sample size of 120 patients per group was estimated to have a power of 99% to detect a difference in complete resolution of heartburn between either omeprazole dosage and/or placebo and a power of 80% to detect a difference in complete resolution of heartburn between the 2 omeprazole dosages. Study discontinuation and patient compliance were analyzed using the Fisher exact test.

based on intraesophageal pH monitoring. Differences in patient outcomes for the 2 dosage levels and the potential influence of other variables on symptom resolution were examined.

RESULTS

A total of 359 patients were randomized to 1 of the 3 treatment arms (omeprazole, 20 mg; omeprazole, 10 mg; or placebo). The 3 groups were comparable with regard to demographic characteristics, consumption of caffeine and alcohol, smoking, and the percentage of time with intraesophageal pH of 4.00 or lower (**Table 1**). Of the 359 patients, 355 were included in the intention-to-treat population (based on efficacy analysis of diary card data); 4 patients were excluded because they had no diary card data. For the GERD symptoms other than heartburn (acid regurgitation, dysphagia, epigastric pain, and nausea, which were evaluated by investigators during the patients' visits), all patients with available data ($n = 354$) were included in the efficacy analysis, whether or not they had

diary card data. Compliance with treatment (defined as consumption of $\geq 75\%$ of study medication and completion of $\geq 75\%$ of the diary cards) was 98% in the omeprazole 20-mg group, 97% in the omeprazole 10-mg group, and 98% in the placebo group.

RESOLUTION OF HEARTBURN

Success of treatment was determined in several ways, one of which was to calculate the proportion of patients with no heartburn each day (**Figure 2**). The proportion of patients with no heartburn at baseline (day 0) ranged from 5% to 12%, depending on the treatment group. Following initiation of treatment, the daily proportion of patients with no heartburn was consistently greater in the omeprazole 20-mg group (62% on day 7; 67% on day 14) than in the omeprazole 10-mg group (41% on day 7; 46% on day 14) or the placebo group (14% on day 7; 23% on day 14). On the last day of the study, 74% of patients in the omeprazole 20-mg group had no heartburn compared with 49% of patients in the omeprazole 10-mg group and 23% of pa-

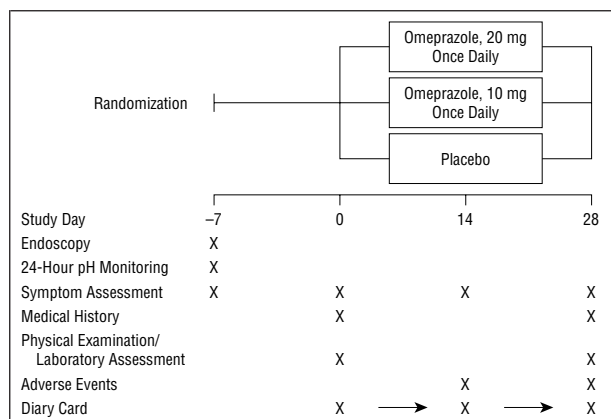


Figure 1. Study design. X indicates when tests were performed or assessment made.

tients in the placebo group. The rate of improvement for the 2 omeprazole groups was most rapid for the first 7 to 10 days of treatment; however, the probability that a patient would experience no heartburn continued to increase, but at a lower rate, over the 4-week period.

A generalized estimating equation model was used to evaluate the relative odds of daily heartburn resolution over time between groups (Figure 2). On any given day, the odds of having no heartburn were approximately double for patients in the omeprazole 20-mg group compared with those in the omeprazole 10-mg group ($P < .001$) and about one third for patients in the placebo group compared with those in the omeprazole 10-mg group ($P < .001$).

Complete resolution of heartburn every day during a full week of treatment was experienced by a significantly greater proportion of patients in the omeprazole 20-mg group compared with the placebo group both during week 2 (41% vs 5%; $P < .001$) and week 4 (48% vs 5%; $P < .001$). Compared with the placebo group, a significantly ($P \leq .001$) greater proportion of patients in the omeprazole 10-mg group also experienced complete resolution of heartburn during week 2 (20%) and week 4 (27%). The difference between the omeprazole 20- and 10-mg groups for the complete resolution of heartburn during all of weeks 2 and 4 was also statistically significant ($P \leq .002$).

The mean daily number of heartburn episodes was significantly lower in the omeprazole 20-mg group than in either the omeprazole 10-mg group ($P \leq .04$) or the placebo group ($P < .001$) during weeks 2 and 4. The mean daily number of heartburn episodes was also significantly ($P < .01$) lower in the omeprazole 10-mg group than in the placebo group during weeks 2 and 4. As would be expected, the mean daily consumption of Gelusil tablets was significantly ($P < .001$) lower in both omeprazole groups than in the placebo group at all evaluation points. The mean number of Gelusil tablets taken per day was more than 3 times greater in the placebo group than in the omeprazole 20-mg group.

RESOLUTION OF OTHER GERD SYMPTOMS

There were statistically significant differences between each omeprazole group when compared with the pla-

Table 1. Baseline Characteristics of Randomized Patients*

Characteristic	No. of Patients (%)			
	Omeprazole, 20 mg Once Daily (n = 118)	Omeprazole, 10 mg Once Daily (n = 118)	Placebo (n = 123)	Total (n = 359)
Age, mean, y	49.5	50.0	49.7	49.7
Sex				
Female	57 (48.3)	53 (44.9)	56 (45.5)	166 (46.2)
Male	61 (51.7)	65 (55.1)	67 (54.5)	193 (53.8)
Race				
White	94 (79.7)	99 (83.9)	98 (79.7)	291 (81.0)
Black	10 (8.5)	7 (5.9)	13 (10.6)	30 (8.4)
Hispanic	13 (11.0)	11 (9.3)	8 (6.8)	32 (8.9)
Other	1 (0.8)	1 (0.8)	4 (3.2)	6 (1.7)
Weekly alcohol consumption				
None	70 (59.3)	73 (61.9)	80 (65.0)	223 (62.1)
1-7 Drinks	39 (33.0)	41 (34.7)	37 (30.1)	117 (32.6)
≥ 8 Drinks	8 (6.8)	4 (3.4)	5 (4.1)	17 (4.7)
Not reported	1 (0.8)	0 (0)	1 (0.8)	2 (0.6)
Daily nicotine use				
No	89 (75.4)	89 (75.4)	89 (72.4)	267 (74.4)
Yes	28 (23.7)	29 (24.6)	34 (27.6)	91 (25.3)
Not reported	1 (0.8)	0 (0)	0 (0)	1 (0.3)
Duration of GERD symptoms, y				
1-5	57 (48.3)	60 (50.8)	63 (51.2)	180 (50.1)
> 5	61 (51.7)	58 (49.2)	60 (48.8)	179 (49.9)
% of time with intraesophageal pH ≤ 4				
< 5 †	4 (3.4)	0 (0)	2 (1.6)	6 (1.7)
5 to < 20	92 (78.0)	95 (80.5)	92 (74.8)	279 (77.7)
20 to < 50	19 (16.1)	17 (14.4)	27 (22.0)	63 (17.5)
≥ 50	3 (2.5)	6 (5.1)	2 (1.6)	11 (3.1)

*GERD indicates gastroesophageal reflux disease.

†Considered evaluable according to intention-to-treat inclusion criteria.

cebo group for the severity scores for acid regurgitation, dysphagia, epigastric pain, and nausea at both weeks 2 and 4. There were no significant differences between the omeprazole 20- and 10-mg groups for any of these 4 symptoms. At baseline, the following proportions of patients reported no symptoms: acid regurgitation, 23%; epigastric pain, 18%; dysphagia, 62%; and nausea, 58%. By week 4, the proportion of patients experiencing no acid regurgitation, epigastric pain, dysphagia, or nausea was significantly higher in the omeprazole 20- and 10-mg groups than in the placebo group (**Figure 3**).

SAFETY AND TOLERABILITY

All of the 359 patients randomized to treatment were included in the safety analysis. Forty percent (n=142) of the patients enrolled in the study reported at least 1 adverse event, but there were no significant differences between any of the groups in the proportion of patients experiencing at least 1 adverse event. The number of adverse events considered to be possibly, probably, or definitely treatment related was similar across the 3 treatment groups: 9% for omeprazole, 20 mg; 13% for omeprazole, 10 mg; and 11% for placebo; again, there

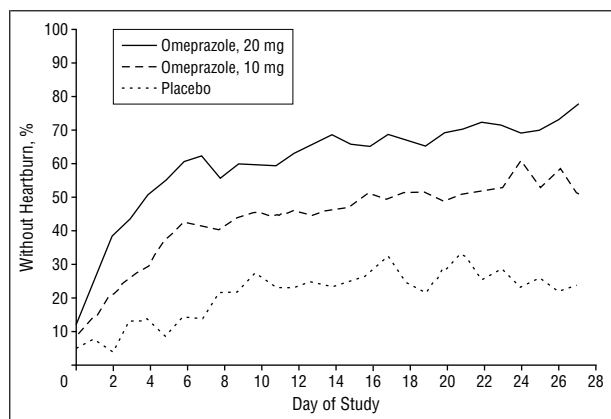


Figure 2. Percentage of patients with no heartburn by day.

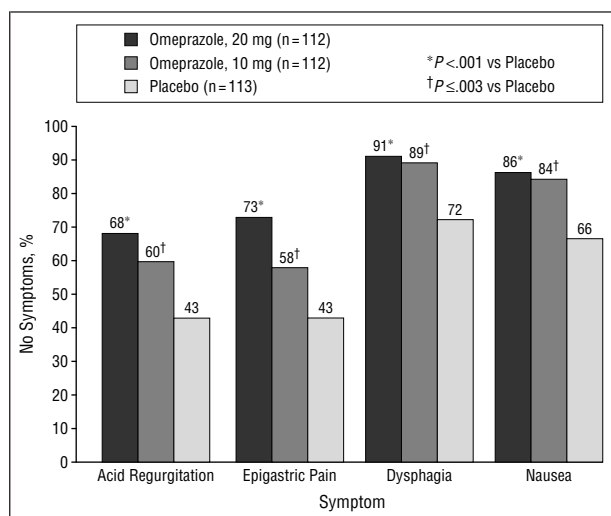


Figure 3. Proportion of patients reporting no symptoms at week 4 of double-blind treatment.

were no significant differences between any of the treatment groups. Only 7 patients (2%) experienced a serious adverse event—4 were in the omeprazole 20-mg group (2 occurrences of cholecystitis, 1 occurrence of right and left ear cholesteatoma, and 1 occurrence of severe cerebral vascular accident); 1 was in the omeprazole 10-mg group (acute myocardial infarction); and 2 were in the placebo group (angina and transient cerebral ischemia). None of these serious adverse events was considered to be related to study medication. Eight patients (2, 3, and 3 patients in the omeprazole 20-mg, omeprazole 10-mg, and placebo groups, respectively) withdrew from the study owing to adverse events. There were no deaths during this study. The most common adverse events observed in this study were diarrhea (6%), headache (6%), and nausea (4%), as shown in **Table 2**. There were no clinically significant changes in laboratory values.

COMMENT

While symptomatic GERD without erosive esophagitis is often perceived by many clinicians to be a mild condition, it can have major implications for a patient's qual-

Table 2. Most Common Clinical Adverse Events (Incidence $\geq 5\%$)

Adverse Event	No. of Patients (%)			
	Omeprazole, 20 mg (n = 118)	Omeprazole, 10 mg (n = 118)	Placebo (n = 123)	Total (n = 359)
Diarrhea	6 (5.1)	8 (6.8)	8 (6.5)	22 (6.1)
Headache	8 (6.8)	7 (5.9)	6 (4.9)	21 (5.8)
Nausea	6 (5.1)	2 (1.7)	8 (6.5)	16 (4.4)
Common cold	4 (3.4)	6 (5.1)	2 (1.6)	12 (3.3)
Vomiting	6 (5.1)*	0 (0)	6 (4.9)*	12 (3.3)
Fever	6 (5.1)	2 (1.7)	1 (0.8)	9 (2.5)

*Significantly different ($P \leq .05$) from omeprazole, 10 mg.

ity of life.⁴ Recognition of the importance of quality-of-life measures for understanding and interpreting both burden of illness and treatment outcomes is increasing among health care providers.^{30,31} Quality-of-life scales can be useful in describing the effects of a disease and its subsequent treatment because they provide data on physical and psychological well-being that may not be fully reflected in standard measurements of clinical outcomes.^{30,31} In a recent study,³² the health-related quality of life in patients with GERD was compared with normative data for a general US population and for patients with diabetes, clinical depression, and hypertension. Compared with the US general population, the patients with GERD reported lower levels of psychological well-being, social functioning, physical functioning, and vitality. This study demonstrated that patients with GERD experience worse pain than patients with diabetes or hypertension, levels of pain similar to those experienced by patients with major depression, and worse social functioning and emotional well-being than those with diabetes or hypertension. The impairments to quality of life observed in this study were similar to findings of previous studies designed to measure these parameters.³³⁻³⁵ Therefore, these studies demonstrate that GERD is a condition that disrupts numerous aspects of patients' daily lives.

The most important treatment goal for these patients is, therefore, complete symptom resolution, which frequently requires profound acid suppression. This was the first US study in which 20-mg and 10-mg dosages of omeprazole were evaluated in patients with symptomatic GERD without erosive esophagitis. The results of this study demonstrate the superiority of omeprazole, 20 mg once daily, compared with omeprazole, 10 mg once daily, and with placebo for the treatment of heartburn, as well as other GERD-related symptoms. Omeprazole, 20 mg, produced a rapid response, as supported by the fact that 62% of the patients in this treatment group were heartburn-free on day 7. Moreover, the fact that nearly three quarters of these patients were heartburn-free on the last day of the study demonstrates that in many patients the response to the 20-mg dosage of omeprazole tends to be sustained over time. Based on the stringent criterion for complete resolution of heartburn during an entire treatment week, omepra-

zole, 20 mg, was also significantly more effective than omeprazole, 10 mg, or placebo. The relative lack of effectiveness of the 10-mg dosage of omeprazole compared with the 20-mg dosage demonstrates a clear dose-response effect and underscores the fact that heartburn, even in the absence of macroscopic changes in the esophagus, is the manifestation of a disease state requiring relatively potent treatment.

It is notable that in this study the response to placebo was very low across all efficacy parameters measuring resolution of heartburn. While there was some response to placebo when resolution of heartburn was examined on a daily basis, the response rate was well below those of the omeprazole treatment groups and on most days did not surpass 25%. Complete resolution of heartburn for an entire week was found in only 5% of patients who received placebo during weeks 2 and 4. Even though the patients in the placebo group took about 3 times as many antacid tablets as those in the omeprazole 20-mg group, this rescue medication was clearly inadequate. These low response rates in the placebo group to taking antacids when needed indicate that treatment with antacids will generally be ineffective for this condition.

Resolution of the other symptoms of GERD (acid regurgitation, epigastric pain, dysphagia, and nausea) was also significantly greater in the omeprazole 20-mg group than in the placebo group. This difference between the omeprazole 20-mg and placebo groups was particularly striking for acid regurgitation and epigastric pain, which were experienced by more than three quarters of the patients at baseline, but by less than one third of the omeprazole 20-mg group compared with more than one half of the placebo group at week 4.

Numerous comparative clinical trials have demonstrated the challenge of achieving complete symptom resolution in patients with GERD with or without reflux esophagitis who are treated either with an H₂RA or a proton pump inhibitor. These studies support the greater efficacy of a proton pump inhibitor over that of an H₂RA for the resolution of GERD symptoms.³⁶ In these studies, omeprazole, 20 mg once daily, produced significantly higher rates of symptom resolution, including relief of heartburn, than did ranitidine, 150 mg twice daily,^{22-24,37,38} or cimetidine, 400 mg 4 times daily.³⁹ In studies comparing lansoprazole and ranitidine, treatment with lansoprazole, 30 mg once daily, resulted in significantly greater relief of heartburn than did ranitidine, 150 mg twice daily.^{25,26}

The findings of the present study are consistent with those of a multicenter trial conducted in Scandinavia in a similar patient population in which Lind et al⁴⁰ found that omeprazole, 20 mg once daily, was significantly more efficacious than either omeprazole, 10 mg daily, or placebo for the treatment of heartburn in patients with symptomatic GERD without erosive esophagitis. There were, however, some differences between the 2 studies based on patient inclusion and exclusion criteria. First, patients were eligible to participate in the Scandinavian study if they had 2 episodes of heartburn in the week prior to randomization, and in many patients, the severity of heartburn was classified

as mild. In our study, patients had to have experienced episodes of heartburn on 4 of the 7 days prior to randomization, and only patients with moderate to severe heartburn were eligible. Second, in the Scandinavian study, patients with pH of 4.00 or lower for less than 5% of the 24-hour monitoring period were permitted to enroll, whereas in our study, these patients were excluded. In a normal asymptomatic population, the percentage of time that a 24-hour pH reading would be 4.00 or lower is expected to be less than 4.2%.⁴¹ These differences between the Scandinavian and the US patient populations underscore not only the challenge of making a definitive diagnosis of GERD, but a relative absence of any clear-cut association between frequency and severity of heartburn, intraesophageal pH levels, and treatment outcomes.

In an effort to gain a better understanding of the role of acid in the pathogenesis of GERD, clinicians have conducted studies to determine why the presence of GERD symptoms, particularly heartburn, often precedes any endoscopic evidence of mucosal damage. According to one hypothesis, dilated intercellular spaces in the esophageal epithelium characterize acid damage in patients with symptoms but with normal-appearing mucosa.^{42,43} In a study designed to test this hypothesis,⁴² dilated intercellular spaces were found in the normal-appearing mucosa of patients with symptomatic nonerosive GERD. The findings of this study are substantiated by those from experimental models.^{44,45} Thus, the presence of dilated intercellular spaces induced by acid before any visible mucosal damage occurs suggests that these dilated spaces may be a very early step in the acid-damage cascade. The presence of dilated intercellular spaces in patients with GERD who have no macroscopic evidence of disease thus offers a possible explanation for the acute onset of symptoms during episodes of acid reflux through access of this acid to sensory neurons within the epithelium.⁴⁴ The findings from these studies thereby provide a rationale for the practice of early and aggressive treatment of symptomatic GERD.

In summary, patients with symptomatic GERD, a condition perceived to be mild by many physicians, frequently require profound acid suppression greater than that afforded by H₂RAs to achieve complete resolution of their symptoms. In this study, 20 mg once daily of omeprazole was the optimal dosage for obtaining early and sustained resolution of heartburn, as well as the other troublesome symptoms of GERD.

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Corresponding author: Joel E. Richter, MD, Department of Gastroenterology, Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195.

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