

Effect of Esomeprazole 40 mg Once or Twice Daily on Asthma

A Randomized, Placebo-controlled Study

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Rationale: Gastroesophageal reflux disease (GERD) is common among patients with asthma; however, studies investigating the effect of proton pump inhibitors on asthma outcomes report conflicting results.

Objectives: To investigate the effect of esomeprazole 40 mg once or twice daily on asthma outcomes in patients with concomitant symptoms of GERD.

Methods: This 26-week, randomized, double-blind, placebo-controlled study (NCT00317044) included adult patients (18–70 yr) with moderate-to-severe asthma and symptomatic GERD. The change in morning peak expiratory flow (primary variable), evening peak expiratory flow, FEV₁, asthma symptoms, Asthma Quality of Life Questionnaire, Reflux Disease Questionnaire, and tolerability were assessed.

Measurements and Main Results: A total of 961 patients were randomized and 828 completed the study. Relative to baseline, improvement in morning peak expiratory flow was observed for both esomeprazole 40 mg once daily (+3.5 L/min; 95% CI, –3.2 to 10.2) and 40 mg twice daily (+5.5 L/min; 95% CI, –1.2 to 12.2), although no statistically significant between-treatment differences were apparent. At treatment end, both doses of esomeprazole significantly improved FEV₁ versus placebo (+0.09 L and +0.12 L; $P = 0.0039$ and $P < 0.0001$, respectively). However, only esomeprazole 40 mg twice daily demonstrated a significant improvement when FEV₁ was calculated over the entire 26-week period (+0.07 L; $P = 0.0042$). Significant improvements in Asthma Quality of Life Questionnaire total score were demonstrated for both esomeprazole doses compared with placebo (+0.28 and +0.41; $P = 0.0006$ and $P < 0.0001$, respectively).

Conclusions: Esomeprazole may improve pulmonary function and asthma-related quality of life. However, the improvements were minor and of small clinical significance.

Clinical trial registered with www.clinicaltrials.gov (NCT00317044).

Keywords: asthma; gastroesophageal reflux disease; proton pump inhibitor; pulmonary function; asthma-related quality of life

Gastroesophageal reflux disease (GERD) is common among patients with asthma, with estimates of GERD prevalence ranging between 35 and 82% (1–4), which is substantially higher than the prevalence of GERD observed in the general population (10–20%) (5). It has been postulated that GERD may be a trigger for asthma (6). Suggested mechanisms by which esophageal is more accurate than gastric reflux could potentially trigger asthma include a vagally mediated esophagobronchial reflex and microaspiration of gastric contents (7).

Proton pump inhibitors (PPIs) are the most effective available therapy for GERD (8), and could be expected to improve asthma outcomes in those with concomitant reflux symptoms.

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Gastroesophageal reflux disease (GERD) is common among patients with asthma and has been postulated as a trigger for respiratory symptoms. Proton pump inhibitors (PPIs) such as esomeprazole are the most effective available therapy for GERD and could be expected to improve asthma outcomes; however, studies to date report conflicting results.

What This Study Adds to the Field

We demonstrate that esomeprazole treatment may improve FEV₁ and asthma-related quality of life in patients with moderate-to-severe asthma and symptomatic GERD. However, the improvements were minor and other variables did not improve. Thus, treatment with PPIs does not seem to be a major means of controlling asthma in patients with concomitant GERD.

However, a meta-analysis of the effectiveness of GERD treatment in patients with asthma found that improvements in asthma outcomes were inconclusive (9). More recently, a large study in patients with asthma who had both GERD and nocturnal respiratory symptoms demonstrated that esomeprazole, administered at a dose of 40 mg twice daily, significantly improved peak expiratory flow (PEF), suggesting that this patient subpopulation might benefit from PPI therapy (10).

In the management of GERD-related asthma, high doses of PPIs are most commonly recommended (11, 12), although to our knowledge there are no studies to substantiate this practice. The aim of the current study, therefore, was to determine the efficacy of esomeprazole, administered at a dose of 40 mg once daily or 40 mg twice daily for 26 weeks, in terms of improving asthma outcomes in patients with moderate-to-severe asthma and symptomatic GERD. Some of the results of this study have been previously reported in the form of abstracts (13, 14).

METHODS

Patients

Men and women (aged 18–70 yr) with a clinical diagnosis of asthma of 6 months' duration or longer according to the American Thoracic Society definition (15), were eligible for study entry. In addition, patients had to demonstrate FEV₁ reversibility of greater than or equal to 12% (and ≥ 0.20 L) after inhalation of a short-acting β_2 -agonist (terbutaline or albuterol), and be receiving daily treatment with an inhaled corticosteroid (ICS) and long-acting β_2 -agonist (LABA) for 3 months or more. Patients also had to have experienced one or more clinically important asthma exacerbation in the previous 12 months. Further inclusion criteria included a 3-month or longer history of one or more of the following symptoms of GERD: a burning feeling behind

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the breastbone and/or pain behind the breastbone (heartburn) and/or an acid taste in the mouth (acid regurgitation), of at least moderate severity and with a frequency of 2 days or longer during the 7 days before the 2-week run-in period (as determined by the validated Reflux Disease Questionnaire [RDQ] [16]), or a documented history of abnormal esophageal 24-hour pH monitoring within 3 years. To be eligible for randomization, patients also had to meet the following criteria on completion of a 2-week run-in period (thereby confirming the diagnosis of moderate-to-severe asthma): mean morning PEF (mPEF) of 50 to 85% of post-bronchodilator PEF (measured at screening visit) during the last 7 days of the run-in period; total asthma symptom score of 1 or greater (nighttime plus daytime) on 4 or more of the last 7 days of the run-in period (score range 0–3, where higher scores = more severe symptoms); and 1 or more symptoms of GERD, as assessed using the RDQ, with at least moderate severity on 2 or more of the last 7 days of the run-in period.

Exclusion criteria included the following: any significant disease or disorder that may influence results or a patient's ability to participate in the study; the presence of alarm symptoms (unintentional weight loss, hematemesis, jaundice, dysphagia, serious or malignant disease); history of smoking 20 or more cigarettes per day for 10 years (≥ 10 pack-years); use of oral, rectal, or parenteral corticosteroids within 30 days before the 2-week run-in period; uninvestigated GERD symptoms within the previous year in patients older than 50 years of age; previous esophageal or gastric surgery; endoscopy-verified reflux esophagitis 16 weeks or less before run-in period; presence of Barrett esophagus with associated dysplasia; use of antacids with an acid-binding capacity of greater than 100 mmol HCl per day during the run-in period; women who were pregnant or breastfeeding, or those of childbearing age who were not using an acceptable form of contraception; and known hypersensitivity to PPIs.

Study Design

This was a 26-week, randomized, double-blind, parallel-group, placebo-controlled study (clinicaltrials.gov identifier: NCT00317044; AstraZeneca study code: D9618C00001) conducted at 155 sites across 13 countries (Argentina, Bulgaria, Canada, Czech Republic, France, Germany, Hungary, Italy, Mexico, Poland, Portugal, Slovakia, and the United States). The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and relevant regulatory requirements, with approval from local ethics committees.

The study design is depicted in Figure 1. All patients provided written, informed consent at the enrollment visit (visit 1), which occurred 7 to 3 days before the start of run-in (visit 2). In order not to affect the FEV₁ reversibility test at visit 2, patients also received information regarding withdrawal of LABAs during the 48 hours before the lung function measurements. Patients who were using inhaled ICS and LABA in the same device were required to change to the inhaled ICS monoproduct at the corresponding dose during this time period. Patients then continued with their normal asthma medication from visit 2 and throughout the study treatment period. During the 2-week run-in period, patients were required to have symptoms of asthma and of GERD, as described above, and no study medication, except for rescue medication (antacids, supplied locally in each country), was allowed. At visit 3 (baseline), eligible patients were

randomized to receive esomeprazole 40 mg once daily or 40 mg twice daily, or matching placebo, for 26 weeks. Study medication was to be taken 30 minutes before breakfast and dinner, and rescue medication was provided for relief of breakthrough GERD symptoms.

Assessments

Self-reported asthma symptoms, PEF measurements, and use of rescue bronchodilators were recorded throughout treatment using daily diaries, whereas spirometry was performed during clinic visits at baseline (visit 3) and at weeks 4, 8, 17, and 26. The effects of treatment on asthma-related quality of life (QOL) were evaluated at baseline and weeks 8 and 26 using the standardized version of the Asthma Quality of Life Questionnaire (AQLQ), where lower scores represent greater QOL impairment for the AQLQ domains (activity limitations, symptoms, emotional function, and environmental stimuli) (17). GERD symptoms were evaluated at the same time points using the RDQ, where higher scores indicate more frequent and/or severe symptoms for the RDQ domains (heartburn, acid regurgitation, and dyspepsia).

The primary end point was the change from baseline in mPEF during the 26-week treatment period. Secondary end points included: change in evening PEF (ePEF); change in FEV₁; change in asthma symptom score (total, morning, and evening) and use of rescue bronchodilators; percentage of asthma symptom-free days; time to first asthma exacerbation and number of severe asthma exacerbations; and change in AQLQ and RDQ scores. Tolerability was evaluated through assessment of adverse events (AEs), laboratory tests, and vital signs.

Statistical Analyses

Assuming a standard deviation of 40 L/min for the change in mPEF from baseline to end of treatment, 338 patients per group were needed to have 90% power to detect a difference between groups assuming a true mean difference of 10 L/min. Thus, approximately 1,015 patients were to be randomized.

The intent-to-treat population (all randomized patients with available efficacy data) was used in the efficacy analyses. Change from baseline in asthma outcomes (mPEF, ePEF, FEV₁, asthma symptom score, and AQLQ domain and total scores) and GERD symptoms (RDQ) were analyzed with analysis of covariance, using baseline as a covariate and treatment and country as factors. Treatment differences were estimated from this model and 95% confidence intervals (CIs) were calculated. In terms of asthma outcomes, changes from the average value during the last 7 days of the run-in period to the average during the entire treatment period were compared between treatment groups, with the exception of AQLQ and RDQ, wherein the change from baseline (visit 3) to the end of treatment was compared between treatments, and in FEV₁, wherein the change from baseline to the mean value measured during the visits 4 through 7 and to the end of treatment (*post hoc*) was compared between treatments.

Time to first severe asthma exacerbation was compared between treatment groups using a Cox proportional hazards model, stratified by country and with treatment as a factor. The number of severe asthma exacerbations was compared between treatments using a Poisson regression model, with treatment and country as factors and time in study as an offset variable.

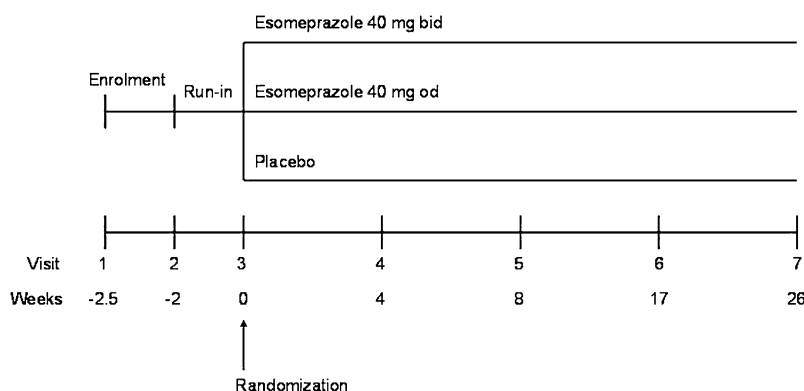


Figure 1. Study design. bid = twice daily; od = once daily.

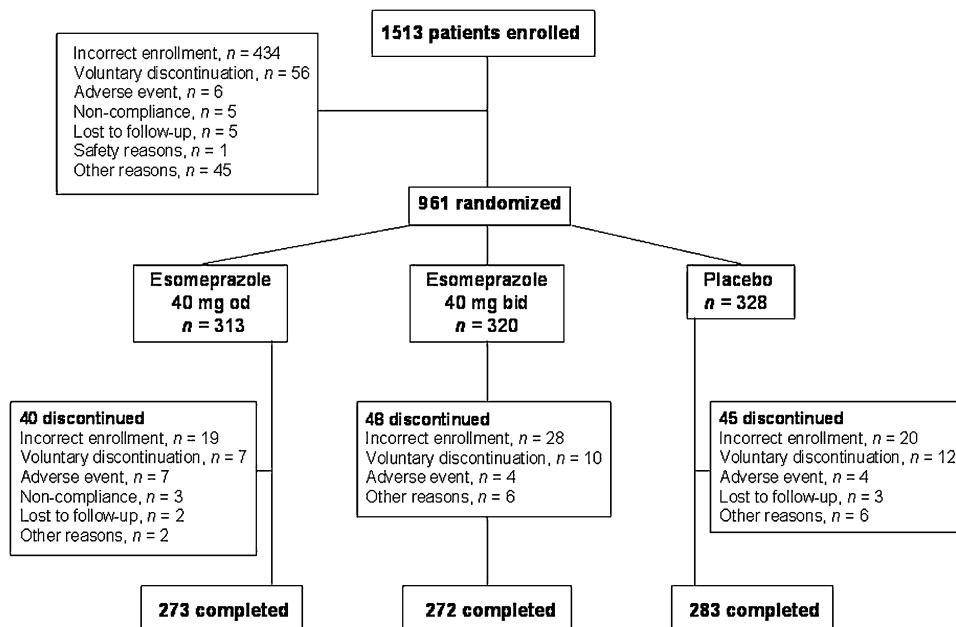


Figure 2. Flow of patients through the study.

All tests were two-sided and *P* values less than or equal to 0.05 were considered statistically significant.

RESULTS

Overall, 1,513 patients were enrolled in the study, of whom 961 continued to meet the study inclusion criteria and were randomized on completion of the run-in period; 828 patients completed the study (Figure 2). Patient demographic and baseline characteristics were similar between the treatment groups (Table 1).

Asthma Outcomes

Compared with baseline, the mean improvement in mPEF during the 26-week treatment period was higher for esomeprazole 40 mg once daily and 40 mg twice daily compared with placebo (mean treatment differences of +3.5 L/min [95% CI, −3.2 to 10.2] and +5.5 L/min [95% CI, −1.2 to 12.2], respectively); however, no statistically significant between-

treatment differences were apparent (Figure 3). Similarly, although all treatment groups demonstrated a mean improvement in ePEF (Figure 3), between-treatment differences relative to placebo were not statistically significant.

Both doses of esomeprazole demonstrated an improvement in FEV₁ throughout the treatment period, relative to placebo (Figure 4). When change from baseline to end of treatment was analyzed, improvements in FEV₁ were significantly greater with esomeprazole 40 mg once daily (+0.09 L; 95% CI, 0.03–0.15; *P* = 0.0039) and esomeprazole 40 mg twice daily (+0.12 L; 95% CI, 0.06–0.18; *P* < 0.0001) versus placebo. When mean improvement in FEV₁ was calculated for the entire 26-week treatment period, only esomeprazole 40 mg twice daily was significantly superior to placebo (difference of +0.07 L; 95% CI, 0.02–0.12; *P* < 0.0042).

Throughout the study period, the adjusted mean change from baseline in AQLQ total score increased for all treatment groups; after 8 weeks and at the end of the 26-week treatment period AQLQ total score increased from 0.6 to 0.8 for

TABLE 1. PATIENT CHARACTERISTICS AT BASELINE

	Esomeprazole		
	40 mg once daily (n = 313)	40 mg twice daily (n = 319)	Placebo (n = 328)
Women, n (%)	240 (77)	240 (75)	247 (79)
Age, yr	45 (19–70)	44 (18–69)	45 (18–70)
Age at asthma diagnosis, yr	14 (0.5–68)	13 (0.6–62)	14 (0.5–62)
Smoking history, pack-years	4 (1–10)	5 (0–9)	5 (0–20)
Spirometry-based variables			
FEV ₁ , L	2.0 (0.7–4.3)	2.1 (0.6–4.4)	2.0 (0.6–4.8)
FEV ₁ , % predicted normal	66.0 (24.3–137.7)	65.8 (24.3–97.2)	66.5 (24.3–113.4)
mPEF, L/min	288 (100–619)	288 (113–610)	286 (103–684)
AQLQ total score	3.8 (1.5–6.3)	3.9 (1.7–6.8)	4.0 (1.6–6.6)
RDQ item score*			
Heartburn	4.1 (1–6)	4.0 (1–6)	4.0 (1–6)
Acid regurgitation	4.2 (1–6)	4.1 (1–6)	4.1 (1–6)
Dyspepsia	3.8 (1–6)	3.8 (1–6)	3.7 (1–6)

Definition of abbreviations: AQLQ = Asthma Quality of Life Questionnaire; mPEF = morning peak expiratory flow; RDQ = Reflux Disease Questionnaire.

Values are mean (range), unless otherwise specified.

* Higher scores indicate more frequent and/or severe symptoms.

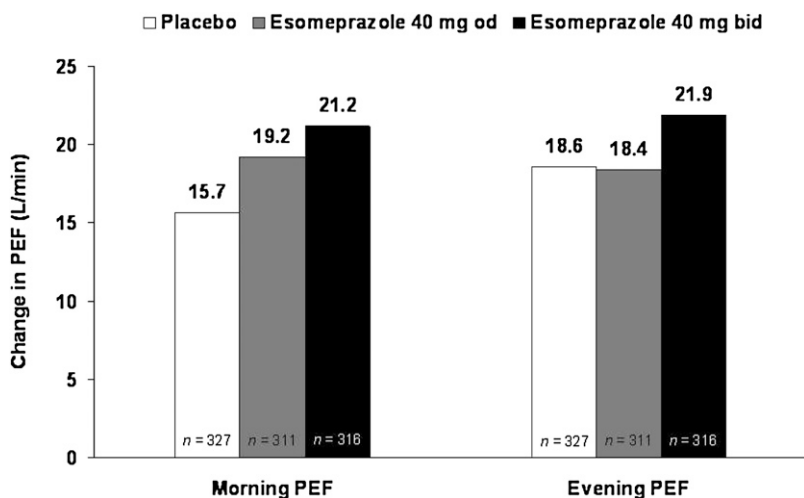


Figure 3. Adjusted mean change from baseline in peak expiratory flow (PEF) during the entire 26-week treatment period.

esomeprazole 40 mg once daily, from 0.7 to 1.0 for esomeprazole 40 mg twice daily, and from 0.5 to 0.6 for placebo. Relative to baseline, both doses of esomeprazole were associated with statistically significant improvements in the AQLQ total score compared with placebo at the end of the 26-week treatment period (Figure 5). Estimated mean differences relative to placebo were +0.28 (95% CI, 0.12–0.44; $P < 0.001$) and +0.41 (95% CI, 0.25–0.57; $P < 0.0001$), respectively, for the esomeprazole 40 mg once daily and 40 mg twice daily doses. Overall, significantly more patients (Chi-square test) receiving esomeprazole 40 mg once daily ($n = 173$, 61%; $P = 0.016$) and 40 mg twice daily ($n = 176$, 62%; $P = 0.001$) had a 0.5 or greater improvement (determined to be the minimal important difference) in AQLQ total score from baseline to treatment end compared with placebo ($n = 151$; 51%). The improvements in AQLQ total score with esomeprazole were paralleled by significant improvements in individual domain scores for activity limitations, symptoms, emotional function, and environmental stimuli (all $P < 0.05$ for both esomeprazole doses vs. placebo).

Severe asthma exacerbation was experienced by 34 (10%), 32 (10%), and 24 (7.5%) patients in the placebo, esomeprazole once daily, and esomeprazole twice daily groups, respectively. With this respect there were no statistically significant differences between the groups, nor were there differences between the groups regarding the time to first severe asthma exacerbation.

There were no significant differences between esomeprazole and placebo groups regarding the use of rescue bronchodilators or the percentage of asthma symptom-free days. Similarly, change in asthma symptom scores was not significantly different between treatment groups. There was a significant difference in morning asthma symptom score between esomeprazole doses ($P = 0.045$); however, this result was not considered clinically relevant.

GERD Outcomes

Mean RDQ heartburn, acid regurgitation, and dyspepsia scores were decreased in all treatment groups by the end of the 26-week treatment period; both esomeprazole 40 mg once daily and 40 mg twice daily demonstrated statistically significant differences in all RDQ domain scores from baseline to treatment end compared with placebo (all $P < 0.0001$) (Figure 6). The difference in treatment outcomes between esomeprazole doses was not significantly different.

The improvement in GERD symptoms was paralleled by a significant reduction in use of rescue antacids among esomeprazole recipients ($P < 0.05$ for both esomeprazole doses vs. placebo).

Tolerability

Overall, there were no differences between treatment groups in the proportion of patients experiencing AEs, most of which were of mild intensity, did not necessitate treatment discontinuation, and were not deemed to be treatment-related by the investigator. The most commonly reported AEs are shown in Table 2. A total of 20 serious AEs were reported by 17 patients (1.8%) during the study (esomeprazole 40 mg once daily, $n = 5$; esomeprazole 40 mg twice daily, $n = 7$; placebo, $n = 5$). None of these events was considered by the investigator to be causally related to study medication. There were no safety concerns during the study.

DISCUSSION

The purpose of this study was to determine the efficacy of long-term esomeprazole treatment for the improvement of asthma outcomes in patients with moderate-to-severe asthma and symptomatic GERD. We found no improvement in most of the outcome variables, including our primary end point (mPEF). However, treatment with esomeprazole was associated with an improvement in FEV₁ and asthma-related QOL, as assessed

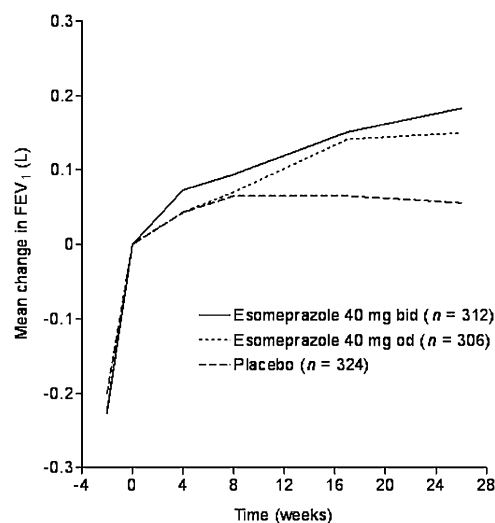


Figure 4. Mean change from baseline in the FEV₁ during the 26-week treatment period.

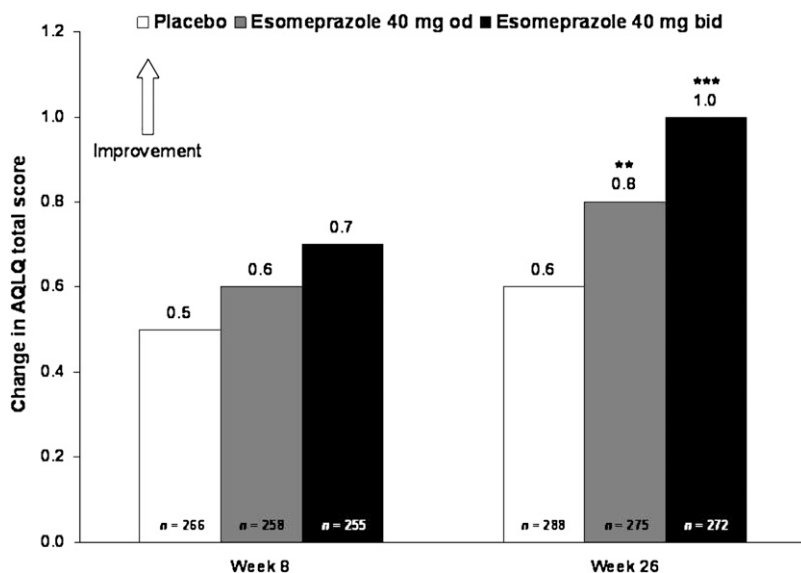


Figure 5. Adjusted mean change from baseline in Asthma Quality of Life Questionnaire (AQLQ) total score, after 8 weeks, and at the end of the 26-week treatment period. ** $P < 0.001$; *** $P < 0.0001$ versus placebo.

using the AQLQ. Both of these outcomes demonstrated continuous improvement throughout the 26-week treatment period. Both esomeprazole doses significantly reduced GERD symptoms and were well tolerated.

As far as we know, the current study is the first major study suggesting that PPI treatment may have some positive effect on FEV_1 . In this respect our study is a continuum to the several previous studies in which the improved variable (if present) has varied from study to study (3, 10, 11, 18–23). This may be due to different study designs and populations, but small improvements in different variables could also be due to chance. We found no improvement with esomeprazole in mPEF, which was unexpected, as in our previous study esomeprazole improved mPEF among patients with asthma with symptomatic GERD and nocturnal asthma symptoms, and the improvement was most pronounced in those patients who required LABAs in addition to ICS (10). On the other hand, the findings of the current study are in accordance with a recent study by Mastronarde and colleagues, who reported that treatment with PPIs did not improve asthma control in patients with unstable asthma

and asymptomatic gastroesophageal reflux (23). Should GERD be a major trigger for asthma, then one would expect to see consistent improvement in asthma outcomes in different studies. As this is not the case, it appears that acid reflux does not seem to be a major trigger for asthma, and PPI treatment does not seem to be a major means of controlling asthma among patients with concomitant GERD, which was also concluded in a recent Cochrane review (9).

Although the results of the current study were mostly negative, we do not regard our study as a conclusive negative study as we found statistically significant improvements in FEV_1 and AQLQ. Recently, DiMango and coworkers reported that patients who have asthma with GERD have lower asthma-related QOL than those without (24). This is in keeping with our finding that, compared with placebo, esomeprazole improved AQLQ to a statistically significant extent. Also in the study by Littner and colleagues total AQLQ score was found to improve with PPI therapy among those patients who had asthma with GERD who in addition to ICS required at least one additional long-term asthma medication to control their

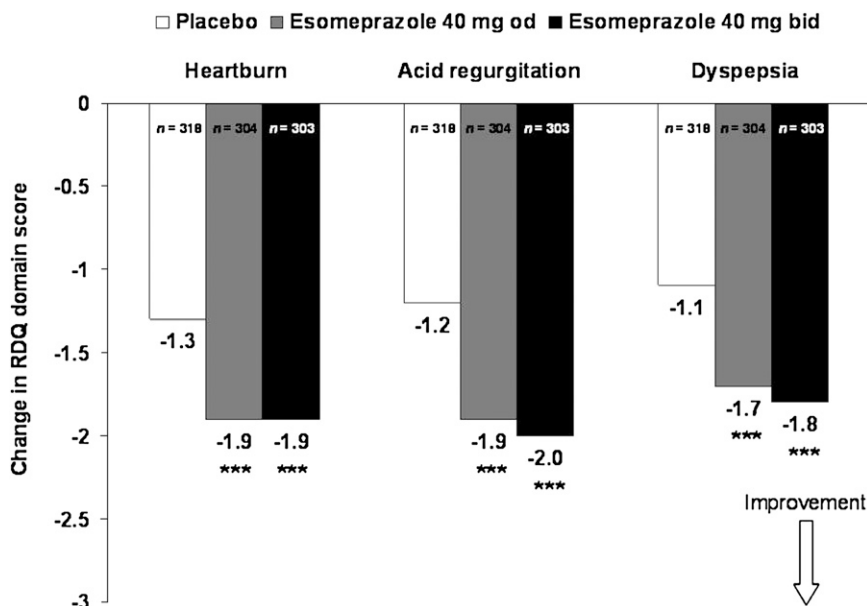


Figure 6. Adjusted mean change from baseline in Reflux Disease Questionnaire (RDQ) domain scores at the end of the 26-week treatment period. *** $P < 0.0001$ versus placebo.

TABLE 2. NUMBER (%) OF PATIENTS WITH THE MOST COMMONLY REPORTED ADVERSE EVENTS

	Esomeprazole		Placebo (n = 328)
	40 mg once daily (n = 313)	40 mg twice daily (n = 319)	
Any adverse event	135 (43.1)	115 (36.1)	144 (43.9)
Upper respiratory tract infection	28 (9.0)	26 (8.2)	37 (11.3)
Bronchitis	16 (5.1)	11 (3.5)	18 (5.5)
Nasopharyngitis	11 (3.5)	5 (1.6)	16 (4.9)
Pharyngitis	11 (3.5)	9 (2.8)	7 (2.1)
Asthma	6 (1.9)	4 (1.3)	10 (3.1)
Headache	5 (1.6)	8 (2.5)	6 (1.8)
Influenza	4 (1.3)	8 (2.5)	4 (1.2)
Sinusitis	9 (2.9)	2 (0.6)	5 (1.5)
Respiratory tract infection	8 (2.6)	3 (0.9)	3 (0.9)
Viral infection	7 (2.2)	5 (1.6)	2 (0.6)
Hypertension	7 (2.2)	4 (1.3)	2 (0.6)

Events reported by $\geq 2\%$ of patients in any treatment group.

asthma (21). In contrast to the latter study, the number of asthma exacerbations was not diminished in the current study, yet another inconsistency.

Although we found esomeprazole to improve FEV₁ and AQLQ, the improvements were minor and of small clinical significance. Again, this may be due to the fact that GERD may not be a major trigger for asthma. On the other hand, there is evidence that patients with more severe GERD might be those who, in terms of asthma outcomes, will benefit most from PPI treatment (11, 25). For safety reasons patients with severe GERD (i.e., the patients who might benefit most from PPI treatment) were excluded from this study, as well as from all other major studies. This might also partly explain why only modest results have been achieved. Another possible explanation might be that PPIs do not stop reflux; rather, they make it nonacidic or weakly acidic, which has been shown to produce pulmonary symptoms (26). Moreover, pH monitoring was not required to confirm the presence of GERD in this study. It is possible, therefore, that not all patients actually had GERD although they did have heartburn, and in the absence of GERD one would not expect a PPI to work properly. However, we do not consider this to be a major source of error in this study.

In the management of GERD-related asthma, high doses of PPIs are most commonly recommended (11, 12). To our knowledge, this is the first major study to compare different doses of any PPI in the management of GERD-related asthma. We show here that both once- and twice-daily dosing of esomeprazole 40 mg were of comparable efficacy. This, and lack of any major improvement, questions previous recommendations and suggests that a standard dose of esomeprazole might well be used in the management of GERD-related asthma. Actually, our results challenge the concept of treating GERD-related asthma with PPIs at all. However, as at least one-third of patients with asthma have GERD (2), it is important to ask patients with asthma about their GERD symptoms, and if present they should be treated adequately. Sometimes, an improvement in asthma may also be achieved. We show here that both FEV₁ and AQLQ continued to improve throughout the current study, a finding that suggest that GERD treatment with a PPI needs to be substantially long before its possible effect on concomitant asthma can be evaluated.

To conclude, the findings of the current study suggest that acid-suppressive therapy with a PPI is not a major means of controlling asthma among patients with concomitant GERD.

However, as we found statistically significant improvements in FEV₁ and AQLQ, future studies are warranted. It would be optimal if these studies could be performed with patients with asthma who present with more severe GERD.

Conflict of Interest Statement: T.O.K. received \$5,001–\$10,000 from AstraZeneca in advisory board fees; \$5,001–\$10,000 from AstraZeneca, \$5,001–\$10,000 from Boehringer Ingelheim, \$1,001–\$5,000 from Pfizer, and \$5,001–\$10,000 from GlaxoSmithKline in promotional lecture fees; and \$5,001–\$10,000 from AstraZeneca in institutional grant/research support. O.J. is deceased and is unable to provide a financial disclosure statement. O.B. is a full-time employee of AstraZeneca. T.L. is a full-time employee of AstraZeneca and holds \$5,001–\$10,000 in stock ownership or options in AstraZeneca.

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