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# Lansoprazole for Children With Poorly Controlled Asthma

## A Randomized Controlled Trial

Writing Committee for the American Lung Association Asthma Clinical Research Centers

**A**STHMA AND GASTROESOPHAGEAL reflux (GER) disease are both common disorders in children, and symptoms of GER are frequently reported among children with asthma.<sup>1-4</sup> Gastroesophageal reflux identified by esophageal pH monitoring often presents with respiratory symptoms<sup>5-7</sup> and frequently occurs in children without characteristic gastrointestinal symptoms.<sup>1,8,9</sup> Untreated GER has been postulated to be a cause of inadequate asthma control in children despite inhaled corticosteroid treatment.

Proton pump inhibitors (PPIs) are often prescribed for poorly controlled asthma regardless of reflux symptoms, and there have been large increases in the use of PPIs among children between 2000 and 2005.<sup>10</sup> Additionally, expert panels have indicated that the utility of testing and treating children with refractory asthma symptoms for asymptomatic GER has been inadequately studied.<sup>3,11</sup> Hence, it is of clinical importance to determine whether antireflux therapy, the most common of which are PPIs, improves control of asthma in children.

In adults, it appears that PPIs may be helpful for asthma in some patients who manifest reflux symptoms but are not

See also p 406 and Patient Page.

Author Video Interview available at [www.jama.com](http://www.jama.com).

**Context** Asymptomatic gastroesophageal reflux (GER) is prevalent in children with asthma. Untreated GER has been postulated to be a cause of inadequate asthma control in children despite inhaled corticosteroid treatment, but it is not known whether treatment with proton pump inhibitors improves asthma control.

**Objective** To determine whether lansoprazole is effective in reducing asthma symptoms in children without overt GER.

**Design, Setting, and Participants** The Study of Acid Reflux in Children With Asthma, a randomized, masked, placebo-controlled, parallel clinical trial that compared lansoprazole with placebo in children with poor asthma control who were receiving inhaled corticosteroid treatment. Three hundred six participants enrolled from April 2007 to September 2010 at 19 US academic clinical centers were followed up for 24 weeks. A subgroup had an esophageal pH study before randomization.

**Intervention** Participating children were randomly assigned to receive either lansoprazole, 15 mg/d if weighing less than 30 kg or 30 mg/d if weighing 30 kg or more (n=149), or placebo (n=157).

**Main Outcome Measures** The primary outcome measure was change in Asthma Control Questionnaire (ACQ) score (range, 0-6; a 0.5-unit change is considered clinically meaningful). Secondary outcome measures included lung function measures, asthma-related quality of life, and episodes of poor asthma control.

**Results** The mean age was 11 years (SD, 3 years). The mean difference in change (lansoprazole minus placebo) in the ACQ score was 0.2 units (95% CI, 0.0-0.3 units). There were no statistically significant differences in the mean difference in change for the secondary outcomes of forced expiratory volume in the first second (0.0 L; 95% CI, -0.1 to 0.1 L), asthma-related quality of life (-0.1; 95% CI, -0.3 to 0.1), or rate of episodes of poor asthma control (relative risk, 1.2; 95% CI, 0.9-1.5). Among the 115 children with esophageal pH studies, the prevalence of GER was 43%. In the subgroup with a positive pH study, no treatment effect for lansoprazole vs placebo was observed for any asthma outcome. Children treated with lansoprazole reported more respiratory infections (relative risk, 1.3 [95% CI, 1.1-1.6]).

**Conclusion** In this trial of children with poorly controlled asthma without symptoms of GER who were using inhaled corticosteroids, the addition of lansoprazole, compared with placebo, improved neither symptoms nor lung function but was associated with increased adverse events.

**Trial Registration** [clinicaltrials.gov](http://clinicaltrials.gov) Identifier: NCT00442013

JAMA. 2012;307(4):373-381

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helpful for those with asymptomatic GER.<sup>12-14</sup> An open-label prospective study evaluated 44 children with moderate, persistent asthma and GER disease who showed clinical improve-

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ment in asthma symptoms after 1 year of treatment with esomeprazole and metoclopramide. Children who continued the combination treatment for 6 months had fewer asthma exacerbations than those who switched to ranitidine.<sup>15</sup>

We conducted a trial to study the efficacy of PPIs in children with poor asthma control without symptomatic GER. The primary hypothesis was that children with symptomatic asthma taking inhaled corticosteroids would have improved asthma control with lansoprazole treatment compared with placebo. We also investigated whether asymptomatic GER as identified by pH probe testing would identify children who respond to PPI treatment.

## METHODS

### Study Design

The Study of Acid Reflux in Children With Asthma was a randomized (allocation ratio, 1:1), double-masked, placebo-controlled, parallel clinical trial designed to evaluate the effectiveness of lansoprazole for treatment of asthma in children. The study was conducted at 19 American Lung Association Asthma Clinical Research Center sites from April 2007 to April 2011. The study was approved by the institutional review board at each center; legal guardians signed informed consent statements and participants signed assent statements according to local regulatory policy.

Children were randomly assigned to receive either lansoprazole (15 mg/d for children weighing <30 kg; 30 mg/d for children weighing ≥30 kg) or a matching placebo. A permuted-block treatment assignment schedule stratified by clinical center was used; treatment assignment schedules were generated by the data coordinating center using the Stata Ralloc procedure version 3.2.3 (Stata Corp). Study drug kits were identified by unique identification numbers and were masked to participants, clinical personnel, and data analysts throughout the study. Clinical center personnel, usually a coordinator, requested treatment assignment by key-

ing eligibility information into a program on the study Web site that released the study drug kit identification code.

After the screening and randomization visits, participants returned to the clinical centers for assessments every 4 weeks for 24 weeks. Throughout the study, children kept daily diaries to record morning peak expiratory flow, asthma symptoms, nocturnal awakenings, use of short-acting  $\beta$ -agonists (excluding routine use before exercise), oral corticosteroid use, and unscheduled health care visits for asthma symptoms. Ambulatory esophageal pH monitoring prior to randomization was conducted in a subgroup of children who agreed to the procedure at 13 clinical centers with the capability of doing pH probe studies. Participants were paid, on average, \$50 for each study visit and \$200 for undergoing a pH probe study.

### Participant Selection

Participants were between 6 and 17 years of age and had physician-diagnosed asthma and labile airways function defined as a 12% or greater increase in postbronchodilator forced expiratory volume in the first second (FEV<sub>1</sub>), a methacholine challenge (provocative dose of methacholine to reduce percent predicted FEV<sub>1</sub> by 20% [PC<sub>20</sub>]) of less than 16 mg/mL, or a positive exercise bronchoprovocation test result of a 20% or greater decrease in FEV<sub>1</sub> after exercise demonstrated within the prior 12 months. Participants were treated with inhaled corticosteroids (≥176  $\mu$ g/d of fluticasone equivalents) and had no change in controller therapies for at least 8 weeks prior to enrollment.

Poor asthma control was defined as any 1 of the following: use of short-acting  $\beta$ -agonists for asthma symptoms 2 or more times per week; nocturnal awakenings with asthma symptoms more than once per week during the month before enrollment; 2 or more emergency department visits, unscheduled physician visits, prednisone courses, or hospitalizations for asthma in the prior year;

or a score of 1.25 or higher on the Asthma Control Questionnaire (ACQ) at the screening visit.

Recruits were excluded from the study if they self-reported any of the following: symptoms of GER requiring treatment; treatment with a PPI or other reflux medications (other than occasional oral antacids); history of antireflux surgery or a previous tracheoesophageal fistula repair; an FEV<sub>1</sub> of less than 60% predicted; history of neonatal respiratory distress or premature birth at less than 33 weeks' gestational age; or other major chronic illnesses. Children with a known sensitivity or intolerance to lansoprazole or aspartame were not enrolled. Other exclusion criteria were nonadherence (<80% completion of daily diaries during run-in); inability to take study medications, perform baseline measurements, or be contacted by telephone; or pregnancy.

Participant characteristics related to race/ethnicity, cigarette or cigar smoke exposure, past asthma treatments, and asthma triggers were collected via interview. Participants were asked to identify their ethnicity (non-Hispanic vs Hispanic) and race (open-ended). These data were used for reporting to the National Heart, Lung, and Blood Institute and for calculating predictive values for lung function. Children were followed up between 2 and 8 weeks before randomization and were eligible for randomization if they completed 80% of daily diary cards, maintained a stable dose of inhaled corticosteroids, had a percent predicted FEV<sub>1</sub> of 60% or greater, and were not pregnant.

### Outcome Measures

The primary outcome measure for the trial was change in ACQ score at the 24-week visit.<sup>16</sup> The ACQ integrates indicators of asthma control, including use of bronchodilators, nocturnal symptoms, cough, activity level, and pulmonary function, and has a range of 0 to 6 (higher values indicate worse asthma control). A 0.5-point change in ACQ score reflects a meaningful clinically important difference in asthma control.

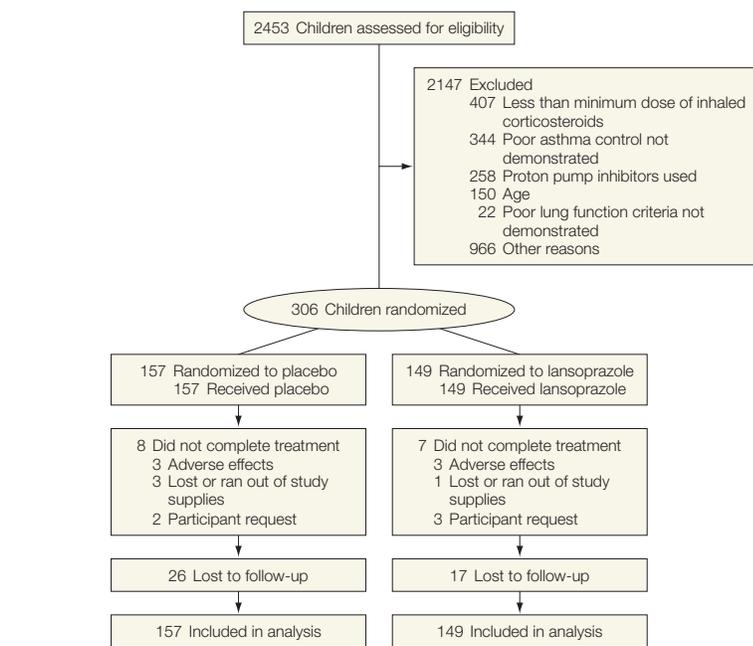
Patients with ACQ scores of 0.75 or less are classified as having well-controlled asthma and those with scores of 1.5 or greater are classified as having inadequately controlled asthma.<sup>17,18</sup>

Secondary outcomes included the rate of acute episodes of poor asthma control<sup>14</sup>; Asthma Symptom Utility Index<sup>19</sup> (ASUI; score range, 0-1.0; meaningful clinically important difference, 0.15 [Christian Bime, MD, written communication to American Thoracic Society, December 2011]); Asthma Control Test for adolescents (aged 12-17 years)/children (aged 6-11 years) (ACT<sup>20</sup>/cACT<sup>21</sup>; score range, 5-25/0-27, respectively; meaningful clinically important difference, 3 for ACT<sup>22</sup> and undefined for cACT); asthma-specific quality of life for children (AQLQ; score range, 1-7; meaningful clinically important difference, 0.4)<sup>23</sup> and for their caregivers (cAQLQ; score range 1-7; meaningful clinically important difference, 0.5)<sup>24</sup>; methacholine PC<sub>20</sub><sup>25</sup>; spirometry<sup>26</sup>; exhaled nitric oxide; gastrointestinal symptoms (score range, 0-441; meaningful clinically important difference undefined)<sup>27</sup>; and nocturnal awakenings.

We defined 2 types of episodes of poor asthma control derived from the daily diaries: an episode of poor asthma control type 1 was a decrease of greater than 30% in morning peak flow rate from personal best (assessed during run-in) for 2 consecutive days, addition of an oral corticosteroid to treat asthma symptoms, or unscheduled contact with a health care practitioner for asthma symptoms. An episode of poor asthma control type 2 also included increased use of short-acting  $\beta$ -agonists from baseline ( $\geq 4$  additional puffs of rescue medication or  $\geq 2$  additional nebulizer treatments in 1 day). Episodes of poor asthma control type 1 excluded use of rescue medications because we were concerned that heartburn symptoms could be mistaken for asthma symptoms and result in increased rescue medication use.

In a post hoc analysis of treatment effect in subgroups defined by either FEV<sub>1</sub> at baseline (percent predicted prebronchodilator FEV<sub>1</sub>  $\leq 80\%$  vs

**Figure 1.** Participant Flow



>80%) or use of oral steroids for asthma in the past year, there was no evidence of an improvement in ACQ score associated with lansoprazole (eTable 1; available at <http://www.jama.com>). There was no statistically significant effect of study site on change in ACQ score ( $P = .07$ ). Participants were questioned about potential adverse effects of treatment at each visit. Subsequent to a US Food and Drug Administration (FDA) advisory on the risk of bone fractures in adults,<sup>28</sup> clinics were asked to review participant records for fractures.

Esophageal pH studies were performed prior to randomization at 13 clinical centers according to a standard protocol and were centrally reviewed. At least 16 hours of monitoring was required for evaluation. The thresholds used for the definition of pathological GER were esophageal pH of 4 or lower for 6% or more of the time for a 6- to 11-year-old and for 4% or more of the time for a 12- to 17-year-old.<sup>3</sup>

### Sample Size

The planned sample size of 300 participants provided 90% power to de-

tect a 0.6-unit change in the primary outcome, ACQ score, assuming an SD of 1.5 with a 2-sided type I error rate of 5%. The sample size was inflated by 5% to account for missing data. We estimated 80% to 90% power to detect a difference of 0.85 to 1.0 in ACQ score in the subgroup of participants who underwent pH probes.

### Data Analysis

All analyses were conducted according to treatment assignment and all available data were incorporated. Longitudinal models estimated the change from baseline to 6 months in a measurement using generalized estimating equations with an unstructured or exchangeable covariance matrix to adjust for repeated measures<sup>29</sup>; saturated means models including indicators for each visit and each visit  $\times$  treatment interaction were constructed with missing data indicators to maintain data structure. Hence, all participants with baseline or follow-up data were included in the models to estimate treatment effects. Data were assumed to be missing at random. The visits were defined as ordinal variables by visit code.

**Table 1.** Characteristics of Study Participants

Characteristics	Treatment Group	
	Placebo (n = 157)	Lansoprazole (n = 149)
Demographic characteristics <sup>a</sup>		
Age at randomization, mean (SD), y	11 (3)	11 (3)
Male, No. (%)	102 (65)	86 (58)
Race/ethnicity, No. (%)		
White	52 (33)	50 (34)
Black	79 (50)	75 (50)
Hispanic	17 (11)	17 (11)
Other	9 (6)	7 (5)
pH probe positive test result, No. (%) <sup>b</sup>	20 (38)	29 (47)
Exposed to secondhand smoke, No. (%)	29 (18)	25 (17)
Asthma characteristics		
Age at asthma onset, mean (SD), y	3 (3)	4 (3)
Unscheduled asthma care in past year, No. (%)	109 (69)	115 (77)
Oral corticosteroids for asthma in past year, No. (%)	98 (62)	108 (72)
Use of rescue inhaler 2 or more times/wk, No. (%)	118 (75)	109 (73)
Daily use of ICS/LABA, No. (%)	91 (58)	86 (58)
Daily use of antileukotriene, No. (%)	86 (55)	81 (54)
Inhaled corticosteroid treatment at enrollment, No. (%)		
Fluticasone/salmeterol	81 (52)	79 (53)
Fluticasone	34 (22)	26 (17)
Budesonide	16 (10)	21 (14)
Budesonide/formoterol	10 (6)	7 (5)
Beclomethasone	11 (7)	7 (5)
Mometasone or triamcinolone	5 (3)	9 (6)
Asthma questionnaire scores, mean (SD)		
ACQ at screening (score range, 0-6) <sup>c</sup>	1.6 (0.8)	1.6 (0.8)
ACQ at randomization	1.2 (0.8)	1.2 (0.8)
ASUI (score range, 0-1) <sup>d</sup>	0.82 (0.14)	0.82 (0.15)
ACT (ages 12-17 y) (score range, 5-25) <sup>b,d</sup>	19 (4)	19 (4)
Children's ACT (ages 6-11 y) (score range, 0-27) <sup>b,d</sup>	20 (4)	20 (4)
Mini-AQLQ (score range, 1-7) <sup>d</sup>	5.5 (1.1)	5.4 (1.2)
Caregiver AQLQ (score range, 1-7) <sup>d</sup>	5.4 (1.5)	5.6 (1.4)
GER disease symptom assessment, median (IQR) <sup>c</sup>		
Score (score range, 0-441)	9 (2-220)	7 (2-28)
No. of symptoms (range, 0-9)	2 (1-4)	3 (1-4)
Pulmonary function, mean (SD)		
Prebronchodilator FEV <sub>1</sub> , % predicted <sup>a</sup>	92.4 (14.6)	91.3 (17.1)
Postbronchodilator FEV <sub>1</sub> , % predicted <sup>a,b</sup>	99.7 (14.1)	99.6 (15.4)
Prebronchodilator FVC, % predicted <sup>a</sup>	101.1 (14.6)	100.4 (13.8)
Postbronchodilator FVC, % predicted <sup>a,b</sup>	102.9 (15.1)	103.0 (13.2)
Peak flow, % predicted <sup>e</sup>	97.3 (22.1)	92.7 (20.0)
Change in FEV <sub>1</sub> after bronchodilator <sup>b</sup>	8.5 (10.9)	10.9 (11.3)
Change in FVC after bronchodilator <sup>b</sup>	2.2 (6.6)	3.4 (5.8)
PC <sub>20</sub> , mg/mL	2.5 (3.7)	3.4 (4.0)
Other self-reported conditions, No. (%)		
GER disease	2 (1)	3 (2)
Eczema	62 (39)	71 (48)
Sinusitis	44 (28)	44 (30)
Rhinitis	80 (51)	101 (68)
Food allergies	43 (27)	38 (26)
Allergies worsen asthma	124 (79)	121 (81)

Abbreviations: ACQ, Asthma Control Questionnaire; ACT, asthma control test; AQLQ, asthma quality-of-life questionnaire; ASUI, Asthma Symptom Utility Index; FEV<sub>1</sub>, forced expiratory volume in the first second; FVC, forced vital capacity; GER, gastroesophageal reflux; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β-agonist; PC<sub>20</sub>, provocative dose of methacholine to reduce percent predicted FEV<sub>1</sub> by 20%.

<sup>a</sup>Collected via interview.

<sup>b</sup>Treatment group denominators for placebo and lansoprazole, respectively, are 53 and 62 for pH probe positive test result, 71 and 71 for the ACT, 86 and 78 for the cACT, 153 and 104 for postbronchodilator FEV<sub>1</sub> and FVC and change in FEV<sub>1</sub> and FVC after bronchodilator, and 108 and 107 for PC<sub>20</sub>.

<sup>c</sup>Lower value indicates less severe asthma/GER.

<sup>d</sup>Higher value indicates less severe asthma.

<sup>e</sup>Predicted values according to Hankinson et al.<sup>26</sup>

Negative binomial regression models were used to evaluate differences in the rate of episodes of poor asthma control<sup>30</sup>; participants without diary card data were excluded from these analyses. We planned to evaluate the treatment effect in subgroups defined by pH probe test results; a differential effect of treatment was evaluated by a test of interaction.

There was 1 interim analysis during the trial after approximately 50% of the participants completed follow-up. *P* values were 2-sided and *P* ≤ .05 was considered statistically significant; *P* values were not adjusted for multiple looks or multiple comparisons. Post hoc sensitivity analyses were performed including measures of asthma severity and study site, a stratification variable, in the model. Data were analyzed using SAS version 9.2 (SAS Institute Inc) and Stata version 11 (Stata Corp).

## RESULTS

### Recruitment and Follow-up

A total of 2453 children were screened for eligibility. Three hundred six children were randomized; 157 were randomly assigned to receive placebo and 149 to receive lansoprazole (FIGURE 1). More than 88% of participants completed the study and 94% of follow-up visits were completed. Baseline characteristics of participants completing the study (n = 263) were similar to those who did not complete the final visit (n = 43), with the following exceptions: postbronchodilator FEV<sub>1</sub> and forced vital capacity (FVC) were higher in those who completed the study (FEV<sub>1</sub>, 110% vs 95%; *P* = .03 and FVC, 104% vs 99%; *P* = .04), and montelukast use was more common (57% vs 40%; *P* = .02). Self-reported adherence to study treatments was high in both groups according to diary cards and interviews at study visits; study drug was reported to be taken on more than 90% of follow-up days in both groups.

### Characteristics of Study Participants

The demographic and asthma characteristics at baseline were similar in the

**Table 2.** Questionnaire Scores and Lung Function Measures at 24 Weeks of Follow-up

Questionnaires	No. of Participants <sup>a</sup>	Mean (95% CI)					P Value	
		24-Week Score		Score Change From Baseline		Treatment Effect, Difference in Change, Lansoprazole vs Placebo <sup>b</sup>	Treatment Effect <sup>c</sup>	Interaction With GER <sup>d</sup>
		Placebo	Lansoprazole	Placebo	Lansoprazole			
Asthma control								
Asthma Control Questionnaire	306	1.0 (0.9 to 1.1)	1.1 (0.9 to 1.2)	-0.2 (-0.4 to -0.1)	-0.1 (-0.2 to 0.1)	0.2 (-0.0 to 0.3)	.12	.50
Asthma Symptom Utility Index	306	0.88 (0.86 to 0.90)	0.86 (0.83 to 0.88)	0.06 (0.03 to 0.09)	0.03 (0.01 to 0.06)	-0.03 (-0.07 to 0.01)	.14	.38
Asthma Control Test for ages 12-17 y	142	20.2 (19.4 to 21.1)	20.2 (19.3 to 21.1)	1.6 (0.5 to 2.7)	1.0 (0.2 to 1.7)	-0.6 (-1.9 to 0.7)	.37	.86
Asthma Control Test for ages 6-11 y	164	21.9 (21.1 to 22.8)	20.9 (19.9 to 21.9)	2.0 (1.0 to 2.9)	1.2 (0.3 to 2.1)	-0.7 (-2.0 to 0.6)	.27	.33
Quality of life								
Pediatric quality of life	306	6.0 (5.9 to 6.2)	5.8 (5.7 to 6.0)	0.5 (0.3 to 0.7)	0.4 (0.3 to 0.6)	-0.1 (-0.3 to 0.2)	.65	.48
Caregiver quality of life	300	6.0 (5.8 to 6.2)	6.1 (5.9 to 6.3)	0.6 (0.4 to 0.9)	0.4 (0.2 to 0.7)	-0.2 (-0.5 to 0.1)	.21	.46
Pulmonary function								
Prebronchodilator, FEV <sub>1</sub> , L	306	2.3 (2.1 to 2.4)	2.2 (2.1 to 2.4)	0.0 (-0.0 to 0.1)	0.0 (-0.0 to 0.1)	0.0 (-0.1 to 0.1)	.99	.27
FEV <sub>1</sub> bronchodilator response, %	120	10.8 (7.7 to 14.0)	10.7 (7.0 to 14.5)	2.2 (-1.2 to 5.7)	-0.1 (-4.0 to 3.9)	-2.3 (-7.6 to 2.9)	.38	.002
Prebronchodilator, FVC, L	306	2.9 (2.7 to 3.1)	2.9 (2.7 to 3.0)	0.1 (0.0 to 0.1)	0.1 (0.0 to 0.1)	0.0 (-0.1 to 0.1)	.68	.22
PC <sub>20</sub> , mg/mL	119	2.5 (1.7 to 3.4)	2.6 (2.0 to 3.3)	0.0 (-0.9 to 1.0)	0.1 (-0.8 to 1.1)	-0.8 (-2.1 to 0.4)	.20	.80

Abbreviations: FEV<sub>1</sub>, force expiratory volume in 1 second; FVC, forced vital capacity; GER, gastroesophageal reflux; PC<sub>20</sub>, provocative dose of methacholine to reduce percent predicted FEV<sub>1</sub> by 20%.

<sup>a</sup>Numbers are based on the number of participants with 1 or more measurements during the study with the exception of FEV<sub>1</sub> bronchodilator response and PC<sub>20</sub>, which are based on the number of participants with the measurement at the final visit. FEV<sub>1</sub> bronchodilator response was assessed at the final visit in 62 and 58 participants assigned to placebo and lansoprazole, respectively; PC<sub>20</sub> was assessed at the final visit in 63 and 56 participants assigned to placebo and lansoprazole, respectively. For the adult Asthma Control Questionnaire (ages 12-17 years), 71 participants in each treatment group completed at least 1 questionnaire; for the children's Asthma Control Questionnaire (ages 6-11 years), 86 and 78 participants completed at least 1 questionnaire in the placebo and lansoprazole groups, respectively.

<sup>b</sup>For the Asthma Control Questionnaire and PC<sub>20</sub>, a negative number favors lansoprazole; for all other measures, a positive treatment effect favors lansoprazole.

<sup>c</sup>P values for treatment effect based on generalized estimating equation models including all data points.

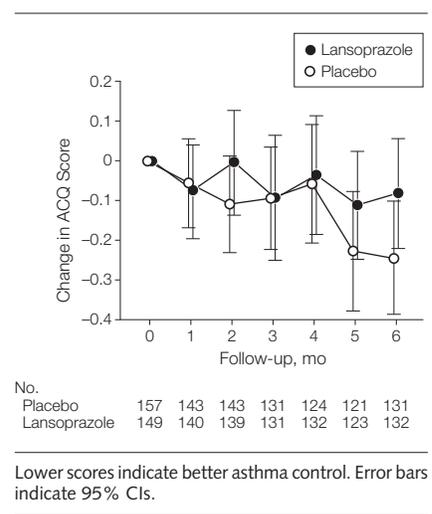
<sup>d</sup>P values for a differential treatment effect in patients with positive pH probe status in the subgroup of patients (n=115) with those data.

2 treatment groups (TABLE 1). The children had a mean age of 11 years, there were more boys than girls, and 50% of participants were black. Most participants required an intervention (urgent care, oral prednisone course, or frequent use of rescue medication) for asthma symptoms in the year prior to enrollment. Mean baseline FEV<sub>1</sub> was 99% of predicted in both treatment groups. Children treated with lansoprazole had greater change in FEV<sub>1</sub> in response to a bronchodilator (10.9% vs 8.5% in the placebo group; *P* = .02). Among the subgroup with methacholine provocation results at randomization, bronchial responsiveness was elevated in both groups but relatively less in the lansoprazole group (PC<sub>20</sub>, 3.4 mg/mL vs 2.5 mg/mL in the placebo group; *P* = .04).

**GER Status**

One hundred fifty-two participants underwent 24-hour esophageal pH monitoring studies. Of these, 115 had adequate results for interpretation, 49 (43%) of whom had abnormal esophageal acid exposure as assessed by frequent acid reflux events, prolonged acid reflux episodes (>5 minutes), or overall 24-hour esophageal acid reflux greater than established thresholds. Gastrointestinal symptom scores were not different between patients with normal vs abnormal pH probe study results (mean scores, 15 [95% CI, 10-20] vs 20 [95% CI, 12-27], respectively). There were no differences in prebronchodilator percent predicted FEV<sub>1</sub> or FVC between participants with a positive pH probe study result and those with a negative result (FEV<sub>1</sub>, 91%

**Figure 2.** Change in Asthma Control Questionnaire (ACQ) Score in Children With Poor Asthma Control Receiving Lansoprazole vs Placebo



No.	157	143	143	131	124	121	131
Placebo							
Lansoprazole	149	140	139	131	132	123	132

Lower scores indicate better asthma control. Error bars indicate 95% CIs.

[SD, 16%] vs 93% [SD, 15%];  $P = .45$  and FVC, 101% [SD, 14%] vs 102% [SD, 14%];  $P = .80$ ).

**Effects of Treatment on Asthma Outcomes**

The mean ACQ score at screening was high and consistent with poor asthma control in both groups (1.6 for both groups;  $P = .96$ ). Between the screening and randomization visits, ACQ

scores decreased in both groups. After randomization, the ACQ score decreased by less than the meaningful clinically important difference in both groups (lansoprazole,  $-0.1$ ; 95% CI,  $-0.2$  to  $0.1$  and placebo,  $-0.2$ ; 95% CI,  $-0.4$  to  $-0.1$ ); the change was not statistically different ( $P = .12$ ) between treatment groups (TABLE 2 and FIGURE 2). There were no significant treatment effects for any of the second-

ary indexes of asthma control, including the ASUI, ACT, cACT, AQLQ, and cAQLQ (Table 2). Likewise, there was no significant treatment effect on lung function, including prebronchodilator FEV<sub>1</sub> or FVC, over the 6-month follow-up (Table 2). The magnitude of bronchial hyperresponsiveness increased slightly (decrease in methacholine PC<sub>20</sub>) in the lansoprazole treatment group from baseline to month 6 of the study, but there was no treatment effect. There was no significant treatment effect on episodes of poor asthma control type 1 or 2 rates (TABLE 3).

**Table 3.** Episodes of Poor Asthma Control by Treatment Assignment

	Treatment Group		Relative Risk (95% CI)	P Value <sup>a</sup>
	Placebo (n = 149)	Lansoprazole (n = 146)		
No. of person-years	62.8	63.9		
<b>Episodes of Poor Asthma Control 1</b>				
No. of events	184	230		
No. of events/person-year	2.9	3.6	1.2 (0.9-1.7)	.30
Patients with ≥1 event, No. (%)	83 (56)	84 (58)		.75
Exacerbation components				
Peak flow, 30% decrease				
No. of events	139	190		
No. of events/person-year	2.3	3.0	1.3 (0.9-2.0)	.20
Patients with ≥1 event, No. (%)	51 (34)	62 (42)		.15
Urgent care				
No. of events	43	43		
No. of events/person-year	0.7	0.7	1.0 (0.6-1.6)	.93
Patients with ≥1 event, No. (%)	33 (22)	34 (23)		.82
New use of oral steroids				
No. of events	45	52	1.1 (0.8-1.6)	.48
No. of events/person-year	0.7	0.8		
Patients with ≥1 event, No. (%)	44 (30)	49 (34)		.46
<b>Episodes of Poor Asthma Control 2</b>				
No. of events	273	333		
No. of events/person-year	4.4	5.2	1.2 (0.9-1.5)	.20
Patients with ≥1 event, No. (%)	106 (71)	104 (71)		.99
Rescue medications				
No. of events	151	191		
No. of events/person-year	2.6	3.1	1.2 (0.9-1.7)	.28
Patients with ≥1 event, No. (%)	68 (49)	79 (57)		.19

<sup>a</sup>Based on negative binomial regression.

**Table 4.** Adverse Events

	Treatment Group, No. (%)		Relative Risk (95% CI)	P Value <sup>a</sup>
	Placebo (n = 150)	Lansoprazole (n = 147)		
Upper respiratory tract infection	74 (49)	93 (63)	1.3 (1.1-1.6)	.02
Sore throat	59 (39)	77 (52)	1.3 (1.0-1.6)	.02
Group A <i>Streptococcus</i>	11 (7)	6 (4)	0.8 (0.5-1.1)	.23
Bronchitis	3 (2)	10 (7)	2.2 (0.8-6.1)	.04
Pneumonia	5 (3)	4 (3)	0.9 (0.5-1.6)	.76
Otitis media	10 (7)	12 (8)	1.1 (0.7-1.8)	.62
Acute sinusitis	17 (11)	16 (11)	1.0 (0.7-1.4)	.90

<sup>a</sup>By Mantel-Haenszel test.

**Subanalysis of Children With Abnormal Esophageal pH Study Results**

Among the 115 children with adequate 24-hour esophageal monitoring studies, 43% (n=49) had positive results for GER; 38% (n=20) who received placebo had GER vs 47% (n=29) who received lansoprazole ( $P = .33$ ). In a subanalysis of children with GER, there was no significant effect of lansoprazole treatment on any of the study outcomes, including the ACQ, ASUI, ACT or cACT, asthma-related quality of life, lung function, or bronchial hyperresponsiveness (eTable 2 and eTable 3).

**Adverse Events**

Ten participants in the lansoprazole group and 9 in the placebo group had 1 or more serious adverse events. The most common serious adverse event in both groups was asthma exacerbation (15 of 25 reports). Treatment with lansoprazole was associated with a greater prevalence of upper respiratory tract infections, sore throats, and episodes of bronchitis (TABLE 4).

Activity-related bone fractures were not different in children treated with lansoprazole vs placebo (6/149 vs 1/157;  $P = .06$ ). Children who had fractures were between ages 7 and 14 years and all had been receiving inhaled corticosteroids throughout the trial; 2 (1 in each group) had also received a course of oral prednisone during the trial. One

fracture, in the lansoprazole group, occurred on the day the patient was randomized. The others occurred after 2 months (n=1), 5 months (n=3), and 6 months (n=2) of follow-up.

## COMMENT

Among children with poorly controlled asthma, lansoprazole treatment had no effect on asthma control measures. This was the case even though GER was prevalent (43% as evidenced by positive esophageal pH test results) in the study sample. In a sub-analysis of the effects of lansoprazole restricted to participants with documented GER, we found no effect of lansoprazole on any of the aforementioned indicators of asthma control. Nor was lansoprazole effective in subgroups defined by markers of asthma severity (either FEV<sub>1</sub> at baseline or oral steroid use in the past year). The results of this clinical trial are uniformly negative regarding the benefit of acid suppression therapy on symptom relief, lung function, airways reactivity, or quality of life.

Previous clinical trials in children with symptomatic GER and respiratory symptoms have not shown a clear benefit of PPI treatment on respiratory outcomes. In children, most with demonstrable GER, PPI improved asthma symptoms<sup>31</sup> or improved airways reactivity.<sup>32</sup> However, a placebo-controlled trial of omeprazole in 38 children with asthma and GER showed no significant effect of omeprazole on asthma outcomes.<sup>33</sup> These results, in conjunction with ours, indicate that PPI therapy for poorly controlled asthma is not warranted.

Although our results are robust, there are hypotheses about the role of GER in asthma that we did not address. We focused on patients without symptomatic GER because these children do not have an independent indication for PPI treatment. The possible role of non-acid reflux in worsening asthma control is unclear, and the observed failure of acid-suppressive therapy to improve asthma does not address this mechanism. It is also possible that the

dose of PPI was not adequate to suppress all acid production; however, we did not think it was justified to use doses that exceeded the FDA-approved dose of lansoprazole in children. We also did not conduct on-treatment pH probe studies to confirm acid suppression. Furthermore, adherence to study drug, although high by self-report, could have influenced our results.

Our study does not refute the possibility that GER may trigger chronic cough in children.<sup>34</sup> In a recent study in nonasthmatic children with chronic cough, episodes of GER preceded cough in 22 of 26 patients.<sup>35</sup> In adults, proximal reflux has been reported to be associated with worse asthma control and health-related quality of life despite lack of physiologic impairment or increase in asthma symptoms.<sup>36</sup>

We confirmed previous data suggesting a high prevalence of GER in asthmatic children, and our results do not support routine esophageal pH testing to identify children who respond to PPIs, nor do they support trials of PPIs for poorly controlled asthma. In our trial, participants with positive pH probe study results did not have significantly worse measures of lung function.

Our study raises important questions about adverse effects of lansoprazole treatment of children with asthma. The lansoprazole group had significantly more self-reported episodes of respiratory symptoms, including sore throats and bronchitis. In a clinical trial of lansoprazole vs placebo in infants, lansoprazole was associated with more lower respiratory tract infections.<sup>37</sup> In addition, PPI use has been associated with increased risk of community-acquired pneumonia in adults and children,<sup>38-41</sup> which is thought to be related to a reduction in the host defense against bacterial colonization imparted by low gastric acid.<sup>42-44</sup>

The use of PPIs in children has increased dramatically in the past decade, from about 875 000 prescriptions in 2002 to 2.6 million in 2009,

which represents about 5% of children in the United States at that time.<sup>45</sup> The increase, especially among infants, along with safety signals in adults, has resulted in 2 FDA advisory board reviews of existing data related to the use of PPIs in children and infants within the past 2 years.<sup>46,47</sup> Both committees recognized that there were limited data, mostly from short-term studies, and the pediatric committee voted to receive updated reports on the safety of PPI use in children.<sup>45</sup> Our results reinforce the need for continued study of PPI safety in children.

In conclusion, the results of our study indicate that PPI treatment of children with poorly controlled asthma without symptomatic GER was not an effective therapy for asthma and there may be significant safety concerns for long-term PPI use in children that warrant further study.

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**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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**Funding/Support:** This study was supported by the American Lung Association Asthma Clinical Research

Centers Infrastructure Award and National Institutes of Health/National Heart, Lung, and Blood Institute grants U01 HL080450 (Dr Holbrook) and U01 HL080433 (Dr Teague). Lansoprazole and placebo were provided by Takeda Pharmaceuticals; albuterol was provided by GlaxoSmithKline.

**Role of the Sponsor:** Takeda and GlaxoSmithKline had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript. The American Lung Association and National Heart, Lung, and Blood Institute reviewed the protocol and/or had a role in the management/review of the study.

**Online-Only Material:** eTables 1 through 3 and the Author Video Interview are available at <http://www.jama.com>.

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