The Efficacy of Proton Pump Inhibitors for the Treatment of Asthma in Adults

A Meta-analysis

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Background: Gastroesophageal reflux disease occurs frequently among patients with asthma. Therapy with proton pump inhibitors (PPIs) to improve asthma control remains controversial. We sought to evaluate the efficacy of PPIs in treatment of asthma using objective and subjective outcome measures.

Methods: A literature search was undertaken using MEDLINE (1950-January 2010), PubMed (1950-January 2010), EMBASE (1980-January 2010), and Cochrane Central Register of Controlled Trials (through January 31, 2010). Randomized, placebo-controlled trials evaluating the efficacy of PPIs for treatment of asthma in adults were selected. The primary outcome of interest was morning peak expiratory flow (PEF) rate. Secondary outcomes included objective (evening PEF rate and forced expiratory volume in 1 second) and subjective (asthma symptoms score and Asthma Quality of Life Questionnaire score) measures. Influence of study characteristics on outcomes was examined by subgroup analyses and meta-regression.

Results: Eleven trials (2524 patients) met inclusion criteria. Overall, patients had a higher mean morning PEF rate after treatment with PPIs compared with placebo (mean difference, 8.68 L/min [95% confidence interval, 2.35-15.02]). No significant single large-study effect, temporal effect, or publication bias was seen. Subgroup analysis revealed a trend toward a larger improvement in morning PEF rate in studies enrolling only patients with gastroesophageal reflux disease (mean difference, 16.90 L/min [95% confidence interval, 0.85-32.95]). Analyses of secondary outcomes (asthma symptoms score, Asthma Quality of Life Questionnaire score, evening PEF rate, and forced expiratory volume in 1 second) showed no significant difference between PPIs and placebo.

Conclusions: Proton pump inhibitor therapy in adults with asthma results in a small, statistically significant improvement in morning PEF rate. The magnitude of this improvement, however, is unlikely to be of meaningful clinical significance. There is insufficient evidence to recommend empirical use of PPIs for routine treatment of asthma.

Arch Intern Med. 2011;171(7):620-629

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Asthma is a common disease, affecting approximately 7% of the population in the United States and 300 million people worldwide. It is defined as a chronic disorder of the airways characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation. Gastroesophageal reflux disease (GERD), the passage of gastric contents into the esophagus, is the most common digestive system disorder in the United States, affecting roughly one-third of the population. The association between asthma and GERD has been a topic of much investigation in recent decades. The 2 conditions often coexist, with GERD being reported in 40% to 80% of patients with asthma.

Gastroesophageal reflux disease–associated respiratory symptoms include cough, dyspnea, and wheezing. Reflux is postulated to cause bronchoconstriction directly, through microaspiration into the airways, as well as indirectly, via vagally mediated effects of acid on the upper airway or esophagus. In addition, bronchial asthma may favor the development of reflux by several mechanisms, eg, changes in the pressure gradient between the thorax and the abdomen may cause displacement of the lower esophageal sphincter into the chest, asthma-induced pulmonary hyperinflation can exacerbate diaphragmatic dysfunction, and lower esophageal sphincter tone can be decreased by frequent use of bronchodilators. Because gastroesophageal reflux
may act as a trigger for asthma, medical therapy has been a topic of much investigation. The cornerstone of medical treatment for acid reflux is the proton pump inhibitor (PPI), which has proven efficacy in the treatment of GERD and esophagitis. \(^{12}\) Expert opinion guidelines \(^{13,14}\) on the management of GERD recommend empirical therapy for patients with typical esophageal symptoms, such as heartburn or regurgitation. In the absence of a concomitant esophageal syndrome, empirical therapy is more controversial. Several groups \(^{15-20}\) have investigated the efficacy of different PPIs on asthma outcomes through randomized controlled trials (RCTs). Some studies \(^{17,20-22}\) have indicated that symptoms, lung function, or both can be improved with treatment of acid reflux; others \(^{16,18,19,23}\) have not demonstrated measurable improvement with acid suppression. A Cochrane Library systematic review \(^{24}\) published in 2003 examined the effects of several antireflux treatments (medical and surgical) on asthma outcomes in children and adults. The most recent systematic review \(^{25}\) published in 2009, studied whether treatment of GERD with PPIs improved asthma symptoms in children. Both studies were limited by small numbers of RCTs using PPIs with conflicting results and made no definitive recommendations regarding the use of PPIs for patients with asthma. Since the Cochrane Library systematic review, to our knowledge no meta-analysis has been published examining the effects of PPI therapy in adults with asthma. Furthermore, several large RCTs \(^{15-17,20,26}\) have been published in recent years. The objective of this meta-analysis was to evaluate the efficacy of PPI use on asthma control in adults with or without symptomatic GERD with respect to improvement in objective and subjective asthma outcome measures.

**STUDY SELECTION**

Two authors (E.C. and K.L.O.) independently reviewed the results of the search and selected all randomized placebo-controlled trials of any PPI used for treatment of asthma in adults (\(\geq 18\) years). For study inclusion, all patients needed to have an asthma diagnosis established by clinical history, physician's diagnosis, or evidence of variable expiratory airflow obstruction such as change in peak expiratory flow (PEF) rate or forced expiratory volume in 1 second (FEV\(_1\)). Studies also needed to report at least 1 clinical asthma outcome measure (eg, PEF rate, FEV\(_1\), asthma symptoms score, or quality-of-life assessment). We considered 4 weeks of daily therapy as the minimum duration, based on previous GERD studies \(^{15,21}\) that demonstrated stable symptom improvement after 4 to 6 weeks of PPI therapy. We excluded studies if they were published only in abstract form, did not report posttreatment asthma outcome measures, did not demonstrate adequate randomization, or did not include a placebo or PPI monotherapy arm.

**OUTCOME MEASURES**

Our primary outcome measure was the mean difference in morning PEF rate after treatment between participants receiving PPIs vs placebo. Morning PEF rate is a commonly used objective indicator for airway obstruction. It is inexpensive, widely available, and often included in asthma clinical research. Studies \(^{29}\) have shown that PEF rate indices, especially the morning prebronchodilator PEF, correlate strongly with airway hyperresponsiveness. Secondary objective measures of lung function included evening PEF rate and FEV\(_1\). Secondary subjective measures of asthma outcome included the standardized Asthma Quality of Life Questionnaire (AQLQ[S]) score and asthma symptoms score (scale, 0-3). \(^{30}\) The overall quality-of-life score on AQLQ[S] is derived from calculating the mean across a 32-item questionnaire in which patients are asked to respond to each item on a 7-point Likert scale, with 1 indicating maximal impairment and 7 indicating no impairment.

**DATA SYNTHESIS AND STATISTICAL ANALYSIS**

For continuous outcomes, the weighted mean difference and 95% confidence interval (CI) were calculated. The primary meta-analyzer for this meta-analysis was the mean difference in morning PEF rate between the placebo and study groups at the end of the trial. Because of the anticipated variability in patient population and study design, we used the random-effects models, with significance accepted at \(P < .05\). Pooled trial results were evaluated with the \(I^2\) statistic, with cut-off points of 25%, 50%, and 75% to quantify low, moderate, and high degrees of heterogeneity between studies. \(^{30}\) Potential sources for clinical heterogeneity among studies were specified a priori, including a planned subgroup analysis according to whether studies required a diagnosis of GERD for inclusion and meta-regression analyses based on weeks of PPI therapy and cumulative PPI dosage used to examine the effect of different lengths of treatment and drug dosage. One-study-removed analysis was performed on the pooled trial results to examine the effect of single

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**METHODS**

**DATA SOURCES AND SEARCHES**

A literature search was undertaken using MEDLINE (1950 to January 2010), EMBASE (1980 to January 2010), and the Cochrane Central Register of Controlled Trials for RCTs on the use of PPIs for asthma published through January 31, 2010. The following search terms were used as both keywords and medical subject heading terms as applicable: asthma, gastro-esophageal reflux, gastroesophageal reflux disease, gastro-esophageal reflux, proton pump inhibitor, omeprazole, rabeprazole, pantoprazole, esomeprazole, and rabeprazole. The titles, abstracts, and keywords of identified articles were evaluated for relevance, and the references lists of these articles were reviewed for additional articles. No language restrictions were applied.
large studies; a cumulative analysis was conducted to explore time trends by publication year. Finally, we assessed the possibility of publication bias with a funnel plot and the Duval and Tweedie trim and fill method. All analyses were conducted using meta-analysis software (Comprehensive Meta-Analysis, Version 2; Biostat, Englewood, New Jersey). The meta-analysis was carried out in accordance with the Meta-analysis of Observational Studies in Epidemiology guidelines.\(^\text{13}\)

**RESULTS**

The search strategy yielded 777 articles, 25 of which were complete reports on RCTs published in English. The 752 excluded articles included duplicate citations, non-peer-reviewed abstracts, animal studies, case reports, observational studies, editorials, letters, reviews, meta-analyses, and practice guidelines. Of the 25 clinical trials identified, 11 RCTs\(^\text{15-23,26,34}\) that investigated PPI use in patients with asthma were included. Fourteen studies were excluded because the sample

**STUDY SELECTION**

<table>
<thead>
<tr>
<th>Source</th>
<th>Location</th>
<th>Study Design</th>
<th>Study Group</th>
<th>Control Group</th>
<th>Asthma Diagnosis</th>
<th>GERD Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ford et al.(^\text{19}) 1994</td>
<td>Europe</td>
<td>RCT, crossover</td>
<td>10</td>
<td>10</td>
<td>Clinical diagnosis plus improvement in PEF rate (\geq 15%) after bronchodilator use</td>
<td>Esophagitis shown on endoscopy or abnormal results of esophageal pH monitoring</td>
</tr>
<tr>
<td>Teichtahl et al.(^\text{20}) 1996</td>
<td>Australia</td>
<td>RCT, crossover</td>
<td>20</td>
<td>20</td>
<td>Clinical diagnosis plus FEV(_1), reversibility (\geq 15%) with bronchodilator, diurnal variation in PEF rate (&gt;19%), positive results of methacholine challenge</td>
<td>Abnormal results of esophageal pH monitoring</td>
</tr>
<tr>
<td>Levin et al.(^\text{21}) 1998</td>
<td>North America</td>
<td>RCT, crossover</td>
<td>9</td>
<td>9</td>
<td>Clinical diagnosis plus FEV(_1), reversibility (\geq 15%) after bronchodilator; daily use of asthma medication</td>
<td>History of reflux symptoms and abnormal results of esophageal pH monitoring</td>
</tr>
<tr>
<td>Borree et al.(^\text{22}) 1999</td>
<td>Europe</td>
<td>RCT</td>
<td>15</td>
<td>13</td>
<td>Positive results of methacholine challenge test with (&gt;20%) fall in FEV(_1); reversibility with ipratropium bromide; current use of ICS, baseline FEV(_1), (&gt;1.25) L</td>
<td>Abnormal results of esophageal pH monitoring</td>
</tr>
<tr>
<td>Kijlstra et al.(^\text{23}) 1999</td>
<td>Europe</td>
<td>RCT, crossover</td>
<td>52</td>
<td>52</td>
<td>Clinical diagnosis of asthma plus FEV(_1), reversibility (\geq 15%) after bronchodilator use or (20%) decrease in FEV(_1), with methacholine challenge; or (\geq 20%) diurnal variation in PEF rate</td>
<td>Abnormal results of esophageal pH monitoring</td>
</tr>
<tr>
<td>Littner et al.(^\text{24}) 2005</td>
<td>North America</td>
<td>RCT</td>
<td>99</td>
<td>108</td>
<td>Clinical diagnosis of asthma plus FEV(_1), (50%-80%) predicted, FEV(_1), reversibility (\geq 12%), current use of ICS</td>
<td>History of reflux symptoms</td>
</tr>
<tr>
<td>Kijlstra et al.(^\text{25}) 2006</td>
<td>Europe, North America, South America</td>
<td>RCT</td>
<td>387</td>
<td>383</td>
<td>Clinical diagnosis of asthma plus use of ICS or leukotriene modifiers (&gt;3) mo, FEV(_1), (50%-80%) predicted, FEV(_1), reversibility (\geq 12%), mean morning PEF rate (&lt;80%) predicted</td>
<td>Not required</td>
</tr>
<tr>
<td>dos Santos et al.(^\text{26}) 2007</td>
<td>South America</td>
<td>RCT</td>
<td>22</td>
<td>22</td>
<td>Clinical diagnosis of asthma plus FEV(_1), FEV(_1)/VC &lt;90% predicted and FEV(_1), reversibility (&gt;7%) after bronchodilator use or positive results of methacholine challenge test</td>
<td>Abnormal results of esophageal pH monitoring</td>
</tr>
<tr>
<td>Peterson et al.(^\text{27}) 2009</td>
<td>North America</td>
<td>RCT</td>
<td>23</td>
<td>8</td>
<td>Clinical diagnosis of exercise-triggered asthma</td>
<td>Not required</td>
</tr>
<tr>
<td>Mastronarde et al.(^\text{28}) 2009</td>
<td>North America</td>
<td>RCT</td>
<td>200</td>
<td>193</td>
<td>Clinical diagnosis of asthma plus positive results of methacholine challenge test or FEV(_1), reversibility (\geq 12%) with bronchodilator, daily ICS use for (\geq 8) wk, JACQ score (\geq 1.5), or (\geq 1) asthma exacerbation in past 12 mo</td>
<td>Not required</td>
</tr>
<tr>
<td>Kijlstra et al.(^\text{29}) 2010</td>
<td>Europe, North America, South America</td>
<td>RCT</td>
<td>632 (319 in twice-daily group)</td>
<td>328</td>
<td>Clinical diagnosis of asthma plus FEV(_1), reversibility (\geq 12%) with bronchodilator, daily ICS and LABA use for (\geq 3) mo, and (\geq 1) asthma exacerbation in past 12 mo</td>
<td>History of reflux symptoms or history of abnormal results of esophageal pH monitoring</td>
</tr>
</tbody>
</table>

Abbreviations: FEV\(_1\), forced expiratory volume in 1 second; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; JACQ, Juniper Asthma Control Questionnaire\(^\text{24}\); LABA, long-acting \(\beta\)-agonist; PPI, peak expiratory flow; RCT, randomized controlled trial.
added children or adolescents,15-37 the patients did not have a diagnosis of asthma,38 the trials were not randomized or not placebo-controlled,39-67 or the treatment included medications in addition to PPIs to treat GERD.46 Figure 1 shows the flowchart for study inclusion.

Eleven RCTs investigated the effects of treatment with PPI on asthma (2524 patients) (Table 1).15-23,26,34,49 Seven studies used a parallel design and 4 were crossover trials.17,19,21,34 Asthma was diagnosed most often in accordance with American Thoracic Society guidelines50 and/or by pulmonary function testing indicating expiratory airflow obstruction with or without bronchodilator reversibility. One study22 included patients with exercise-triggered asthma that had been clinically diagnosed by a pulmonologist. A diagnosis of GERD was required for inclusion in 8 studies,15,17-19,21,23,26,34 The criteria for GERD varied among studies and included history of symptoms, endoscopy-proved esophagitis, and/or 24-hour pH monitoring. Three studies16,20,22 did not require patients to have a diagnosis of GERD for inclusion. All 11 studies had a Jadad score of 5 and were of acceptable methodologic quality for inclusion in the meta-analysis.

Treatment protocols contained moderate variation. Included studies used omeprazole, lansoprazole, pantoprazole, esomeprazole, or rabeprazole, with an equivalent daily dosing range of 20 mg to 80 mg. Treatment duration ranged from 4 weeks to 26 weeks. Asthma outcomes were reported inconsistently among the studies and therefore not all studies were included in all analyses. Objective measures of lung function, such as evening PEF rate and FEV1, were reported in several studies. Subjective outcomes, such as asthma symptoms scores and AQLQ(S) scores, were not consistently reported (Table 2).

META-ANALYSIS

In the analysis of the primary end point, 8 of 9 included studies15,16,19,20,26,34 showed improved morning PEF rate in the PPI arm, although the 95% CI of 6 of these studies15,16,19,20,26,34 crossed the neutral (zero) line. The overall meta-analysis demonstrated a small but statistically significant improvement (8.68 L/min; [95% CI, 2.35-15.02]; P = .007) in morning PEF rate in participants who received PPI therapy (Figure 2A). The I² index was 30.09%, suggesting moderate heterogeneity.31 In the I-study-removed analysis, the outcomes of pooled analysis remained the same, without significant deviation from the overall result when individual studies were removed, suggesting no significant effect from single large studies. Cumulative analysis showed consistent results, with the outcomes favoring a small benefit of PPI use as more studies were added. Publication bias was evaluated with a funnel plot, which demonstrated balanced study results without the need for study imputation. The Duval and Tweedie trim and fill analysis32 further supported the lack of publication bias, with no studies trimmed and no significant change in the point estimate (Figure 3, Figure 4, and Figure 5).

A subgroup analysis was carried out based on studies that required GERD diagnosis for inclusion15,18,19,21,23,26,34 vs studies that did not16,20 (Figure 2B). Both sub-

### Table 2. Summary of Results of PPI Therapy on Asthma Outcomes

<table>
<thead>
<tr>
<th>Source</th>
<th>PPI Treatment</th>
<th>AM PEF, L/min</th>
<th>PM PEF, L/min</th>
<th>FEV1, L</th>
<th>Asthma Symptoms Score</th>
<th>AQLQ(S) Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ford et al19 1994</td>
<td>Omeprazole, 20 mg, once daily for 24 wk</td>
<td>7 (-63.38 to 82.38)</td>
<td>3 (-66.7 to 72.7)</td>
<td>NA</td>
<td>0 (-0.57 to 0.57)</td>
<td>NA</td>
</tr>
<tr>
<td>Jacobson et al24 1996</td>
<td>Omeprazole, 40 mg, once daily for 2 wk</td>
<td>14 (-46.13 to 74.13)</td>
<td>10 (-81.70 to 101.70)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Levin et al37 1998</td>
<td>Omeprazole, 20 mg, once daily for 8 wk</td>
<td>37.8 (10.9 to 64.6)</td>
<td>31.2 (3.2 to 59.2)</td>
<td>0.13 (-0.17 to 0.43)</td>
<td>NA</td>
<td>1.18 (0.18-2.18)</td>
</tr>
<tr>
<td>Boeke et al20 1998</td>
<td>Omeprazole, 40 mg, twice daily for 12 wk</td>
<td>-13 (-90.29 to 64.29)</td>
<td>NA</td>
<td>-0.02 (-0.56 to 0.52)</td>
<td>-0.03 (-0.46 to 0.40)</td>
<td>NA</td>
</tr>
<tr>
<td>Kiljander et al,15 1999a</td>
<td>Omeprazole, 20 mg, once daily for 8 wk</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Littner et al26 2006</td>
<td>Lansoprazole, 30 mg, twice daily for 24 wk</td>
<td>6 (-18.52 to 30.52)</td>
<td>0 (-24.58 to 24.58)</td>
<td>-0.1 (-0.31 to 0.11)</td>
<td>0.14 (-0.03 to 0.31)</td>
<td>NA</td>
</tr>
<tr>
<td>Kiljander et al34 2007</td>
<td>Esomeprazole, 40 mg, twice daily for 16 wk</td>
<td>6.3 (-0.28 to 12.88)</td>
<td>5.4 (-0.06 to 10.86)</td>
<td>NA</td>
<td>NA</td>
<td>0.03 (-0.1 to 0.15)</td>
</tr>
<tr>
<td>dos Santos et al22 2007</td>
<td>Pantoprazole, 40 mg, once daily for 12 wk</td>
<td>60 (13.3 to 106.7)</td>
<td>54 (-8.06 to 116.06)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Peterson et al22 2009</td>
<td>Rabeprazole, 20 mg, once or twice daily for 10-12 wk</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.53 (-0.29 to 1.34)</td>
</tr>
<tr>
<td>Mastronarde et al26 2009</td>
<td>Esomeprazole, 40 mg, twice daily for 24 wk</td>
<td>6 (-3.99 to 15.99)</td>
<td>NA</td>
<td>0.025 (-0.03 to 0.08)</td>
<td>NA</td>
<td>-0.098 (-0.21 to 0.17)</td>
</tr>
<tr>
<td>Kiljander et al20 2010</td>
<td>Esomeprazole, 40 mg, once or twice daily for 26 wk</td>
<td>Once daily: 3.5 (1.2-5.8)</td>
<td>Once daily: 10 (9.2-10.2)</td>
<td>Once daily: -0.2 (0.2-1.2)</td>
<td>Once daily: 0.09 (0.03 to 0.15)</td>
<td>Once daily: 0.28 (0.12 to 0.44)</td>
</tr>
</tbody>
</table>

**Abbreviations:** AM PEF, morning peak expiratory flow; AQLQ(S), standardized Asthma Quality of Life Questionnaire; CI, confidence interval; FEV1, forced expiratory volume in 1 second; NA, not available; PM PEF, evening PEF; PPI, proton pump inhibitor.

4 Data were expressed as medians and quartiles only.
groups showed small but statistically significant improvements in morning PEF rate with PPI therapy, although a larger benefit was seen in the subgroup of studies containing only patients with GERD (16.90 L/min; [95% CI, 0.85–32.95] vs 6.21 L/min [0.71–11.71]). The difference in morning PEF rate improvement between the 2 subgroups was statistically significant (P = .006), according to analysis of variance. Meta-regression analyses were carried out on the basis of treatment duration and cumulative PPI dosage. There was no evidence of any significant relationship between treatment length (β = −0.007; P = .35) or cumulative PPI dosage (β = −0.001; P = .05) and morning PEF rate outcome (Figure 6 and Figure 7).

Six studies included in the analysis reported data on evening PEF rate, with 5 showing a mean difference favoring PPI use. One study displayed no treatment effect, with a mean difference in evening PEF rate of zero. The overall meta-analysis revealed a trend toward benefit with PPI therapy in patients with asthma (9.865 L/min [95% CI, −1.294 to 21.015]; P = .08) that did not reach statistical significance (Figure 8A). Mean change in FEV₁ was reported in 6 studies, as another objective asthma outcome after treatment (Figure 8B). Five of those studies showed no significant change in FEV₁ level between the PPI and placebo groups, and 1 study demonstrated a small but statistically significant improvement. The outcome of the meta-
analysis demonstrated no significant benefit of PPIs on FEV₁ (0.056 L [95% CI, −0.023 to 0.134]; P = .17).

Subjective treatment outcomes were evaluated using the asthma symptoms score and the AQLQ(S) score. The 3 studies18,19,26 that reported the asthma symptoms score found no significant difference in symptom improvements with PPIs vs placebo (Figure 8C). The overall meta-analysis similarly demonstrated no treatment benefits with PPI use (0.109 [95% CI, −0.042 to 0.026]; P = .16). Four studies15,16,20,21 used AQLQ(S) to measure quality of life before and after treatment (Figure 8D). Three studies15,20,21 showed a difference in means favoring PPI use, although one of them20 failed to achieve statistical significance. Meta-analysis of the 4 studies revealed no significant difference in mean AQLQ(S) after therapy between the 2 treatment arms (0.197 [95% CI, −0.078 to 0.472]; P = .16).

ADVERSE EVENTS

Data on the total number of adverse events were reported in only 4 RCTs (2154 patients).15,16,20,26 Overall, 34 of 1216 patients (2.8%) who received a PPI experienced serious adverse events compared with 31 of 938 patients (3.3%) who received a placebo. The most commonly reported adverse events were asthma exacerbation, nasopharyngitis, bronchitis, pneumonia, headache, nausea, and back pain. None of the studies reported a statistically significant difference in the rate of serious adverse events between the PPI and placebo arms. The overall relative risk of experiencing serious adverse events with PPIs compared with placebo was 0.85 (95% CI, 0.52-1.37).

COMMENT

For our primary outcome of interest, morning PEF rate, we evaluated 9 RCTs (2167 patients) and found a small, statistically significant improvement in patients with asthma treated with PPI vs placebo. Stratification of studies based on whether GERD was an inclusion criterion demonstrated an incremental benefit for patients diagnosed as having GERD. Although statistically significant, physiologic benefits of PPI therapy for asthma were noted, these improvements were small and likely represent minimal clinical benefit. Furthermore, PPI therapy appeared to have little effect on evening PEF rate, FEV₁, asthma symptoms, or quality of life.

To our knowledge, the present study is the largest meta-analysis to date exploring the relationship between PPI therapy and asthma, an area that continues to remain controversial. The largest previous analysis on PPIs in asthma was published in 2003 by the Cochrane Collaboration.24 The Cochrane Collaboration study also found no overall improvement in asthma outcomes after treatment with PPIs, but it was limited by the low number of studies and small sample sizes, as only 3 studies involving PPIs could be analyzed for our primary outcome, morning PEF rate. With several large, multicenter RCTs published in recent years, the present meta-analysis is able to provide a 20-fold greater number of patients for measurement of this outcome. The larger sample of studies also allowed us to conduct a more robust analysis of secondary outcomes, evaluation of possible sources of heterogeneity, and assessment for publication bias.

Given the large patient population analyzed in this study, we believe that it contributes to scientific knowledge and clinical care of patients with asthma. Although our
analysis did not find any statistically significant difference in the rate of serious adverse events between patients receiving PPIs and those receiving placebo, chronic acid suppression has become increasingly linked to complications such as pneumonia, bone loss, enteric infections, and bacterial overgrowth.51-54 Within this context, establishing clear benefits of chronic PPI use on objective asthma outcomes has gained considerable importance. The relatively small improvements in morning PEF rate after treatment with PPIs demonstrated by our analysis should be weighed against the lack of improvement among other objective and subjective asthma outcomes as well as the risk of complications associated with chronic acid suppression. Furthermore, other literature suggests that greater improvements in PEF rate are necessary to affect clinical outcomes. Santanello et al55 demonstrated the average minimal patient perceivable improvement for PEF rate to be 18.79 L/min (95% CI, 0.7-36.9). Randomized controlled trials56-59 involving inhaled corticosteroids, bronchodilators, and leukotriene inhibitors generally demonstrate PEF rate improvements in the range of 25 to 40 L/min. Our results fall below the range of minimal patient perceivable improvement for PEF rate as well as improvements seen with other medical therapies, suggesting minimal clinical benefit for routine asthma care.

Subgroup analysis from our study demonstrated an incremental improvement in PEF rate (16.9 L/min) in the subpopulation of patients with asthma and GERD. This improvement was also small; however, it approached the minimal patient perceivable improvement and fell within the range of PEF rate (15-20 L/min) traditionally used as target and deemed effective in clinical trials for asthma therapies.60 Although the clinical significance of this added benefit remains unclear, it does raise the possibility of a physiological mechanism between GERD and asthma. In addition, it suggests that a subpopulation of patients with asthma and GERD may receive clinically significant benefit from PPI therapy. Within the limitations of this meta-analysis, however, we were not able to identify the specific clinical features of this subpopulation.

The association between asthma and GERD has been well established in clinical studies, and several causal relationships have been proposed, including microaspiration, vagal reflex, and airway hyperresponsiveness.61,62 There are some possible explanations for the small improvement with PPIs observed in our meta-analysis. First, the primary mechanism of action of PPI therapy is acid suppression. Proton pump inhibitors may have less benefit if nonacidic reflux is a contributor to asthma severity and symptoms. Suppression of acid secretion does not protect against reflux and aspiration of the other components of gastric contents. In studies63,64 of lung transplant recipients with GERD, higher levels of both pepsin and bile acids were found in the bronchoalveolar lavage fluid obtained from patients with signs of graft failure compared with those without such signs, suggesting that acidic secretions from the stomach may be only one of many irritants aspirated during reflux. Second, it is possible that PPI therapy is beneficial only in certain subpopulations of patients with asthma, particularly those with pathologic vs physiological acid reflux. Our study suggests that routine use of PPIs in most patients with asthma is unlikely to result in significant clinical benefit. Future investigations should focus...
on the effect of minimizing reflux and the optimal identification of subgroups of patients with asthma and GERD who may benefit the most from PPI therapy. In a study conducted by Harding et al,65 most patients with asthma and no reflux symptoms (62%) had abnormal findings during 24-hour esophageal pH monitoring. Furthermore, participants with asymptomatic GERD had higher amounts of proximal esophageal acid exposure compared with those with symptomatic GERD. Therefore, the role of tests such as manometry, intraesophageal impedance, and proximal pH monitoring in the care of patients with asthma should be further explored.

There are several limitations to our study. Of 11 RCTs, 2 reported the primary outcome of interest in a form that could not be extracted and combined. However, we do not believe that these excluded trials would have significantly affected our conclusions. The 1999 study by Kiljander et al,17 which reported medians and quartiles, was relatively small. Similarly, the study by Peterson et al,22 in which PEF rate was not measured, was small, with 31 participants randomized to 3 arms. Another problem was that significantly fewer studies could be combined to evaluate some of our secondary outcome measures. This led to decreased power for these outcomes; however, results between studies have been generally consistent.

Heterogeneity among studies could also be a limitation. Asthma diagnoses were based on a range of methods from clinical guidelines to spirometry. Asthma severity in the various studies ranged from typical to treatment refractory. Similarly, GERD diagnoses were based on varied criteria...

Figure 8. Meta-analysis of secondary outcomes, including (A) evening PEF rate, (B) FEV₁, (C) asthma symptoms score, and (D) AQLQ(S). AQLQ(S) indicates standardized Asthma Quality of Life Questionnaire; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; PEF, peak expiratory flow; PPI, proton pump inhibitor.
toria ranging from clinical symptoms to endoscopy to pH probe results. In 2 of the 9 RCTs, GERD was not a prerequisite for inclusion. Finally, the duration of PPI therapy varied. Our analysis demonstrated only moderate statistical heterogeneity across studies (I²=30.09%). In the studies that did not specify GERD as an inclusion criterion, postenrollment testing revealed a GERD prevalence of 33% to 75%, which is consistent with observational data.4,6,66-69 We evaluated the role of GERD as an inclusion criterion by dichotomizing the studies into those requiring GERD for enrollment vs those that did not and noted a modest improvement with PPI therapy in the studies requiring a GERD diagnosis. This suggests a small, but measurable benefit for patients with asthma and GERD. Finally, our meta-regression did not demonstrate any relationship between the duration of PPI therapy or cumulative PPI dosage and asthma outcomes.

Our results show that the empirical use of PPI therapy for adults with asthma results in a small, statistically significant improvement in morning PEF rate. However, these small benefits are unlikely to be clinically significant. The increase in morning PEF rate was greater among participants enrolled in studies that had GERD as an inclusion criterion. Analyses of secondary outcomes (other signs and symptoms of asthma and quality of life) showed no significant difference between PPIs and placebo. There is insufficient evidence to support the routine use of PPIs in the treatment of asthma. Further studies should focus on clarifying the pathologic roles of symptomatic and silent GERD in patients with concurrent asthma, exploring the clinical utility of physiological studies such as esophageal impedance and pH monitoring, and identifying patients who may receive benefits from PPI therapy.

Accepted for Publication: September 29, 2010.

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Financial Disclosure: None reported.

Additional Contributions: Michael Stoto, PhD, Adjunct Professor of Biostatistics (Harvard School of Public Health) and Professor of Health Services Administration and Population Health (Georgetown University School of Nursing & Health Studies) provided support and guidance in the design and statistical analysis of this study. He did not receive compensation for his assistance.

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