Efficacy of Esomeprazole for Treatment of Poorly Controlled Asthma

The American Lung Association Asthma Clinical Research Centers*

ABSTRACT

BACKGROUND

Gastroesophageal reflux is common among patients with asthma but often causes mild or no symptoms. It is not known whether treatment of gastroesophageal reflux with proton-pump inhibitors in patients who have poorly controlled asthma without symptoms of gastroesophageal reflux can substantially improve asthma control.

METHODS

In a parallel-group, double-blind trial, we randomly assigned 412 participants with inadequately controlled asthma, despite treatment with inhaled corticosteroids, and with minimal or no symptoms of gastroesophageal reflux to receive either 40 mg of esomeprazole twice a day or matching placebo. Participants were followed for 24 weeks with the use of daily asthma diaries, spirometry performed once every 4 weeks, and questionnaires that asked about asthma symptoms. We used ambulatory pH monitoring to ascertain the presence or absence of gastroesophageal reflux in the participants. The primary outcome was the rate of episodes of poor asthma control, as assessed on the basis of entries in asthma diaries.

RESULTS

Episodes of poor asthma control occurred with similar frequency in the placebo and esomeprazole groups (2.3 and 2.5 events per person-year, respectively; P=0.66). There was no treatment effect with respect to individual components of the episodes of poor asthma control or with respect to secondary outcomes, including pulmonary function, airway reactivity, asthma control, symptom scores, nocturnal awakening, or quality of life. The presence of gastroesophageal reflux, which was documented by pH monitoring in 40% of participants with minimal or no symptoms, did not identify a subgroup of patients that benefited from treatment with proton-pump inhibitors. There were fewer serious adverse events among patients receiving esomeprazole than among those receiving placebo (11 vs. 17).

CONCLUSIONS

Despite a high prevalence of asymptomatic gastroesophageal reflux among patients with poorly controlled asthma, treatment with proton-pump inhibitors does not improve asthma control. Asymptomatic gastroesophageal reflux is not a likely cause of poorly controlled asthma. (ClinicalTrials.gov number, NCT00069823.)

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GASTROESOPHAGEAL REFLUX AND ASTHma, both of which are common conditions, often coexist in the same patient. Persons with asthma are particularly prone to asymptomatic gastroesophageal reflux. Esophageal pH-monitoring studies have shown that 32 to 84% of persons with asthma have abnormal acid reflux,[1-5] and about half of patients with asthma who have reflux have no symptoms.[3,6-8] However, the role of gastroesophageal reflux in the development or persistence of asthma symptoms is not known. Symptoms of asthma — cough and chest discomfort — may overlap with those of gastroesophageal reflux, making it difficult to distinguish between the two conditions.[9] Moreover, the causal relationship between asthma and gastroesophageal reflux is complex. Acid reflux causes bronchoconstriction through microaspiration into the airways, as well as through reflex-mediated effects of acid on the esophagus or upper airway.[10-18] Conversely, asthma-related bronchoconstriction can induce acid reflux. Descent of the diaphragm with hyperinflation increases the pressure gradient between the abdomen and thorax and may cause the lower esophageal sphincter to herniate into the chest, where its barrier function is diminished.[19,20] This process may be exacerbated by the accentuated negative inspiratory pleural pressure in acute asthma, which opposes the tone of the lower esophageal sphincter. Furthermore, beta-agonists and methylxanthine bronchodilators may decrease the tone of the lower esophageal sphincter, but it has been difficult to show that these agents actually worsen reflux.[21]

Proton-pump inhibitors are effective in suppressing the production of gastric acid and reducing symptoms of gastroesophageal reflux, whether or not asthma is present.[22,23] Previous trials have had conflicting results regarding the beneficial effects of treatment with proton-pump inhibitors in patients with asthma who have frequent symptoms of gastroesophageal reflux disease.[23,24] Whether proton-pump inhibitors improve asthma control in patients with minimal or no symptoms of gastroesophageal reflux is unknown, and whether objective measurement of acid reflux can be used to tailor treatment with proton-pump inhibitors to individual patients has not been established.[25,26] Current guidelines recommend that physicians consider evaluating patients who have poorly controlled asthma, especially those with nighttime symptoms, for gastroesophageal reflux disease, even in the absence of suggestive symptoms of the disease. If gastroesophageal reflux is present, treatment recommendations include the use of a proton-pump inhibitor.[27] However, patients with asthma who are receiving treatment for gastroesophageal reflux incur substantially higher diagnostic and treatment costs than do patients with asthma of similar severity who are not receiving treatment for this diagnosis.[28]

We compared esomeprazole with placebo in patients with poorly controlled asthma. Our primary objective was to determine whether acid-suppression therapy would improve asthma symptoms. A secondary objective was to determine whether ambulatory esophageal pH monitoring would identify patients with minimal or no symptoms of gastroesophageal reflux who might have a response to treatment.

METHODS

PARTICIPANT SELECTION

We conducted a randomized, placebo-controlled, double-blind trial of esomeprazole (Nexium, AstraZeneca) in patients who had asthma that was inadequately controlled despite therapy with moderate or high doses of inhaled corticosteroids. Inclusion criteria were an age of 18 years or older; a diagnosis of asthma by a physician, with the diagnosis supported by either a positive methacholine challenge test or documentation of a 12% increase in the forced expiratory volume in 1 second (FEV_1) after use of a bronchodilator; at least 8 weeks of stable use of an inhaled corticosteroid at a dose equivalent to 400 μg of fluticasone per day or more[27]; and poor asthma control as defined by either a score on the Juniper Asthma Control Questionnaire (JACQ) of 1.5 or higher[29] (on a scale of 0 to 6, with lower scores indicating better control of symptoms and with 0.5 as the minimal clinically important difference between scores) or the occurrence of more than one acute episode of asthma requiring unscheduled medical care in the previous year. Participants were excluded if they had smoked cigarettes within the previous 6 months or had a history of 10 or more pack-years of smoking; had an FEV_1 of less than 50% of their predicted value[30]; had undergone surgery for reflux or peptic ulcer; had clinical indications for acid-suppression treatment (i.e., two or more epi-

sodes per week of heartburn requiring antacids); had used antireflux medication within the previous month; or were taking drugs that could interact with proton-pump inhibitors, such as theophylline, iron supplements, warfarin, antifungal drugs, or digitalis. Participants were also excluded if they were pregnant, could not tolerate proton-pump inhibitors, or had any serious illness that would interfere with participation in the trial. The study was approved by the institutional review board at each participating center, and all participants provided written informed consent.

STUDY DESIGN

The study was conducted at 19 clinical centers from October 2004 through early May 2008. Data were analyzed at the coordinating center at Johns Hopkins University. The study was designed as a two-group, parallel-design, randomized clinical trial to test the hypothesis that esomeprazole was superior to placebo in improving asthma control. Participants who met the eligibility criteria were enrolled in a 2- to 8-week run-in period during which time they completed baseline daily asthma diaries and underwent pH testing. Participants were randomly assigned in a 1:1 ratio to receive either 40 mg of esomeprazole twice daily or a similar-appearing placebo. Participants and study staff were unaware of the group assignments. The randomization schedule was stratified according to clinic site with the use of a permuted block design with concealed allocation. After randomization, participants returned to the clinic for assessments of outcome measures every 4 weeks for 24 weeks.

OUTCOME MEASURES

For the duration of the trial, participants maintained diaries to record morning peak expiratory flow, asthma symptoms, nocturnal awakening, and use of beta-agonists. The primary outcome measure was the rate of episodes of poor asthma control. Such episodes were defined by a decrease of 30% or more in the morning peak expiratory flow rate on 2 consecutive days, as compared with the patient's best rate during the run-in period; an urgent visit, defined as an unscheduled health care visit for asthma symptoms; or the need for a course of oral prednisone for treatment of asthma. Use of a beta-agonist was not included as a criterion in this definition because of the possibility that participants might use beta-agonists for treatment of symptoms related to gastroesophageal reflux. In a secondary analysis, we added to the above definition the use of beta-agonists for asthma symptoms (four or more inhalations in 1 day at a dose above the baseline dose).[31] The outcome measure we used — episodes of poor asthma control — incorporates key measures that are clinically relevant and are responsive to therapy such as inhaled corticosteroids. Other asthma symptoms recorded in daily diaries were considered to be secondary outcomes.

Secondary outcomes recorded at each visit were the results of spirometry before and after inhalation of 180 μg of albuterol,[32] the score on the JACQ,[29] the score on the Asthma Symptom Utility Index,[33] the score on the Mini Asthma Quality of Life Questionnaire (MiniAQLQ),[34] and the score on the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36).[35] Methacholine airway reactivity, expressed as the inhaled methacholine concentration causing a 20% reduction in FEV_1 (PC_{20}), was measured at baseline and at 24 weeks in participants with an FEV_1 that was 70% or more of their predicted value.[36]

The presence or absence of esophageal reflux was ascertained with the use of ambulatory pH monitoring.[37] Studies were reviewed for technical quality at a central reading center. To be considered technically satisfactory, a study had to have a total recording time of 16 hours or more and include at least one meal and 2 hours of monitoring while the patient was lying down. Reflux was considered to be present if the pH was less than 4.0 for more than 5.8% of the total time, more than 8.2% of the time the patient was upright, or more than 3.5% of the time the patient was lying down.[38] Symptoms of gastroesophageal reflux were assessed with the use of the Gastroesophageal Reflux Disease Symptom Assessment Scale (GSAS)–Distress Version, which measures both the number and the severity of symptoms.[39]

STUDY OVERSIGHT

The study was designed and supervised by the steering committee of the American Lung Association Asthma Clinical Research Centers, which approved the publication of the study. The data were collected at the clinical centers and were analyzed at the data coordinating center (see Appendix). The writing committee wrote the manu-

script and takes full responsibility for the accuracy and completeness of the article. Esomeprazole and matching placebo were donated by Astra-Zeneca, but AstraZeneca had no role in the design or conduct of the study or in the analysis or interpretation of the data. The American Lung Association Asthma Clinical Research Centers are not bound by any confidentiality agreement with respect to the study results.

STATISTICAL ANALYSIS

We calculated that with a sample size of 400 participants, the study would have 77 to 97% power, with a two-sided type I error rate of 5% and 10% loss of data, to show a relative difference of 33% in the proportion of participants having one or more episodes of poor asthma control, assuming a rate of 40 to 60% in the control group. The primary outcome was the rate of episodes of poor asthma control; by basing the power calculation on the proportion of participants in each group who had one or more events, rather than on the event rate, we obtained a conservative estimate of power. All analyses were performed according to treatment assignment, and all available data were included in the evaluations, regardless of whether or not they discontinued the assigned treatment (modified intention-to-treat analysis). Negative binomial regression models were used to evaluate differences in the rate of episodes of poor asthma control and in the rates of the individual components.[40] Linear regression techniques were used to evaluate the mean differences from baseline; robust variance estimates were calculated with generalized estimating equations.[41] Analyses of treatment-effect modification for key covariates such as pH-monitoring results, age, sex, race or ethnic group, asthma severity, GSAS distress score, and presence or absence of obesity; self-reported gastroesophageal reflux disease, sinusitis, or rhinitis; use of long-acting beta-agonists; and history of exposure to cigarette smoke were performed by creating an interaction term and evaluating the term's significance in a model with the main effects (study drug and covariate). The reported results were not adjusted for baseline covariates unless there was evidence of an imbalance across the treatment groups at baseline. P values of less than 0.05 (two-sided) were considered to indicate statistical significance. P values were not adjusted for multiple comparisons.
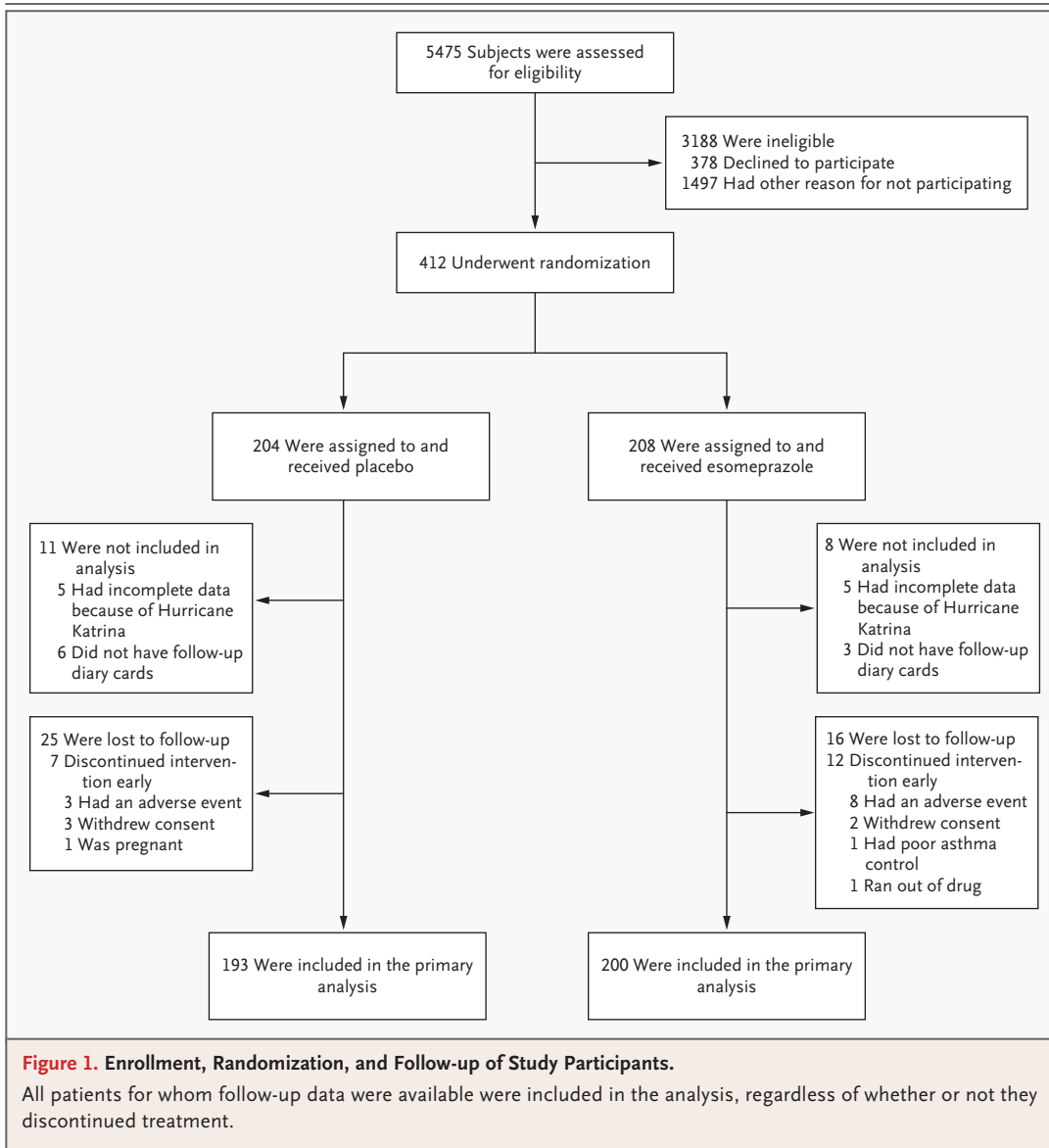
RESULTS

CHARACTERISTICS OF THE PARTICIPANTS

A total of 412 patients were randomly assigned to one of the two groups in the study (Fig. 1). Because of Hurricane Katrina, data from 10 patients in New Orleans were incomplete and were not included in the analysis. The majority of the patients were women, and most had lung function that was at the low end of the normal range and very poor asthma control, as evidenced by a mean JACQ score of 1.9.[29] Approximately 15% of the participants reported that they had a history of gastroesophageal reflux, but the mean symptom scores were low. Gastroesophageal reflux, as assessed by ambulatory pH monitoring, was present in 41% of the patients in the placebo group and 40% of the patients in the esomeprazole group. The asthma characteristics were similar in the two study groups (Table 1).

When we defined an adherent participant as one who took both doses of the drug or placebo on at least 80% of the days during the study period, the rate of adherence in the placebo group was similar to the rate in the esomeprazole group, as assessed by diary cards (86% and 84%, respectively; P=0.53) and as assessed by pill counts (82% in each group, P=0.91). Ninety-four percent of the participants in the placebo group and 91% of the participants in the esomeprazole group took one or more doses of the study drug on at least 80% of the days (P=0.21). Esomeprazole was generally very well tolerated, but a few more participants in the esomeprazole group than in the placebo group discontinued treatment because of adverse effects (nine vs. three participants). Few serious adverse events were reported in either the esomeprazole group or the placebo group (11 and 17 events, respectively, P=0.25); three hospitalizations for asthma exacerbations were reported in the esomeprazole group and four in the placebo group. One patient in the esomeprazole group died after surgery for a bronchial carcinoid that was discovered during the study (Table 2).

EPISODES OF POOR ASTHMA CONTROL

Overall, the participants had persistent, poorly controlled symptoms of asthma. Approximately 42% of the participants had an episode of poor asthma control according to the definition that did not include the use of beta-agonists as a cri-

Figure 1. Enrollment, Randomization, and Follow-up of Study Participants.

All patients for whom follow-up data were available were included in the analysis, regardless of whether or not they discontinued treatment.

terion, and 61% had an episode according to the definition that included the increased use of beta-agonists. Over the course of the 24 weeks of follow-up, about 18% of the patients required an urgent care visit or a course of prednisone. The annualized rates of episodes of poor asthma control and of the individual components (a fall in the peak expiratory flow rate, an urgent care visit, a course of corticosteroids, and increased use of beta-agonists) did not differ significantly between the treatment and placebo groups. Night awakening due to asthma occurred on one or more occasions in about half of the participants, and the

rate did not differ significantly between the two groups (Table 3).

SECONDARY OUTCOMES

Pulmonary function as measured by spirometry, bronchodilator response, peak expiratory flow rate, and airway reactivity did not change during the study and did not differ significantly between the two groups. Asthma symptoms, asthma control, and quality of life, as assessed by questionnaires, all improved slightly during the trial but did not differ significantly according to the group assignment. Gastroesophageal-reflux-symptom

Table 1. Baseline Characteristics of the Study Participants.*

Characteristic	Placebo (N=199)	Esomeprazole (N=203)
Age at randomization — yr	42±13	42±13
Male sex — %	28	36
Race or ethnic group — %†		
White	52	50
Black	37	39
Hispanic	9	9
Other	3	2
Former smoker — %	20	15
Body-mass index‡		
Mean	32±8	32±9
≥30 — %	54	50
Age at onset of asthma — yr	17±17	17±16
Use of inhaled short-acting beta–agonist for asthma ≥2 times/wk — %	83	79
Unscheduled health care visit for asthma in previous year — %	63	54
Use of corticosteroids for asthma — %		
Oral corticosteroids in previous year	52	48
Inhaled corticosteroids		
Daily use	100	100
Combination of fluticasone and salmeterol	75	79
Asthma scores§		
JACQ	1.9±0.8	1.8±0.8
ASUI	0.74±0.18	0.76±0.15
MiniAQLQ	4.7±1.2	4.7±1.2
SF-36 quality-of-life score¶		
Physical component	42±10	43±10
Mental component	49±10	50±11
Pulmonary function		
No. of participants with measurement	198	203
FEV$_1$		
Prebronchodilator — % of predicted value‖	78±15	76±16
Postbronchodilator — % increase from prebronchodilator value	10±10	11±16
FVC		
Prebronchodilator — % of predicted value‖	87±16	87±14
Postbronchodilator — % increase from prebronchodilator value	5±8	6±11
PC$_{20}$		
No. of participants with measurement	92	83
Mean — mg/ml	2.7±4.0	3.8±4.4
PC$_{20}$ contraindicated — no./total no. (%)	102/198 (52)	117/202 (58)

Characteristic	Placebo (N = 199)	Esomeprazole (N = 203)
pH monitoring		
No. of participants with data	151	153
Positive result — %	41	40
GSAS**		
No. of participants assessed	199	203
No. of symptoms	7±3	6±4
Distress score	0.60±0.46	0.51±0.47
Conditions other than asthma — %††		
No. of participants with data	199	203
Gastroesophageal reflux disease	19	10
Eczema	20	10
Sinusitis	43	34
Rhinitis	61	58
Food allergies	24	15
Allergies that worsen asthma	78	78

Table 1. (Continued.)

* Plus–minus values are means ±SD. MiniAQLQ denotes Mini Asthma Quality of Life Questionnaire, ASUI Asthma Symptom Utility Index, FEV_1 forced expiratory volume in 1 second, FVC forced vital capacity, GSAS Gastroesophageal Reflux Disease Symptom Assessment Scale, JACQ Juniper Asthma Control Questionnaire, PC_{20} the concentration of inhaled methacholine causing a 20% reduction in FEV_1, and SF-36 Medical Outcomes Study 36-Item Short-Form General Health Survey.
† Race or ethnic group was self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Scores on the JACQ range from 0 to 6, with lower scores indicating better asthma control and 0.5 as the minimal clinically important difference; scores on the ASUI range from 0 to 1, with higher scores indicating less severe asthma; scores on the MiniAQLQ range from 1 to 7, with higher scores indicating better quality of life and 0.5 as the minimal clinically important difference.
¶ Scores on the SF-36 range from 1 to 100, with higher scores indicating better quality of life and 5 as the minimal clinically important difference.
‖ Predicted values for FEV_1 and FVC are from Hankinson et al.[30]
** The number of symptoms on the GSAS ranges from 0 to 15. The distress score ranges from 0 to 3, with lower numbers indicating less distress.
†† These conditions were self-reported.

scores, which were, by design, low at baseline, showed small improvements during the study, but did not differ significantly according to the group assignment (Table 4).

SUBGROUP ANALYSES

We performed prespecified subgroup analyses to determine whether we could identify a subgroup that was likely to benefit from esomeprazole therapy. For all outcomes, there was no significant interaction between abnormal gastroesophageal reflux, as assessed by pH monitoring, and the group assignment, indicating that patients with documented gastroesophageal reflux did not have a response to treatment with proton-pump inhibitors that differed from the response of patients without documented reflux. Neither the body-mass index nor the presence or absence of night awakening identified a group of patients who had a response to proton-pump inhibitors. In addition, there was no interaction of treatment effect with age; race or ethnic group; sex; obesity; former smoking status; asthma control or severity scores; use of long-acting beta-agonists; self-reported sinusitis, rhinitis, or gastroesophageal reflux; or the GSAS distress score.

DISCUSSION

The purpose of this trial was to determine whether the use of a proton-pump inhibitor, esomeprazole, in doses large enough to suppress gastric

Table 2. Serious Adverse Events.

Event	Esomeprazole	Placebo
Asthma exacerbation requiring hospitalization	3	4
Hospitalization or emergency department visit for surgery, trauma, or other acute illness	6	10
Pneumonia	1	0
Death from complications after surgery for endobronchial tumor	1	0
Hospitalization for possible cardiac ischemia	0	2
Pregnancy*	0	1
Total	11	17

* Pregnancy was considered an adverse event requiring discontinuation because the drug is recommended for use during pregnancy only if clearly needed.

acid, would improve asthma control in patients with inadequately controlled asthma who did not have frequent symptoms of gastroesophageal reflux. We used a dose of esomeprazole that was higher than that typically used to treat symptomatic gastroesophageal reflux in order to increase our confidence that there was adequate suppression of gastric acid.[42] Moreover, we performed ambulatory esophageal pH-monitoring studies to establish whether persons with documented acid reflux might benefit more from therapy with a proton-pump inhibitor than persons without documented acid reflux. After following 402 patients for 6 months, we were not able to show any treatment benefit with respect to the primary outcome — the rate of episodes of poor asthma control — or with respect to secondary outcomes, including asthma symptoms, nocturnal awakening, quality of life, and lung function. Moreover, there was no significant difference in asthma-related outcomes between patients in whom reflux was documented and those in whom it was not.

A systematic review of 12 small trials concluded that, although most of the studies showed that asthma-related outcomes were better when the patients were treated with proton-pump inhibitors, some of the studies had design flaws and the studies did not show consistent improvement in the same asthma outcomes.[25] More recently, Littner and colleagues reported the results of a 6-month placebo-controlled trial involving 207 patients with moderate-to-severe asthma and definite symptoms of gastroesophageal reflux.[23] Treatment with 30 mg of lansoprazole twice daily did not improve the primary outcome of daily

asthma symptoms, but it did result in a reduction in exacerbations and an improvement in asthma-related quality of life. The reduction in exacerbations was greatest among patients taking more than one class of medication for control of asthma. Kiljander and colleagues[24] conducted a three-strata, 24-week, multicenter, international trial involving patients with asthma who had nocturnal asthma symptoms, symptoms of gastroesophageal reflux, or both, and who were treated with 40 mg of esomeprazole twice daily. Overall, there was no efficacy in terms of daily peak expiratory flow rate, exacerbations, or asthma symptoms. However, in the stratum of 350 patients who had both symptoms of gastroesophageal reflux and nocturnal asthma symptoms, the peak expiratory flow rate improved, but there was no benefit with respect to FEV_1, rescue-inhaler use, symptom scores, or nocturnal awakening. The esomeprazole-related improvement was most pronounced among patients who were taking long-acting beta-agonists.

This study differs from previous trials in that we excluded patients who had symptoms of gastroesophageal reflux two or more times per week. Our rationale was that these patients already have an indication for acid-suppression treatment, irrespective of their asthma. In our study population, we found no benefit from proton-pump inhibitors with respect to any primary or secondary asthma-related outcome measure. Moreover, ambulatory pH-monitoring studies did not identify a subgroup that was likely to benefit from therapy with proton-pump inhibitors. We also did not find that patients taking long-acting beta-agonists were more likely to have a response to proton-pump inhibitors. Therefore, taken as a whole, the weight of evidence indicates that proton-pump inhibitors should not be routinely prescribed for asthma symptoms if the patient does not have symptoms of gastroesophageal reflux. It should be noted, however, that this trial was designed as a superiority trial rather than a noninferiority trial. Thus, we cannot exclude the possibility that there is a small beneficial or harmful treatment effect. Among patients with asthma who have symptoms of gastroesophageal reflux, treatment with proton-pump inhibitors reduces these symptoms but probably has little effect on the asthma. Because diagnostic tests for and drug treatment of gastroesophageal reflux in patients with asthma contribute substantially to the cost of asthma

Table 3. Episodes of Poor Asthma Control and Component Events.*

Variable	Placebo (N=193)	Esomeprazole (N=200)	Incidence-Rate Ratio, Esomeprazole vs. Placebo (95% CI)	P Value	
				Esomeprazole vs. Placebo†	Gastroesophageal-Reflux Interaction‡
Asthma episodes, according to definition that did not include use of beta-agonists as a criterion					
No. of events	201	224			
No. of events/person-yr	2.3	2.5	1.1 (0.8–1.5)	0.66	0.93
Patients with ≥1 event (%)	42	42			
Exacerbation components					
≥30% drop in peak expiratory flow on 2 consecutive days					
No. of events	141	180			
No. of events/person-yr	1.7	2.1	1.2 (0.8–2.0)	0.35	0.99
Patients with ≥1 event (%)	26	28			
Urgent care visit					
No. of events	53	51			
No. of events/person-yr	0.6	0.6	0.9 (0.6–1.5)	0.79	0.44
Patients with ≥1 event (%)	17	18			
New use of oral corticosteroids					
No. of events	50	48			
No. of events/person-yr	0.6	0.5	0.9 (0.6–1.3)	0.62	0.85
Patients with ≥1 event (%)	24	21			
Asthma episodes, according to definition that included increased use of beta-agonists					
No. of events	367	383			
No. of events/person-yr	4.4	4.3	1.0 (0.8–1.3)	0.87	0.19
Patients with ≥1 event (%)	63	60			
Use of rescue medications					
No. of events	248	241			
No. of events/person-yr	3.0	2.8	0.9 (0.7–1.3)	0.62	0.05
Patients with ≥1 event (%)	46	45			
Night awakening					
No. of events	2518	2409			
No. of events/person-yr	30	28	0.9 (0.6–1.4)	0.70	0.31
Patients with ≥1 event (%)	55	52			

* Incidence-rate ratios and P values were estimated with the use of negative binomial regression models with robust variance estimates.
† P values are for the treatment effect of esomeprazole as compared with placebo.
‡ P values are for the modification of the treatment effect by pH-monitoring results, as estimated by linear regression.

Table 4. Change in Secondary Outcomes from Baseline to 24 Weeks.*

Variable	Mean Change from Baseline to 24 Weeks (95% CI)		Treatment Effect (95% CI)	P Value	
	Placebo	Esomeprazole		Esomeprazole vs. Placebo†	Gastro-esophageal-Reflux Interaction‡
Pulmonary function					
Prebronchodilator FEV_1 (liters)	−0.02 (−0.06 to 0.01)	0.00 (−0.04 to 0.04)	0.03 (−0.03 to 0.08)	0.36	0.55
Prebronchodilator FVC (liters)	−0.03 (−0.06 to 0.01)	0.00 (−0.04 to 0.05)	0.03 (−0.03 to 0.09)	0.30	0.77
Postbronchodilator FEV_1 (% change from prebronchodilator value)	−0.4 (−1.6 to 0.9)	−1.3 (−3.4 to 0.7)	−1.0 (−3.4 to 1.5)	0.43	0.38
Peak flow rate (liters/min)	3.2 (−3.5 to 9.9)	9.2 (1.8 to 16.6)	6.0 (−3.9 to 16.0)	0.24	0.03
PC_{20} (mg/ml)§	1.5 (0.2 to 2.9)	0.3 (−1.4 to 0.9)	−1.8 (−3.6 to −0.1)	0.04	0.68
Asthma scores¶					
JACQ	−0.3 (−0.4 to −0.2)	−0.2 (−0.3 to −0.1)	0.1 (0.0 to 0.2)	0.11	0.73
ASUI	0.05 (0.03 to 0.07)	0.02 (0.01 to 0.04)	−0.02 (−0.05 to −0.02)	0.11	0.75
MiniAQLQ	0.3 (0.2 to 0.4)	0.3 (0.2 to 0.4)	−0.1 (−0.2 to 0.1)	0.33	0.81
SF-36 score‖					
Physical component	2.0 (1.1 to 2.9)	1.1 (0.3 to 1.9)	−0.9 (−2.0 to 0.4)	0.16	0.58
Mental component	0.0 (−1.8 to 1.1)	0.4 (−0.5 to 1.4)	0.5 (−1.1 to 2.2)	0.56	0.46
Gastric symptoms					
GSAS score**	−0.17 (−0.21 to −0.12)	−0.16 (−0.20 to −0.11)	0.01 (−0.05 to 0.07)	0.76	0.99
No. of symptoms	−1.7 (−2.1 to −1.3)	−1.9 (−2.3 to −1.6)	−0.2 (−0.8 to 0.3)	0.39	0.39

* The analyses are based on data from 191 participants in the placebo group and 201 in the esomeprazole group, with the following exception: 41 participants in the placebo group and 37 in the esomeprazole group for measurement of PC_{20}. ASUI denotes Asthma Symptom Utility Index, FEV_1 forced expiratory volume in 1 second, FVC forced vital capacity, GSAS Gastroesophageal Reflux Disease Symptom Assessment Scale, JACQ Juniper Asthma Control Questionnaire, MiniAQLQ Mini Asthma Quality of Life Questionnaire, PC_{20} the concentration of inhaled methacholine causing a 20% reduction in FEV_1, and SF-36 Medical Outcomes Study 36-Item Short-Form General Health Survey.
† P values were calculated with the use of linear regression.
‡ P values, which are for modification of the treatment effect by pH-monitoring results, were calculated with the use of linear regression; the number of participants with pH-monitoring data available was 303, 151 in the placebo group and 152 in the esomeprazole group.
§ Values were adjusted for the baseline value. PC_{20} was not achieved at 24 weeks in 18 of 59 participants (31%) in the placebo group and 20 of 57 (35%) in the esomeprazole group, representing a treatment effect of 4 percentage points (P=0.60).
¶ Scores on the JACQ range from 0 to 6, with lower scores indicating better asthma control and 0.5 as the minimal clinically important difference; scores on the ASUI range from 0 to 1, with higher scores indicating less severe asthma; scores on the MiniAQLQ range from 1 to 7, with higher scores indicating better quality of life and 0.5 as the minimal clinically important difference.
‖ Scores on the SF-36 range from 1 to 100, with higher scores indicating better quality of life and 5 as the minimal clinically important difference.
** The distress score of the GSAS ranges from 0 to 3, with lower numbers indicating less distress.

care, limited use of these measures seems warranted.[28]

The presence of asymptomatic gastroesophageal reflux, which was noted in nearly half of our study participants with poorly controlled asthma, was not predictive of a treatment effect, indicating that asymptomatic gastroesophageal reflux may not be a frequent cause of poor asthma control. In addition, the failure of proton-pump inhibitors to improve methacholine reactivity suggests that airway inflammation from microaspiration or esophageal reflexes is not a common contributing mechanism of poor asthma control in patients who have persistent asthma symptoms despite the use of inhaled corticosteroids.

Although the dose of esomeprazole used in this study is highly effective in suppressing gastric acid throughout the day, and is larger than the dose that is routinely prescribed for symptoms of gastroesophageal reflux, it does not prevent alkaline reflux, which may also trigger esophageal reflexes mediating neurogenic inflammation in the airways.[43] On occasion, nocturnal gastric acid breakthrough may occur with even high-dose proton-pump inhibitors, though it does not necessarily lead to reflux in asymptomatic persons.[44]

Furthermore, asymptomatic gastroesophageal reflux may have other adverse health consequences, such as the development of Barrett's esophagus and a predisposition to esophageal cancer, that are not related to asthma. Accordingly, the use of ambulatory esophageal pH monitoring in patients with asthma ought to be based on the need to diagnose and treat esophageal disease rather than asthma.

In summary, we have found that there is no benefit of treatment with a proton-pump inhibitor in patients with poorly controlled asthma who have minimal or no symptoms of gastroesophageal reflux. Ambulatory pH monitoring and clinical characteristics do not identify a subgroup that is likely to benefit from such treatment.

APPENDIX

The members of the research group for the trial were as follows: **Baylor College of Medicine, Houston** — N.A. Hanania (principal investigator), M. Sockrider (coprincipal investigator), L. Giraldo (principal clinic coordinator), R. Valdez, E. Flores (coordinators); **Columbia University–New York University Consortium, New York** — J. Reibman (principal investigator), E. DiMango, L. Rogers (coprincipal investigators), C. Cammarata, K. Carapetyan (clinic coordinators at New York University), J. Sormillon, E. Simpson (clinic coordinators at Columbia University); **Duke University Medical Center, Durham, NC** — L. Williams (principal investigator), J. Sundy (coprincipal investigator), G. Dudek (principal clinic coordinator), R. Newton, A. Dugdale (coordinators); **Emory University School of Medicine, Atlanta** — W.G. Teague (principal investigator), A. Fitzpatrick, S. Khatri (coprincipal investigators), R. Patel (principal clinic coordinator), J. Peabody, E. Hunter, D. Whitlock (coordinators); **Illinois Consortium, Chicago** — L. Smith (principal investigator), J. Moy, E. Naureckas, C.S. Olopade (coprincipal investigators), J. Hixon (principal clinic coordinator), A. Brees, G. Rivera, S. Sietsema, V. Zagaja (coordinators); **Indiana University, Asthma Clinical Research Center, Indianapolis** — M. Busk (principal investigator), C. Williams (coprincipal investigator), P. Puntenney (principal clinic coordinator), N. Busk (coordinator); **University of Pennsylvania, Philadelphia** — F. Leone (principal investigator), M. Hayes-Hampton (principal clinic coordinator); **Louisiana State University Health Sciences Center, Ernest N. Morial Asthma, Allergy, and Respiratory Disease Center, New Orleans** — W.R. Summer (principal investigator), G. Meyaski (principal clinic coordinator); **National Jewish Medical and Research Center, Denver** — S. Wenzel, R. Katial (principal investigators), L. Lopez (principal clinic coordinator); **Nemours Children's Clinic–University of Florida Consortium, Jacksonville** — J. Lima (principal investigator), K. Blake (coprincipal investigator), A. Santos (principal clinic coordinator), K. Vega, L. Lambiase, T. Langford, D. Schaeffer, J. Lang, M. McRae (coordinators); **North Shore–Long Island Jewish Health System, New Hyde Park, NY** — J. Karpel (principal investigator), R. Cohen (coprincipal investigator), R. Ramdeo (principal clinic coordinator); **Northern New England Consortium (formerly Vermont Lung Center at the University of Vermont), Colchester, VT** — C.G. Irvin (principal investigator), A.E. Dixon, D.A. Kaminsky (coprincipal investigators), R. Colletti (GI consultant), S.M. Burns, L.M. Bourassa, S.E. Lang, L.V. Griffes (coordinators), R. Pratt, K.B. Nakos, K.J. Girard; **Ohio State University Medical Center–Nationwide Children's Hospital, Columbus** — J. Mastronarde (principal investigator), K. McCoy (coprincipal investigator), J. Parsons (coinvestigator), J. Drake (principal clinic coordinator), R. Compton, L. Raterman, D. Cosmar (coordinators); **University of Alabama at Birmingham, Birmingham** — L.B. Gerald (principal investigator), W.C. Bailey (coprincipal investigator), S. Erwin (principal clinic coordinator), A. Kelley, D. Laken (coordinators); **University of Miami at Miami–University of South Florida, Tampa** — A. Wanner (principal investigator, Miami), R. Lockey (principal investigator, Tampa), E. Mendes (principal clinic coordinator for University of Miami), S. McCullough (principal clinic coordinator for University of South Florida), B. Fimbel, M. Grandstaff (coordinators); **University of Minnesota, Minneapolis** — M.N. Blumenthal (principal investigator), G. Brottman, J. Hagen (coprincipal investigators), A. Decker, D. Lascewski, S. Kelleher (principal clinic coordinators), K. Bachman, C. Quintard, C. Sherry (coordinators); **University of Missouri–Kansas City School of Medicine, Kansas City** — G. Salzman (principal investigator), D.

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REFERENCES

1. Field SK, Underwood M, Brant R, Cowie RL. Prevalence of gastroesophageal reflux symptoms in asthma. Chest 1996;109:316-22.
2. Harding SM, Guzzo MR, Richter JE. 24-h esophageal pH testing in asthmatics: respiratory symptom correlation with esophageal acid events. Chest 1999;115:654-9.
3. Sontag SJ, O'Connell S, Khandelwal S, et al. Most asthmatics have gastroesophageal reflux with or without bronchodilator therapy. Gastroenterology 1990;99:613-20.
4. Vincent D, Cohen-Jonathan AM, Leport J, et al. Gastro-oesophageal reflux prevalence and relationship with bronchial reactivity in asthma. Eur Respir J 1997;10:2255-9.
5. Simpson WG. Gastroesophageal reflux disease and asthma: diagnosis and management. Arch Intern Med 1995;155:798-803.
6. Harding SM, Guzzo MR, Richter JE. The prevalence of gastroesophageal reflux in asthma patients without reflux symptoms. Am J Respir Crit Care Med 2000;162:34-9.
7. Irwin RS, Curley FJ, French CL. Difficult to control asthma: contributing factors and outcome of a systematic management protocol. Chest 1993;103:1662-9.
8. Kiljander TO, Laitinen JO. The prevalence of gastroesophageal reflux disease in adult asthmatics. Chest 2004;126:1490-4.
9. Fish JE, Peters SP. Gastroesophageal reflux and upper airways disease in severe asthma. In: Holgate ST, Boushey HA, Fabbri LM, eds. Difficult asthma. London: Martin Dunitz, 1999:77-91.
10. Richter JE. Asthma and gastroesophageal reflux disease: the truth is difficult to define. Chest 1999;116:1150-2.
11. Harding SM, Richter JE. The role of gastroesophageal reflux in chronic cough and asthma. Chest 1997;111:1389-402.
12. Ekström T, Tibbling L. Esophageal acid perfusion, airway function, and symptoms in asthmatic patients with marked

bronchial hyperreactivity. Chest 1989;96:995-8.
13. Herve P, Denjean A, Jian R, Simonneau G, Duroux P. Intraesophageal perfusion of acid increases the bronchomotor response to methacholine and to isocapnic hyperventilation in asthmatic subjects. Am Rev Respir Dis 1986;134:986-9.
14. Wu DN, Tanifuji Y, Kobayashi H, et al. Effects of esophageal acid perfusion on airway hyperresponsiveness in patients with bronchial asthma. Chest 2000;118:1553-6.
15. Cuttitta G, Cibella F, Visconti A, Scichilone N, Bellia V, Bonsignore G. Spontaneous gastroesophageal reflux and airway patency during the night in adult asthmatics. Am J Respir Crit Care Med 2000;161:177-81.
16. Jack CI, Calverley PM, Donnelly RJ, et al. Simultaneous tracheal and oesophageal pH measurements in asthmatic patients with gastro-oesophageal reflux. Thorax 1995;50:201-4.
17. Tuchman DN, Boyle JT, Pack AI, et al. Comparison of airway responses following tracheal or esophageal acidification in the cat. Gastroenterology 1984;87:872-81.
18. Harding SM, Schan CA, Guzzo MR, Alexander RW, Bradley LA, Richter JE. Gastroesophageal reflux-induced bronchoconstriction: is microaspiration a factor? Chest 1995;108:1220-7.
19. Choy D, Leung R. Gastro-oesophageal reflux disease and asthma. Respirology 1997;2:163-8.
20. Zerbib F, Guisset O, Lamouliatte H, Quinton A, Galmiche JP, Tunon-De-Lara JM. Effects of bronchial obstruction on lower esophageal sphincter motility and gastroesophageal reflux in patients with asthma. Am J Respir Crit Care Med 2002;166:1206-11.
21. Lacy BE, Mathis C, DesBiens J, Liu MC. The effects of nebulized albuterol on esophageal function in asthmatic patients. Dig Dis Sci 2008;53:2627-33.
22. Donnellan C, Sharma N, Preston C, Moayyedi P. Medical treatments for the

maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease. Cochrane Database Syst Rev 2005;2:CD003245.
23. Littner MR, Leung FW, Ballard ED II, Huang B, Samra NK. Effects of 24 weeks of lansoprazole therapy on asthma symptoms, exacerbations, quality of life, and pulmonary function in adult asthmatic patients with acid reflux symptoms. Chest 2005;128:1128-35.
24. Kiljander TO, Harding SM, Field SK, et al. Effects of esomeprazole 40 mg twice daily on asthma: a randomized placebo-controlled trial. Am J Respir Crit Care Med 2006;173:1091-7.
25. Coughlan JL, Gibson PG, Henry RL. Medical treatment for reflux oesophagitis does not consistently improve asthma control: a systematic review. Thorax 2001;56:198-204.
26. Gibson PG, Henry RL, Coughlan JL. Gastro-oesophageal reflux treatment for asthma in adults and children. Cochrane Database Syst Rev 2003;2:CD001496.
27. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR3): guidelines for the diagnosis and management of asthma: full report. Bethesda, MD: National Heart, Lung, and Blood Institute, 2007. (Accessed March 16, 2009, at http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.)
28. Dal Negro RW, Turco P, Micheletto C, et al. Cost analysis of GER-induced asthma: a controlled study vs. atopic asthma of comparable severity. Respir Med 2007;101:1814-20.
29. Juniper EF, Bousquet J, Abetz L, Bateman ED. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med 2006;100:616-21.
30. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;159:179-87.
31. American Lung Association Asthma

Clinical Research Centers. Clinical trial of low-dose theophylline and montelukast in patients with poorly controlled asthma. Am J Respir Crit Care Med 2007;175:235-42.

32. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-38.

33. Revicki DA, Leidy NK, Brennan-Diemer F, Sorensen S, Togias A. Integrating patient preferences into health outcomes assessment: the multiattribute Asthma Symptom Utility Index. Chest 1998;114: 998-1007.

34. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. Eur Respir J 1999;14:32-8.

35. Bousquet J, Knani J, Dhivert H, et al. Quality of life in asthma. I. Internal consistency and validity of the SF-36 questionnaire. Am J Respir Crit Care Med 1994; 149:371-5.

36. Crapo RO, Casaburi R, Coates AL, et al. Guidelines for methacholine and exercise challenge testing — 1999: this official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med 2000;161:309-29.

37. DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Am J Gastroenterol 2005;100:190-200.

38. Richter JE, Bradley LA, DeMeester TR, Wu WC. Normal 24-hr ambulatory esophageal pH values: influence of study center, pH electrode, age, and gender. Dig Dis Sci 1992;37:849-56.

39. Damiano A, Handley K, Adler E, Siddique R, Bhattacharyja A. Measuring symptom distress and health-related quality of life in clinical trials of gastroesophageal reflux disease treatment: further validation of the Gastroesophageal Reflux Disease Symptom Assessment Scale (GSAS). Dig Dis Sci 2002;47:1530-7.

40. Keene ON, Jones MR, Lane PW, Anderson J. Analysis of exacerbation rates in asthma and chronic obstructive pulmonary disease: example from the TRISTAN study. Pharm Stat 2007;6:89-97.

41. Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986;73:13-22.

42. Harding SM, Richter JE, Guzzo MR, Schan CA, Alexander RW, Bradley LA. Asthma and gastroesophageal reflux: acid suppressive therapy improves asthma outcomes. Am J Med 1996;100:395-405.

43. Canning BJ, Mazzone SB. Reflex mechanisms in gastroesophageal reflux disease and asthma. Am J Med 2003;115:Suppl 3A: 45S-48S.

44. Ours TM, Fackler WK, Richter JE, Vaezi MF. Nocturnal acid breakthrough: clinical significance and correlation with esophageal acid exposure. Am J Gastroenterol 2003;98:545-50.

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