

## ORIGINAL CONTRIBUTIONS

### Esophagus

# Management Strategy for Patients With Gastroesophageal Reflux Disease: A Comparison Between Empirical Treatment With Esomeprazole and Endoscopy-Oriented Treatment

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**OBJECTIVES:** Whether patients with typical gastroesophageal reflux disease (GERD) symptoms and without alarm features should be treated empirically or undergo endoscopy first is a debated issue. In this study, our aim was to assess the efficacy, and to compare the direct costs and impact on health-related quality of life (HRQL), of two treatment strategies (empirical vs endoscopy-oriented treatment) in a large population of patients with GERD.

**METHODS:** In total, 612 patients were randomized to either empirical treatment with esomeprazole 40 mg once daily (od) (group 1, N = 309) or endoscopy and treatment according to endoscopic findings (group 2, N = 303, esomeprazole 40 mg od in patients with reflux esophagitis and esomeprazole 20 mg od in patients without esophagitis) for 4 wk, followed by esomeprazole 20 mg od maintenance treatment in both groups. Direct costs and HRQL were analyzed in both treatment arms.

**RESULTS:** At the end of the acute treatment phase (week 4), 267 patients in group 1 (86.4%) and 265 patients in group 2 (87.5%) were considered responders to treatment (intention-to-treat analysis,  $P = 0.878$ ). Empirical treatment proved to be cost-effective by saving 38.72 euros per treated patient. At the end of the maintenance phase (week 24), a similar proportion of patients responded to treatment in the two groups (71.8% vs 68.3%,  $P = 0.389$ ). HRQL improved from baseline to week 24 in both groups (difference between study groups not significant).

**CONCLUSIONS:** In patients with GERD, empirical treatment with esomeprazole proved to be cost-effective compared with endoscopy-oriented treatment, and did not negatively affect patient HRQL. These results should be taken into account in the management of GERD patients in clinical practice.

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## INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common medical problem with a broad spectrum of symptoms and varying degrees of severity. Heartburn and acid regurgitation are the typical symptoms of the disease, although some patients may have atypical manifestations of GERD (1). Furthermore, GERD causes a substantial impairment in quality of life in a number of patients (2). In population-based studies conducted in western countries, heartburn was reported at least once per month by 25% and daily by 5% of the subjects (3). Since GERD symptoms and esophagitis are mainly due to

abnormal exposure of esophageal mucosa to acid, suppression of gastric acid secretion is the best approach currently available for both short- and long-term management of the disease (4). Indeed, treatment of GERD with proton pump inhibitors (PPIs) relieved symptoms and healed esophagitis in more than 80% of patients within 8 wk of treatment, and proved to be able to maintain patients in remission with a very favorable safety profile during up to 5 yr of continuous treatment (5, 6).

One of the most debated issues in GERD is whether patients with typical symptoms and without alarm features

should be treated empirically, or undergo endoscopy first (7). In fact, on the one hand, several factors (such as the high prevalence of GERD in the general population, the low prevalence of both esophagitis and complications in unselected patients, and the high response rate to treatment) support an empirical approach for therapeutic management. On the other hand, endoscopy is the only diagnostic tool capable of differentiating erosive and nonerosive forms of GERD as well as complications of GERD, and identifying patients who may need endoscopic follow-up such as those with Barrett's esophagus (7–9). Moreover, advocates of endoscopy suggest that the reassurance provided by the result of the instrumental examination should improve patient quality of life. However, if endoscopy has to be carried out, no consensus exists on the timing of examination (7). Furthermore, the use of endoscopy depends on costs, accessibility, and timing in relation to treatment (7, 10).

In Italy, the prevalence of GERD symptoms in the general population ranges between 21% and 45% (11), and it has been estimated that about 720,000 patients seek medical care annually because of GERD symptoms. Thus, the high number of affected patients causes a considerable economic burden to society, and pragmatic and cost-effective management of the disease is advisable, especially in the current cost-containment environment. In this setting, the aims of this study were to assess the efficacy, and compare the costs and impact on health-related quality of life (HRQL), of two treatment strategies: empirical treatment *versus* endoscopy-oriented treatment in patients with typical symptoms of GERD without alarm features.

## PATIENTS AND METHODS

### Study Design

This was an open, multicenter, randomized, parallel-group study. Patients aged 18–70 yr presenting at gastroenterology centers with at least 3 months of typical symptoms suggestive of GERD (heartburn with or without acid regurgitation) and without alarm symptoms (unintentional weight loss, recurrent dysphagia, anemia [men, <14 g/dL; women, <12 g/dL], hematemesis, melena) were eligible for the study. Criteria for exclusion were current or historical evidence of the following diseases/conditions: previous esophageal, gastric, or duodenal surgery; Zollinger-Ellison syndrome; achalasia; scleroderma and primary esophageal spasms; esophageal stricture; upper gastrointestinal malignancy including dysplastic changes in the esophagus; active malignant disease except for minor superficial skin disease; unstable diabetes mellitus; cerebral vascular disease; alcohol and/or drug abuse; familial history of esophageal or gastric cancer; or continuous treatment with nonsteroidal anti-inflammatory drugs. The study was given a favorable opinion in writing by an independent ethics committee. We obtained written informed consent from each patient before conducting any procedure specifically for the study. The study was performed in accordance with the ethical principles in the Declaration of

Helsinki, Good Clinical Practice, and applicable regulatory requirements.

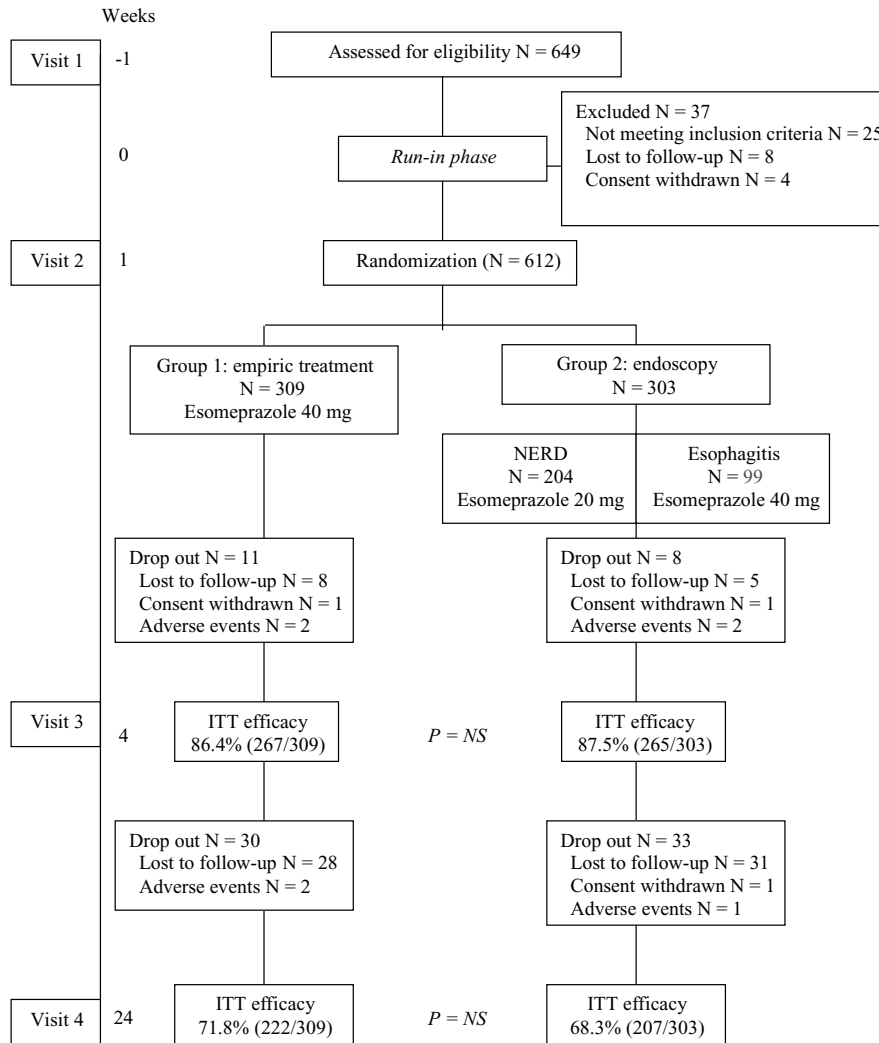
At enrollment (visit 1), patients were included in a run-in period of 1 wk, during which they recorded their symptoms in a daily diary (completed at bedtime). Briefly, the patients had to rate the severity of their symptoms of heartburn and regurgitation on a four-point scale that was graded as follows: 0 = none, 1 = mild (awareness of symptoms, but easily tolerated), 2 = moderate (discomfort sufficient to cause interference with normal activities), 3 = severe (incapacitating, with inability to perform normal activities). At the end of the 1-wk run-in period (visit 2), only patients whose symptoms of heartburn (with or without regurgitation) with a sum of symptom scores of 5 or more during the last 7 days of the run-in period and a sum of symptom scores of 2 or more during the last 3 days of the run-in period were randomized to empirical treatment with esomeprazole 40 mg once daily (od) for 4 wk (group 1) or basal endoscopy (group 2). The investigated patients (group 2) were treated according to their endoscopic diagnosis: patients with esophagitis grade A–D (according to the Los Angeles classification) (12) were treated with esomeprazole 40 mg od for 4 wk, while patients without esophagitis (nonerosive reflux disease, NERD) were treated with esomeprazole 20 mg od for 4 wk. Patients in any treatment group who were free from symptoms following 4 wk of treatment were treated for a further 20 wk with esomeprazole 20 mg od maintenance therapy (Fig. 1).

### Evaluation of Response

The outcome variable was the assessment of responders or nonresponders after a short treatment period of 4 wk and after a long treatment period of a further 20 wk. The end point was based on symptom scores recorded over the last 7 days before the visit. The patients judged their symptoms of heartburn with or without regurgitation on the same four-graded scale used during the run-in period. A responder to the 4-wk acute treatment phase was a patient whose sum of symptom scores over the last 7 days before visit 3 was 0 or 1. A responder to the 20-wk maintenance phase was a patient whose sum of symptom scores over the last 7 days before visit 4 was 0 or 1.

### Cost Analysis

The primary financial aim was to assess the direct medical cost of the management of patients with GERD using empirical treatment and treatment following endoscopy, and was obviously limited to the acute phase of treatment. Medical costs (in euros) sustained by the health-care provider were related to drugs, health-care visits, and tests (*i.e.*, endoscopy), and were calculated on an intention-to-treat (ITT) basis. Briefly, for each patient, we calculated the cost of the first visit (20.66 euros) and of the acute-phase treatment (group 1: 56.22 euros per patient, group 2: 56.22 euros per patient with esophagitis and 43.40 euros per patient with NERD); for group 2 patients, we also calculated the cost of endoscopy. In the economic analysis of the empirical therapy arm (group 1), treatment



**Figure 1.** CONSORT flow diagram of subjects’ progress through the phases of the study. Successful treatment is shown on an intention-to-treat analysis in the two treatment arms. Group 1: empiric treatment with esomeprazole 40 mg once daily (od) for 4 wk. Group 2: basal endoscopy (patients with Los Angeles grade A–D esophagitis received esomeprazole 40 mg od for 4 wk, patients without esophagitis received esomeprazole 20 mg od for 4 wk).

failure was considered an indication for endoscopy, and for conservative reasons, dropouts were also considered as an indication for endoscopy. Therefore, for each patient in group 1 who failed treatment or dropped out, we also calculated the cost of a second visit (12.81 euros) and the endoscopy (56.81 euros). The total cost per patient was then compared between groups. The costs of drugs, visits, and endoscopy were calculated using the Italian Health Service tariffs.

**Evaluation of HRQL**

The impact of treatment on aspects of HRQL (as measured by the dimensions of sleep quality, emotions, and the ability to eat and drink what one likes) was assessed by means of the Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire after both the acute (4 wk) and maintenance (24 wk) phases of treatment. The QOLRAD questionnaire consists of 25 items combined into five dimensions: emotional (6 items), sleep (5 items), food/drink (6 items), physi-

cal/social (5 items), and vitality (3 items). The answer to each question is scored on a 7-grade Likert scale, from maximum (score 1) to minimum (score 7), and the lower the value, the more severe the impact on daily functioning. The reliability, validity, and responsiveness of the QOLRAD questionnaire have been documented in international studies in subjects with heartburn (13, 14). Previous studies have revealed that a change of 0.5 represents a minimum important change in the QOLRAD score (15).

**Statistical Methods**

For the variables evaluated, an ITT analysis was performed. All randomized patients who received at least one dose of the study drug were included in the ITT population. The  $\chi^2$  test was used to compare the proportions of patients who responded to treatment both at the end of the acute phase and at the end of the maintenance phase between treatment arms (i.e., group 1 vs group 2). In terms of symptom score,

an additional analysis was performed in order to verify the significance of the change from randomization to the end of the acute phase, and from the end of the acute phase to the end of the maintenance phase, for each patient, by means of *t*-test for paired data. Furthermore, the *t*-test was used to compare symptom scores between the two groups at the end of both the acute and maintenance phases.

The sample size was calculated assuming a response rate to treatment of 85%; under these circumstances, 200 patients were required in each treatment group to be able to detect a 10% difference between treatments with an  $\alpha$  value of 2.5% ( $2\alpha = 5\%$ ) and a power ( $1-\beta$ ) of 80%. Considering a 20% dropout rate or lost to follow-up data, it was estimated that a sample of at least 500 (2N) patients was needed to assess for eligibility. A significance level of 0.05 was used in statistical tests. The change in QOLRAD scores from baseline was assessed as (final value – baseline value)/baseline value. QOLRAD dimension scores were compared between treatment arms by means of analysis of covariance with the baseline value as the covariate. Data are shown as mean  $\pm$  SD.

## RESULTS

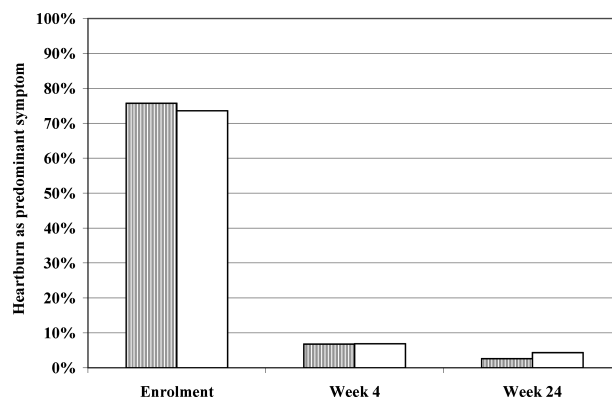
### Efficacy

In total, 649 patients were enrolled into the study. The mean age of the patients was 43.6 yr, 368 were male (56.7%), and 646 were white (99.5%). Among them, 37 patients (5.7%) were not randomized and 612 patients (94.3%) returned after the 1-wk run-in phase and were therefore randomized to empirical treatment with esomeprazole 40 mg od (group 1, N = 309) or endoscopy and treatment according to endoscopic findings (group 2, N = 303, esomeprazole 40 mg od in patients with esophagitis and esomeprazole 20 mg od in patients with NERD). The two treatment groups were well matched in terms of demographic and clinical variables (Table 1). In particular, heartburn was identified as the predominant symptom in 75.7% (234 patients) and 73.6% (223 patients) of patients in group 1 and 2, respectively ( $\chi^2 = 0.263$ ,  $P = 0.609$ ). Among patients who underwent endoscopy (group 2), 204 patients had NERD (67.3%) and 99 had reflux esophagitis (32.7%; 58 patients had grade A, 29 grade B, 10 grade C, and 2 grade D).

**Table 1.** Main Demographic and Clinical Variables of the Study Population Subdivided According to Randomization

Variable	Units	Group 1* (N = 309)	Group 2* (N = 303)
Gender	Male (%)	181 (58.6)	169 (55.8)
Age	Mean (SD)	43.7 (12.9)	43.5 (13.4)
Heartburn	N (%)	296 (95.8)	289 (95.4)
Regurgitation	N (%)	265 (85.8)	242 (79.9)

\*Group 1: empirical treatment with esomeprazole 40 mg once daily (od) for 4 wk. Group 2: basal endoscopy (patients with Los Angeles grade A–D esophagitis received esomeprazole 40 mg od for 4 wk, patients without esophagitis received esomeprazole 20 mg od for 4 wk).



**Figure 2.** Proportion of patients reporting heartburn as the predominant symptom at the various time points of the study in group 1 (striped bars) and group 2 (white bars). Group 1: empirical treatment with esomeprazole 40 mg once daily (od) for 4 wk. Group 2: basal endoscopy (patients with Los Angeles grade A–D esophagitis received esomeprazole 40 mg od for 4 wk, patients without esophagitis received esomeprazole 20 mg od for 4 wk).

Figure 1 shows the Consolidated Standards of Reporting Trials (CONSORT) flow diagram of patient progress throughout the study. At the end of the acute treatment phase (week 4), 267 patients in group 1 (86.4%) and 265 patients in group 2 (87.5%) were considered responders to treatment according to symptom score (ITT analysis,  $\chi^2 = 0.027$ ,  $P = 0.878$ , Fig. 1). At this time point, heartburn was reported as the predominant symptom by 6.8% of the patients in group 1 (N = 21) and 6.9% of the patients in group 2 (N = 21) ( $\chi^2 = 0.009$ ,  $P = 0.929$ , Fig. 2).

At the end of the maintenance phase (week 24), 551 patients (90.0% of the randomized patients) completed the study (90.3% in group 1, 89.4% in group 2), and 71.8% in group 1 (222 patients) and 68.3% in group 2 (207 patients) were considered responders to treatment ( $\chi^2 = 0.748$ ,  $P = 0.389$ , Fig. 1). At this time point, heartburn was the predominant symptom in 2.6% (8 patients) and 4.3% (13 patients) of the patients in group 1 and 2, respectively ( $\chi^2 = 0.872$ ,  $P = 0.355$ ). Figure 2 shows the progressive decrease in heartburn as the predominant symptom in the two treatment arms at various time points during the study.

During the last 7 days of the acute-treatment phase, the mean symptom score decreased from  $8.3 \pm 7.6$  to  $1.8 \pm 3.7$  in group 1 and from  $8.2 \pm 7.6$  to  $1.9 \pm 4.2$  in group 2 (*t*-test for paired data,  $P < 0.0001$  for both treatment arms). During the last 7 days of the maintenance phase (week 24), the mean symptom score further decreased to  $0.6 \pm 1.8$  and  $1.2 \pm 3.1$  in group 1 and group 2, respectively. Although it was not one of the aims of the study, we found that the mean symptom score was not different at the end of the acute phase between the two study groups, while the mean symptom score was significantly lower in group 1 at the end of the maintenance phase (2-sample *t*-test,  $P = 0.0065$ ). When data for all patients were pooled, no statistically significant decrease in the mean symptom score from week 4 to week 24 was observed (paired *t*-test,  $P = 0.175$ ), while subgroup

**Table 2.** Summary of Direct Costs of Treatment in Patients Allocated to Empirical Treatment (Group 1) and Endoscopy-Oriented Treatment (Group 2)\*

Group 1	N	Visit	Treatment	Endoscopy	Total
Acute-phase treatment	309	7,001.94	17,371.98		
Treatment failure	31	397.11		1,761.11	
Dropout	11	140.91		624.91	
Total		7,539.96	17,371.98	2,386.02	27,297.96 88.34 per patient
Group 2	N	Visit	Treatment	Endoscopy	Total
Acute-phase treatment	303	6,865.98		17,213.43	
NERD	204		8,853.60		
Esophagitis	99		5,565.78		
Total		6,865.98	14,419.38	17,213.43	38,498.79 127.06 per patient

\*Group 1: empirical treatment with esomeprazole 40 mg once daily (od) for 4 wk.

Group 2: basal endoscopy (patients with Los Angeles grade A–D esophagitis received esomeprazole 40 mg od for 4 wk, patients without esophagitis received esomeprazole 20 mg od for 4 wk).

#### Costs:

First visit	20.66 euros
Second visit	12.81 euros
Endoscopy (without biopsy)	56.81 euros
Esomeprazole 40 mg	2.01 euros per tablet
Esomeprazole 20 mg	1.55 euros per tablet

Costs of drugs, visits, and endoscopy were evaluated using the Italian Health Service reimbursement parameters. Cost analysis is limited to the acute phase of treatment.

analysis showed a significant decrease within group 1 (paired *t*-test,  $P = 0.015$ ).

#### Cost Analysis

Table 2 shows the summary of costs in the two treatment arms. In group 1, treatment failure was considered an indication for a second visit and endoscopy, and for conservative reasons, we decided to take into account dropouts as treatment failures. In this group, the cost of treatment per patient (esomeprazole 40 mg od) was 56.22 euros for 4 wk, and accounted for 63.6% of the total costs. In group 2, the cost of treatment accounted for 37.4% of the total costs (56.22 euros per patient in patients with esophagitis and 43.40 euros per patient in patients with NERD). The cost of therapeutic management of a patient with GERD in group 1 was 88.34 euros, while in group 2 it was 127.06 euros (difference 38.72 euros), thereby favoring the empirical approach.

#### HRQL

In the ITT population, at randomization, the mean emotional dimension score was  $4.4 \pm 1.3$  in both groups, while the mean scores for the sleep and food/drink dimensions in group 1 and 2 were  $4.3 \pm 1.4$  and  $4.4 \pm 1.4$  and  $3.6 \pm 1.1$  and  $3.7 \pm 1.2$ , respectively. The mean physical/social dimension and vitality dimension scores were  $4.8 \pm 1.4$  and  $4.0 \pm 1.2$  in the two groups, respectively (Fig. 3A and B). QOLRAD scores were also described at the end of both the acute phase and the maintenance phase. In both cases, the dimension mean scores improved.

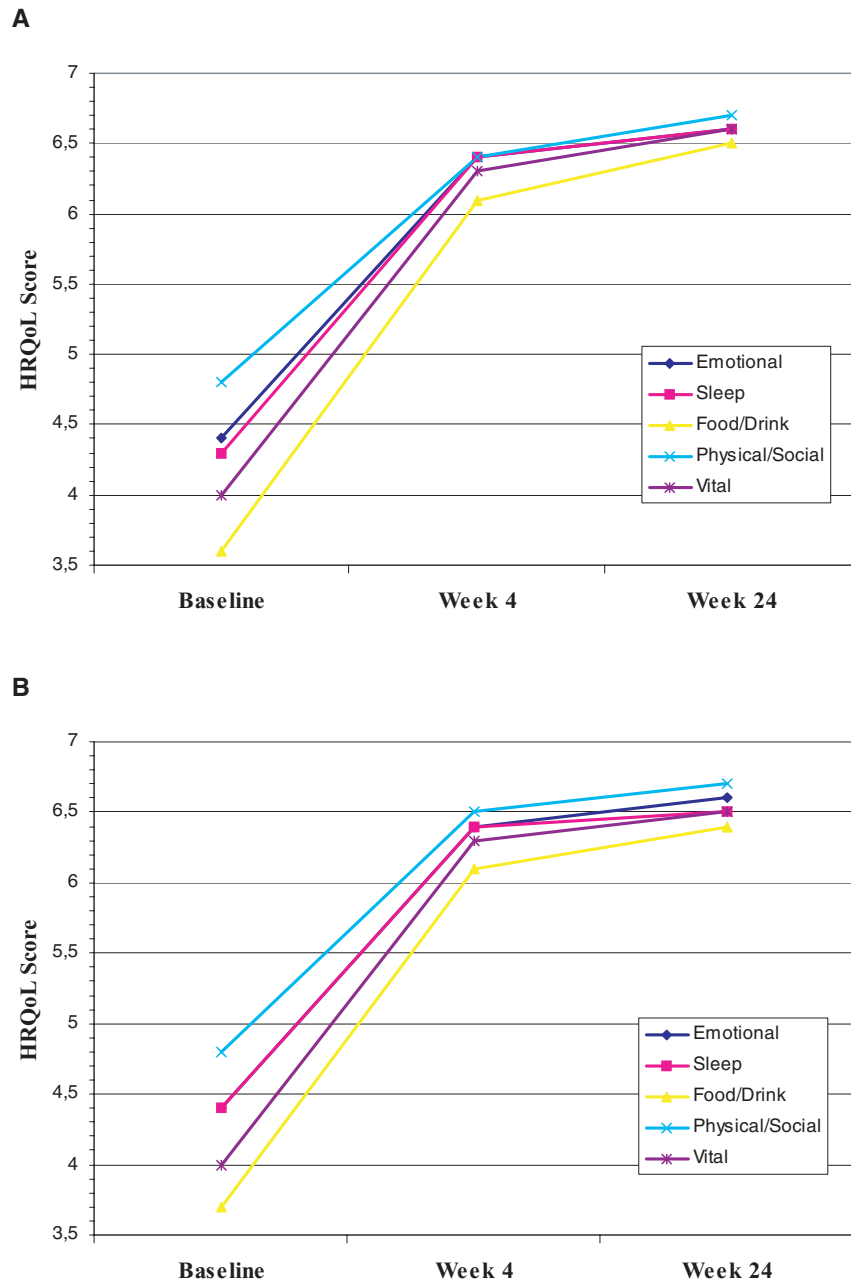
At the end of acute phase, in both groups, the mean score was  $6.4 \pm 0.9$  for the emotional and sleep dimensions,  $6.1 \pm 1.0$  for the food/drink dimension, and  $6.3 \pm 0.9$  for the vital-

ity dimension, while the mean score for the physical/social dimension was  $6.4 \pm 0.9$  in group 1 and  $6.5 \pm 0.8$  in group 2 (Fig. 3A and B). No statistically significant difference in change in QOLRAD score from baseline or in the difference in QOLRAD score between treatment arms at the end of the acute phase was detected.

At the end of the maintenance phase, QOLRAD dimension scores were further improved. In both groups, the mean score was  $6.6 (\pm 0.7)$  for group 1 and  $\pm 0.8$  for group 2) for the emotional dimension and  $6.7 \pm 0.7$  for the physical/social dimension in both groups. Mean scores for the sleep and for the vitality dimensions were  $6.6 \pm 0.8$  and  $6.5 \pm 0.9$  and  $6.6 \pm 0.7$  and  $6.5 \pm 0.9$  for group 1 and 2, respectively. Food/drink dimension scores were  $6.5 \pm 0.8$  in group 1 and  $6.4 \pm 0.8$  in group 2 (Fig. 3A and B). Analysis of covariance performed with the baseline value as the covariate in order to compare treatment groups showed no statistically significant difference.

#### DISCUSSION

GERD is a highly prevalent disease in the general population and its incidence has recently been reported to be rising (3, 11, 16). In the primary care setting, symptom severity is poorly correlated with the presence and severity of esophageal mucosal damage in patients presenting with heartburn with or without regurgitation; indeed, up to 70% of these patients will have a negative endoscopy (*i.e.*, NERD) (17). In patients with GERD, given the need for treatment irrespective of the presence of esophageal mucosal lesions, it is suggested that treatment be started without performing an endoscopy unless there is evidence of alarm symptoms (8).



**Figure 3.** Modifications of the various items of the health-related quality of life (HRQL) score during treatment in group 1 (A) and 2 (B). Group 1: empirical treatment with esomeprazole 40 mg once daily (od) for 4 wk. Group 2: basal endoscopy (patients with Los Angeles grade A–D esophagitis received esomeprazole 40 mg od for 4 wk, patients without esophagitis received esomeprazole 20 mg od for 4 wk).

In studies carried out in small series of patients, this approach proved to be financially effective and able to reduce the number of upper endoscopies performed by 64% (18). This approach was also supported by evidence provided by decision analysis studies that assessed the economic implications of competing strategies in the management of GERD (19, 20). Nevertheless, there is still controversy about whether a patient with typical GERD symptoms should be treated or undergo endoscopy first (21, 22). Fear of a possible undiagnosed malignancy, the impossibility of grading esophagitis and screening for Barrett’s esophagus, and a negative impact

on HRQL determined by the lack of reassurance that would otherwise be provided by endoscopy are the major limitations attributed to empirical treatment. In this regard, the updated American College of Gastroenterology GERD diagnosis and treatment guidelines support empirical treatment for patients presenting with typical GERD symptoms, and suggest endoscopy for those who have symptoms suggestive of complicated disease and Barrett’s esophagus, and when “the patient and physician feel early endoscopy to be appropriate” (23). However, the evidence sustaining this statement is weak and mainly based on expert opinion rather than randomized

trials, and was only graded IV on a four-point hierarchical scale (23).

In this multicenter study carried out on a large series of patients with typical GERD symptoms without alarm features, we observed that, in the short term, empirical treatment with full-dose esomeprazole is as effective as performing screening endoscopy and treating according to endoscopy results. Noteworthy is the fact that this approach is cost-effective, saving 38.72 euros per patient and reducing the number of endoscopies by 86–90%, and quality of life does not seem to be influenced by the absence of “endoscopic reassurance.” Finally, in the long term, maintenance low-dose esomeprazole was equally effective in the two groups of patients.

More than a decade ago, Blustein and colleagues found that, in 742 Canadian patients who underwent upper endoscopy for symptoms suggestive of GERD, endoscopy had a low yield and did not substantially modify the therapeutic approach (9). Interestingly enough, in this “pre-NERD” study, 26% of the patients only had evidence of reflux esophagitis. Our study was carried out in an open-access system, and patients with symptoms suggestive of GERD (heartburn with and without regurgitation) and without alarm symptoms were consecutively enrolled. We recruited a large number of patients, being sure to include patients from all parts of Italy in order to obtain results that can easily be applied to everyday clinical practice, and avoid biases inherent to studies carried out in tertiary referral centers. Indeed, the proportion of patients with reflux esophagitis observed in our study (*i.e.*, 32%) is similar to the one observed in the above-mentioned study (9), and is in keeping with the current literature from recent findings in Italy (24). Our aim was to assess the efficacy of empirical treatment compared with endoscopy-oriented treatment. In fact, the treatment arms were similar in terms of GERD symptoms, and in both study groups esomeprazole resulted in a significant improvement in GERD symptoms. Overall, we found that short-term esomeprazole therapy produced a complete response in 86.9% of the patients, and that the rates of response were not different in the two study groups (86.4% vs 87.5%). These results are in keeping with those recently reported in large series of patients with GERD with and without esophagitis treated with full- or low-dose esomeprazole, respectively (25, 26). Finally, the results obtained during the maintenance phase by low-dose esomeprazole are also in keeping with those obtained in other populations (27). Results of a *post hoc* analysis showing that patients treated empirically had a significantly greater reduction in symptom scores at the end of the maintenance phase as compared with patients who underwent endoscopy seem to suggest that low doses of PPIs may be insufficient for treating NERD patients. In this regard, an explanation for the finding that the difference in symptom scores between groups became apparent at the end of the maintenance phase rather than at the end of the acute phase may be that patients with NERD likely require a more intensive, “step-down” dose-escalating treatment, the benefits of which are more evident in the long term. However,

because this was not among the main aims of the study, future studies specifically addressing this topic are needed to clarify this issue.

The economic analysis was modeled according to a diagnostic algorithm proposed by Bytzer and Blum (8), and considered dropouts as treatment failures. In the short term, the cost analysis showed that the empirical approach saved 38.72 euros per patient treated, and avoided 86–90% of endoscopies. Also, this approach did not seem to influence HRQL, both in the short and in the long term. In contrast, evaluation of HRQL showed that control of symptoms likely had the greatest influence on QOLRAD dimension improvement, and that HRQL further improved during the maintenance phase of esomeprazole treatment. As a matter of fact, QOLRAD scores were not different between patients who underwent endoscopy and those who were treated empirically, at the end of both the acute and the maintenance phase, and as far as the acute phase is concerned, likely ruled out a possible psychological benefit of “endoscopic reassurance.”

This study undoubtedly has some limitations. First of all, we do not have data on how many nonresponding, empirically treated patients actually underwent endoscopy and on the possible results of such an examination. In fact, nonresponders to short-term treatment were managed according to the physicians’ clinical judgment and local availability of resources. Thus, we also do not know how many of these patients underwent esophageal 24-h pH-metry, and the utilization of these resources was therefore not computed in the financial analysis. However, in order to be as conservative as possible in the financial analysis, we took into account a contact with a physician and the performance of an endoscopy for each nonresponding patient and also for dropouts. This should minimize the above-mentioned bias. Bearing in mind these limitations, empirical treatment nevertheless proved to be cost-effective in the management of GERD patients. Another possible drawback of the study is that patients with reflux esophagitis did not undergo a second endoscopy to check for healing of mucosal lesions. In clinical practice, however, healing of esophagitis is usually not confirmed by means of endoscopy, and symptom resolution can be considered a good guide to healing of lesions. Thus, in our opinion, this approach renders the results of the study more easily translatable to everyday clinical practice. Finally, the cost of esomeprazole in other countries may be higher than the cost reported in this study. However, even a simulation that takes into account a cost of 3.26 euros per 40-mg esomeprazole tablet (approximately 4.50 USD) and keeps unaltered the cost of endoscopy and visits still results in saving 15.11 euros per patient treated (20.85 USD).

In conclusion, this study allowed us to confirm both the short- and long-term efficacy of esomeprazole treatment in a large population of patients with GERD and typical symptoms without alarm features. The use of endoscopy for allocating patients to treatment did not add value to the outcome of treatment, did not influence patient quality of life, and was not financially favorable compared

with an empirical approach. These results should be taken into account in the management of GERD patients in clinical practice.

## APPENDIX

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## STUDY HIGHLIGHTS

### What Is Current Knowledge

- Proton pump inhibitors provide relief of symptoms and healing of mucosal damage in the majority of patients with gastroesophageal reflux disease (GERD).
- Current guidelines suggest treating patients with typical GERD symptoms and without alarm features empirically.
- There is little evidence supporting the use of empirical treatment *versus* endoscopy-based treatment.

### What Is New Here

- In this study, we confirmed both the short- and long-term efficacy of esomeprazole treatment in a large population of patients with GERD and typical symptoms without alarm features.
- The use of endoscopy for allocating patients to treatment did not add value to the outcome of treatment, did not influence patient quality of life, and was not financially favorable compared with an empirical approach.
- On these bases, this study provides us with sound evidence supporting the use of empirical treatment for patients with GERD and no alarm symptoms.

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## CONFLICT OF INTEREST

**Guarantor of the article:** Prof. Vincenzo Savarino, M.D.

**Specific author contributions:** Vincenzo Savarino was involved in the study design and was responsible for coordination and performance of the studies, subject recruitment, and drafting of the manuscript. Edoardo G. Giannini was involved in the study design, data and statistical analysis, data interpretation, and drafting of the manuscript. Pietro Dulbecco and Patrizia Zentilin were involved in the study performance, subject recruitment, and data analysis. Sergio Vigneri assisted with the study concept and drafting of the manuscript. Pamela Scarlata was involved with the drafting of the manuscript. All authors approved the final draft submitted.

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