The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.
Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). The Drug Effectiveness Review Project governance group elected to proceed with another update of this report. Please see timeline on the DERP website for details on the date of its release. Prior versions of the report can be accessed at the DERP website.
FIGURES
Figure 1. Esophagitis healing rates at 4 weeks in head-to-head trials of PPIs..................................................63
Figure 2. Esophagitis healing rates at 8 weeks in head-to-head trials of PPIs..................................................64
Figure 3. Rates of complete resolution of symptoms at 4 weeks in head-to-head trials of PPIs..........................65
Figure 4. Healing at 4 weeks in patients with moderate to severe esophagitis.................................................66
Figure 5. Healing at 8 weeks in patients with moderate to severe esophagitis................................................67
Figure 6. PPI vs. H2 Receptor antagonists for esophagitis healing at 8 weeks..............................................68
Figure 7. Duodenal ulcer healing at 4 weeks: PPI vs PPI.................................................................................69
Figure 8. PPI vs. H2 Receptor antagonists for duodenal ulcer healing at 4 weeks...........................................70
Figure 9. Gastric ulcer: PPI vs H2-Antagonist healing at 4 weeks.................................................................72

APPENDICES
Appendix A. Search Strategy .......................................................................................................................73
Appendix B. Quality assessment methods for drug class reviews for DERP ..................................................75
Appendix C. Placebo-controlled randomized trials of PPIs (not included).....................................................79
Appendix D. Abstract-only studies (not included)..........................................................................................83
Appendix E. Results of search and selection of included articles.................................................................93
Appendix F. Esophagitis grading scales used in randomized controlled trials ..............................................94
Appendix G. Studies Currently Under Review / In-Process .........................................................................96

EVIDENCE TABLES – Published in a separate document

Funding:

The funding source, the Center for Evidence-based Policy, is supported by 17 organizations, including 15 state Medicaid programs. These organizations selected the topic and had input into the Key Questions for this review. The content and conclusions of the review are entirely determined by the Evidence-based Practice Center researchers. The authors of this report have no financial interest in any company that makes or distributes the products reviewed in this report.

Suggested citation for this report:

McDonagh MS, Carson S. Drug Class Review on Proton Pump Inhibitors. 2006.
http://www.ohsu.edu/drugeffectiveness/reports/final.cfm
INTRODUCTION

Proton pump inhibitors (PPIs) decrease gastric acid and gastric secretory volume. PPIs act by blocking the enzyme system responsible for active transport of acid into the gastrointestinal lumen, namely the hydrogen/potassium adenosine triphosphatase (H+/K+ ATPase) of the gastric parietal cell, also known as the “proton pump.” Omeprazole, the first drug in this class, was introduced in 1989. Since then, four other PPIs have been introduced: lansoprazole (1995), rabeprazole (1999), pantoprazole (2000) and esomeprazole (2001). In 2003 omeprazole became available over-the-counter in the US. The formulation for the over-the-counter product is omeprazole magnesium, available in other countries as omeprazole multiple unit pellet system (MUPS). Omeprazole is also available in combination with sodium bicarbonate (Zegerid).

PPIs are used to treat peptic ulcers (duodenal and gastric), symptoms of gastroesophageal reflux disease (GERD), healing of erosive esophagitis, and drug-induced ulcers (e.g., non-steroidal anti-inflammatory drugs {NSAIDs}). If H. pylori, the bacterium that causes ulcers, is present, PPIs are given with antibiotics to eradicate H. pylori. The predominant use of PPIs is symptomatic treatment of GERD and gastritis. For gastroesophageal reflux, which causes heartburn and acid regurgitation, the American Gastroenterological Association recommends that patients first try lifestyle modifications and antacids or over-the-counter histamine-2 receptor antagonists (H2-RAs, commonly called “H2-blockers”). If these steps do not completely control heartburn symptoms, PPIs or high doses of H2-RAs may be prescribed. Many clinicians use H2-RAs as the initial therapy for gastroesophageal reflux.

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different PPIs. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative efficacy of different PPIs in patients with symptoms of GERD?

   a. In head-to-head comparisons, what is the comparative efficacy of different PPIs in healing esophagitis, reducing symptoms, and preventing relapse in adult patients with symptoms of GERD?

   b. In comparisons of PPIs and H2-RAs, what is the comparative efficacy of different PPIs in healing esophagitis, reducing symptoms, and preventing relapse of GERD?
Comment. Usually, evidence-based reports emphasize health outcomes, which are events or conditions patients can feel or experience. Heartburn, waking at night, acid regurgitation, and quality of life are examples of health outcomes.

In addition to symptoms, endoscopic healing (or endoscopic recurrence) of esophagitis was identified as a secondary outcome measure for this key question. The severity of symptoms is not a reliable indicator of the presence of esophagitis; to diagnose it, it is necessary to perform endoscopy (direct visualization of the lining of the esophagus). Esophagitis appears as a tear, break, or ulceration in the lining of the esophagus. Endoscopic healing is generally defined as complete re-epithelialization of the ulcer crater(s).

Endoscopic healing is an indicator (also called an intermediate outcome measure), not a health outcome, because patients do not directly feel or experience esophagitis. Patients who have no esophagitis can experience severe heartburn, and some patients who have esophagitis do not have symptoms.

Whenever judgments about efficacy are based on an intermediate measure, it is important to ask how strongly it is related to actual health outcomes. Esophagitis can lead to scarring and narrowing of the esophagus (stricture) or to a condition called Barrett’s esophagus, which is a risk factor for esophageal cancer. Ideally, an evidence-based review would be able to compare PPIs based on how well long-term use prevented these complications. However, there are no data on the comparative efficacy of different PPIs to prevent long-term complications. In most studies of PPIs, patients who have esophagitis before treatment undergo another endoscopy four or eight weeks after beginning treatment to assess healing. There is no evidence that rates of esophageal healing after 4 or 8 weeks of treatment are associated with the risk of stricture or esophageal cancer in the long run. As distinct from symptom relief, the benefit of quicker esophageal healing is also uncertain.

The clinical importance of small differences in healing rates at 4 or 8 weeks is not known. In addition, patients who have clinically significant improvements but who are not completely healed (e.g., those who improve from grade D to grade B) are classified as unhealed. Studies do not report the esophagitis grade of patients classified as “not healed” at followup. While healing rates are reviewed, the main outcome of interest is control of symptoms.

2. What is the comparative efficacy of different proton pump inhibitors in patients with peptic ulcer and NSAID-induced ulcer?

a. In head-to-head comparisons, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with duodenal ulcer?

b. In comparisons of PPIs and H2-RAs, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with duodenal ulcer?

c. In head-to-head comparisons, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with gastric ulcer?
d. In comparisons of PPIs and H2-RAs, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with gastric ulcer?

e. In head-to-head comparisons, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with NSAID-induced ulcer?

f. In comparisons of PPIs and misoprostol, or H2-RAs, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with NSAID-induced ulcer?

g. In head-to-head comparisons, what is the comparative efficacy of different PPIs in preventing NSAID-induced ulcer?

h. In comparisons of PPIs and other drugs or placebo, what is the comparative efficacy of different PPIs in preventing NSAID-induced ulcer?

i. In head-to-head comparisons, what is the comparative efficacy of different PPIs in improving eradication rates in adult patients with Helicobacter pylori?

j. In comparisons of PPIs and H2-RAs, what is the comparative efficacy of different PPIs in improving eradication rates in adult patients with Helicobacter pylori?

**Comment.** In the short term, symptom relief and function are important health outcomes of an episode of ulcer disease. In the long run, the most important determinant of functional status and quality of life is the prevention of recurrences and relapses of ulcers and of their complications (bleeding, hospitalization, and death). Studies of PPIs for ulcer disease are too short-term to address these outcomes directly. Instead they report two intermediate outcome measures. In the past the most commonly used indicator (intermediate outcome measure) for the efficacy of ulcer treatment was “endoscopic healing,” which means that, on repeat endoscopy after treatment, the ulcer is gone. Ulcer disease tends to recur even when the initial ulcer is completely healed. For this reason, endoscopic healing, while it is important as a predictor of relapse, was an imperfect indicator of long-term morbidity from ulcer disease. Since the discovery that H. pylori causes many peptic ulcers, “eradication of H. pylori” has emerged as a more important indicator of the long-term outcome of treatment. Eradication is a well-validated indicator because long-term studies have shown that eradication reduces the risk of ulcers and ulcer complications for several years.

3. What are the comparative incidence and nature of complications (serious or life-threatening or those that may adversely effect compliance) of different PPIs in patients being treated for symptoms of gastroesophageal reflux, peptic ulcer, and NSAID-induced ulcer?
Comment. Another measure of adverse effects is tolerability, measured as the proportion of patients who withdraw from a study due to adverse effects. In general, the PPIs are well tolerated by most patients (mild to moderate gastrointestinal and central nervous system adverse effects are most common).

4. Are there subgroups of patients based on demographics, other medications, or co-morbidities for which one medication or preparation is more effective or associated with fewer adverse effects?

METHODS

Literature Search

To identify articles relevant to each key question, we searched the Cochrane Library (4th Quarter 2005), Medline (1966- November Week 3 2005), Embase (1980-3rd quarter, 2004), and reference lists of review articles. In electronic searches, we combined terms for gastroesophageal reflux and peptic ulcer with terms for PPIs and relevant research designs (see Appendix A for complete search strategies). Pharmaceutical manufacturers were invited to submit dossiers, including citations. All citations were imported into an electronic database (EndNote 9.0).

Study Selection

The abstracts of all citations were assessed for inclusion using predetermined criteria. The full text of citations meeting preliminary inclusion criteria were retrieved and inclusion criteria re-applied. Citation and full-text review was conducted by one reviewer and checked by a second. Disagreements were resolved by consensus.

We included English-language reports of randomized controlled trials of at least 4 weeks’ duration, in adult outpatients with symptoms of gastroesophageal reflux, peptic ulcer, or NSAID-induced ulcer. Interventions included a PPI compared with another PPI, another anti-ulcer drug (e.g., H2-RA, prokinetic agent, or antacid), placebo, surgery, or antibiotics alone. For adverse effects, we also included observational studies. Included medications were omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole. Outcomes were symptoms, endoscopic healing, eradication rates, functional outcomes, quality of life, and adverse effects, including drug interactions.

To evaluate efficacy we included only controlled clinical trials. The validity of controlled trials depends on how they are designed. Randomized, properly blinded clinical trials are considered the highest level of evidence for assessing efficacy.2-4 Clinical trials that are not randomized or blinded, and those that have other methodological flaws, are less reliable, but are also discussed in our report.

Trials that evaluated one PPI against another provided direct evidence of comparative efficacy and adverse event rates. We did not examine in detail placebo-controlled trials if studies using an active control were available for a key question (see Appendix C), and did not examine
in detail active control trials if head-to-head trials were available. In theory, trials that compare PPIs to H2-RA or placebos can also provide evidence about efficacy. However, the efficacy of PPIs in different trials can be difficult to interpret because the patients may be different. We excluded reports that were published in abstract form only (see Appendix D).

To supplement our analyses of published results, we requested and received from the funder additional data from two published trials and one trial that was submitted to the FDA but not published.

To evaluate adverse event rates, we included clinical trials and observational cohort studies. Clinical trials are often not designed to assess adverse events, and may select low-risk patients (in order to minimize dropout rates) or utilize inadequately rigorous methodology for assessing adverse events. Observational studies designed to assess adverse event rates may include broader populations, carry out observations over a longer time period, utilize higher quality methodological techniques for assessing adverse events, or examine larger sample sizes.

**Data Abstraction**

The following data were abstracted from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to followup, method of outcome ascertainment, and results for each outcome. We recorded intention-to-treat results if available and the trial did not report high overall loss to followup. Data were abstracted by one reviewer and checked by another; disagreements were resolved by consensus.

**Validity Assessment**

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix B. These criteria are based on those developed by the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK). We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; and the use of intention-to-treat analysis. Trials that had a fatal flaw in one or more categories were rated poor quality; trials which met all criteria, were rated good quality; the remainder were rated fair quality. As the “fair quality” category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are likely to be valid, while others are only probably valid. A “poor quality” trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. External validity of trials was assessed based on whether the publication adequately described the study population, how similar patients were to the target population in whom the intervention will be applied, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the funding source and role of the funder.
Appendix B also shows the criteria we used to rate observational studies of adverse events. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good quality for adverse event assessment if they adequately met six or more of the seven predefined criteria, fair if they met three to five criteria, and poor if they met two or fewer criteria.

Overall quality ratings for the individual study were based on ratings of the internal and external validity of the trial. A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

**Data Synthesis**

In addition to discussion of the findings of the studies overall, meta-analyses were conducted where possible.

Differences in esophageal or ulcer healing rates are expressed as the “percent risk difference.” This is the difference between the proportions healed in two groups of patients at a given time-point (e.g., at 4 weeks, 80% in group A and 75% in group B is a 5% risk difference). As a measure of the variance around these estimates, the 95% confidence interval (CI) is also reported. If the 95% CI includes 0, then the difference is not statistically significant. Meta-analysis was done using Revman software. Pooling was done using both fixed and random effects models. Results from the random effects models are presented, unless results from the two methods differed, in which case both would be presented. If significant statistical heterogeneity was found, pooling was not conducted.

To determine estimates and 95% confidence intervals of healing and symptom resolution rates for individual drugs from head-to-head trials, we performed a meta-analysis by using a random effects model controlling for the effect of the study. This analysis was conducted using SAS 9.1 (SAS Institute Inc., Cary, NC, USA).

Random effects logistic meta-regression models were fit to estimate the probability of healing with PPI adjusted for healing rate with H2-RA within the same study. The model stratified by type of PPI (lansoprazole, omeprazole, pantoprazole, and rabeprazole). Posterior distributions were simulated using WinBUGS software.

**RESULTS**

**Overview**

Searches and review of reference lists identified 3,073 citations. We excluded 2,493 citations at the title/abstract level. Of 580 articles retrieved for full-text review, we included 68 head-to-head trials, 95 trials with active controls or combination therapy, 11 placebo-controlled trials, and 18 systematic reviews. An additional 22 articles were included for background, methods, and information on drug interactions. We excluded trials for the following reasons: study reported as abstract only or contained no original data, outcome measure not included, study design not included, drug not included or combined drug therapy where the effect of the PPI could not be distinguished, patient population not included, and language other than English.
A diagram summarizing the flow of study inclusion and exclusion is presented in Appendix E. No study of omeprazole in combination with sodium bicarbonate met inclusion criteria.

Most of the randomized trials had fair internal validity, but their applicability to community practice was difficult to determine. These studies generally excluded patients who had serious medical conditions (the decision of what qualified was left to the investigators). Most of the treatment and control groups received standard doses of anti-ulcer drug, but there were instances of a higher or lower than typical dose used. Of those studies that stated the funding source, most were funded by the pharmaceutical industry, and industry employees often served as co-authors.

There is controversy about whether dose comparisons in head-to-head trials of esomeprazole versus omeprazole were appropriate. In the FDA clinical review of esomeprazole, the reviewer indicates that the dose of 40mg esomeprazole is “pharmacodynamically thrice that of the s-isomer” in omeprazole 20mg (see FDA Medical Review, executive summary, page 4). 9 While the FDA-approved doses for treatment of erosive esophagitis are 20 to 40 mg daily for esomeprazole, and 20 mg daily for omeprazole (both for 4 to 8 weeks), it is argued that, because of differences in drug chemistry and pharmacology, there is no clear equivalent dose of omeprazole and esomeprazole.

For this report (update #4), several studies were suggested through the public review process to be included in the report. While many of these did not meet inclusion criteria (above), 6 studies were added to the final report. An addition few were published only very recently and will be included in the next update of this report (see Appendix G).

Key Question 1. Efficacy in GERD

What is the comparative efficacy of different PPIs in patients with symptoms of GERD?

Summary of the Evidence

Symptom relief and esophagitis healing (Patients with erosive esophagitis):

- In 12 head-to-head trials, there was no difference between lansoprazole, omeprazole, pantoprazole, and rabeprazole on the outcome of complete symptom relief at 4 weeks. The only significant difference on this outcome was in the comparison of esomeprazole 40 mg to omeprazole 20 mg. The pooled risk difference in three trials was 10% (95% CI 6%-14%).
- Esomeprazole 40 mg was also compared to lansoprazole 30 mg and to pantoprazole 40 mg for complete symptom relief at 4 weeks with no significant differences.
- Time to relief of heartburn was similar for all PPIs in head-to-head trials, but the methods used to measure and report this outcome varied.
- There is good evidence that there is no comparative difference between omeprazole, lansoprazole, pantoprazole, and rabeprazole for healing of esophagitis or relief of GERD symptoms. Thirteen head-to-head trials, 20 trials of these PPIs versus an H2-RA, and three systematic reviews found these four PPIs to be equally effective.
- Esomeprazole 40mg had higher 4- and 8-week healing rates than omeprazole 20mg.
Three trials compared esomeprazole 40 mg to lansoprazole 30 mg. The pooled healing rate of two trials reporting healing at 4 weeks was 5% higher for esomeprazole (NNT = 20). One of three studies found a significantly higher healing rate for esomeprazole at 8 weeks (NNT=33). Two others found healing rates equivalent at 8 weeks, and the pooled estimate from 3 studies was not significant.

Symptom relief (patients with non-erosive or empirically-treated GERD)
- Three head-to-head trials in patients with endoscopy-negative GERD found no difference between esomeprazole 20 mg and omeprazole 20 mg, pantoprazole 20 mg, and rabeprazole 10 mg. These studies used different outcome measures.
- Limited indirect evidence from placebo- and active-controlled trials suggests similar efficacy for heartburn resolution and complete symptom relief for all five PPIs.

Prevention of relapse (patients with erosive esophagitis):
- For maintenance of healed esophagitis, there is good evidence that there is no comparative difference between omeprazole, lansoprazole, and rabeprazole. The longest-term study (over 5 years) is of omeprazole versus rabeprazole.
- Two 6-month studies found lower relapse rates for esomeprazole 20 mg compared with lansoprazole 15 mg or pantoprazole 20 mg daily.
- Pantoprazole was more effective than ranitidine in one 12-month study, and esomeprazole was more effective that ranitidine in another 6-month study.

Prevention of relapse (patients with non-erosive or empirically treated GERD):
- In a 6-month head-to-head trial of on-demand esomeprazole vs continuous lansoprazole 15 mg in patients with endoscopy negative GERD, more patients discontinued lansoprazole (for any reason), but discontinuations because of heartburn were not significantly different between treatment groups.
- On-demand rabeprazole 10 mg, on-demand esomeprazole 20 mg, and continuous omeprazole 10 mg were more effective than placebo in prevention of relapse of symptoms over 6 months in patients with endoscopy negative GERD.
- There are no head-to-head trials of on-demand treatment of one PPI versus on-demand treatment of another PPI.

Results by baseline severity:
- Among patients with moderate to severe esophagitis at baseline, esomeprazole 40 mg was more effective at healing esophagitis at 4 and 8 weeks than omeprazole 20 mg and lansoprazole 30 mg.
- The pooled risk difference in 3 studies of omeprazole 20 mg vs esomeprazole 40 mg was 16% at 4 weeks and 13% at 8 weeks (NNT=6 at 4 weeks, 8 at 8 weeks).
- The pooled risk difference in 2 studies of lansoprazole 30 mg vs esomeprazole 40 mg was 8% at 4 weeks and 9% at 8 weeks (NNT=13 at 4 weeks, 11 at 8 weeks).
- In one study, pantoprazole 40 mg had a higher healing rate at 8 weeks than esomeprazole 40 mg in patients with moderate (Grade C) esophagitis at baseline.
- Lansoprazole 30 mg and omeprazole 20 mg had equivalent healing rates in patients with moderate to severe esophagitis in two studies.
Evidence in Children

- There are no direct comparisons of PPIs for reflux esophagitis in children. A fair quality placebo-controlled trial in infants did not find omeprazole to be superior to placebo in controlling symptoms or acid-exposure time.

Detailed Assessment

Key Question 1a. Head-to-head comparisons

In head-to-head comparisons, what is the comparative efficacy of different PPIs in healing esophagitis, reducing symptoms, and preventing relapse in patients with symptoms of GERD?

Erosive Esophagitis

We identified 26 randomized controlled trials comparing two or more PPIs in patients with endoscopically-proven GERD (Evidence Table 1).5-7,10-32 One is unpublished,7 and two publications are supplemented with additional data provided by the manufacturer.5,6 Omeprazole was the comparator in most studies. No study of omeprazole in combination with sodium bicarbonate met inclusion criteria. The scales used to grade esophagitis in these studies are described in Appendix F. The comparisons made in head-to-head studies are shown in Table 1 (the number of comparisons adds to 28 because 2 studies compared 3 different PPIs).

Table 1. Number of head-to-head trials, short-term treatment erosive GERD

<table>
<thead>
<tr>
<th></th>
<th>Omeprazole</th>
<th>Lansoprazole</th>
<th>Rabeprazole</th>
<th>Pantoprazole</th>
<th>Esomeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>**********</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>6</td>
<td>**********</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>4</td>
<td>0</td>
<td>**********</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>**********</td>
<td></td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>6</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>**********</td>
</tr>
</tbody>
</table>

Three studies5,12,29 met all criteria for internal validity, one was rated poor,21 and the rest were fair. (Details of quality ratings of included trials are listed in Evidence Table 2.) Pregnant and lactating women, and women of childbearing potential were excluded from all studies, and the majority of patients enrolled were male. No children (i.e., under age 18) were included in these studies.
Relief of Symptoms

Four head-to-head comparisons of PPIs measured symptom relief as a primary outcome, and 14 reported symptoms as a secondary outcome. Symptoms in these studies were assessed through patient diaries, investigator-elicited reports, or both.

Complete symptom resolution

Fourteen head-to-head trials reported the proportion of patients with complete resolution of symptoms at 4 weeks. We performed a random effects meta-analysis of data from these studies to determine an estimate of the proportion who were symptom free at 4 weeks for each drug. Results are shown in Table 2 below. Proportions ranged from 65% to 77%, and 95% confidence intervals overlapped, indicating the drugs are similarly efficacious for complete resolution of symptoms at 4 weeks.

Table 2. Symptom resolution in head-to-head trials in patients with erosive GERD

<table>
<thead>
<tr>
<th>Drug, dose</th>
<th>Complete resolution of symptoms at 4 weeks (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole 40 mg</td>
<td>73% (65%-82%) 5, 6, 10, 12, 16, 20, 29</td>
</tr>
<tr>
<td>Lansoprazole 30 mg</td>
<td>70% (61%-80%) 5, 13, 14, 23, 29</td>
</tr>
<tr>
<td>Omeprazole 20 mg</td>
<td>65% (54%-76%) 6, 12, 13, 16, 24, 26, 27</td>
</tr>
<tr>
<td>Omeprazole 40 mg</td>
<td>76% (65%-87%) 14, 17</td>
</tr>
<tr>
<td>Pantoprazole 20 mg</td>
<td>77% (70%-84%) 27</td>
</tr>
<tr>
<td>Pantoprazole 40 mg</td>
<td>72% (62%-83%) 10, 13, 17, 20, 23, 26, 27</td>
</tr>
<tr>
<td>Rabeprazole 20 mg</td>
<td>69% (52%-86%) 24</td>
</tr>
</tbody>
</table>

Figure 3 shows risk differences in rates of complete symptom resolution at 4 weeks in these trials. In Table 3 we report the difference in complete symptom resolution for comparisons of esomeprazole to other PPIs. The pooled data on the comparison of esomeprazole 40 mg to omeprazole 20 mg significantly favored esomeprazole 40mg; for every 10 persons treated with esomeprazole 40 mg versus omeprazole 20 mg, one additional patient would be symptom-free at four weeks in the esomeprazole group. The pooled data for esomeprazole 40mg versus either lansoprazole 30mg or pantoprazole 40mg did not indicate a significant difference between the drugs.
Table 3. Symptom resolution at 4 weeks in trials of esomeprazole vs another PPI in erosive GERD

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients with complete symptom relief at 4 weeks</th>
<th>Risk difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole 40 mg vs omeprazole 20 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kahrilas 20006</td>
<td>65% vs 57%</td>
<td>8% (2%, 13%)</td>
</tr>
<tr>
<td>Kao 200316</td>
<td>74% vs 51%</td>
<td>23% (3%, 42%)</td>
</tr>
<tr>
<td>Richter 200112</td>
<td>68% vs 58%</td>
<td>10% (6%, 14%)</td>
</tr>
<tr>
<td><strong>Pooled estimate</strong></td>
<td></td>
<td>10% (6%, 14%)</td>
</tr>
<tr>
<td><em>ITT calculated by the reviewers.</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esomeprazole 40 mg vs lansoprazole 30 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Castell 20025</td>
<td>63% vs 60%</td>
<td>3% (0%, 5%)</td>
</tr>
<tr>
<td>Fennerty 2005 (ITT*)</td>
<td>69% vs 61%</td>
<td>8% (2%-14%)</td>
</tr>
<tr>
<td><strong>Pooled estimate</strong></td>
<td></td>
<td>5% (0%, 9%)</td>
</tr>
<tr>
<td>Esomeprazole 40 mg vs pantoprazole 40 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gillessen 200410</td>
<td>35% vs 37%</td>
<td>-2% (-16%, 11%)</td>
</tr>
<tr>
<td>Scholten 200316</td>
<td>70% vs 71%</td>
<td>-1% (-13%, 11%)</td>
</tr>
<tr>
<td><strong>Pooled estimate</strong></td>
<td></td>
<td>-2% (-11%, 7%)</td>
</tr>
</tbody>
</table>

*ITT calculated by the reviewers.

A single study reported complete resolution of symptoms after 1 week of therapy, finding rabeprazole 20 mg daily superior to omeprazole 20 mg daily (27.9% vs 16.6%, P = 0.0013 as calculated from number randomized and using Chi Square analysis).

**Time to Relief of Symptoms**

Thirteen studies reported the time to resolution of symptoms (no heartburn). This measure was reported as the percentage of patients with the outcome after a given time point (e.g., 1 day, 7 days), the median number of days to resolution, or both. In one study this outcome is reported as the number of days needed for 50% and 75% of patients to achieve relief of symptoms. Another measure used was the time to sustained resolution of heartburn, defined as the first of 7 consecutive days without heartburn. This outcome was used only in studies funded by the maker of esomeprazole, so it is not possible to compare this outcome on studies funded by others.

**Esomeprazole vs omeprazole**. In four studies that compared esomeprazole 40mg to omeprazole 20mg, the median number of days to the first resolution of symptoms was similar, but the median number of days to sustained resolution of symptoms favored esomeprazole in the 2 studies reporting this measure (Table 4). More patients taking esomeprazole 40 mg reached first of resolution of symptoms by 1 day and day 7 based on absolute proportions, than those taking omeprazole 20mg. These findings were statistically significant in one study, non-significant in two others, and not assessed in the fourth. The time to sustained resolution of
heartburn was statistically superior with esomeprazole 40mg compared to omeprazole 20mg at 14 days in 2 studies. The differences at other time points were mixed or not statistically assessed.

In a comparison of esomeprazole 20 mg to omeprazole 20 mg, a numerically higher proportion of omeprazole patients started 7 consecutive days without heartburn at day 1; esomeprazole had a higher proportion of patients with sustained relief by day 28; neither comparison was statistically significant, and the median number of days to sustained resolution was similar. This pattern was also seen in the time to first resolution of symptoms.

### Table 4. Time to symptom relief in trials of esomeprazole vs. omeprazole in erosive GERD

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Time to first resolution of heartburn</th>
<th>Time to sustained resolution of heartburn (7 consecutive days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Esomeprazole 20 mg vs omeprazole 20 mg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kahrilas 2000</td>
<td>1 day: 37.9% vs 37.0% (p=0.76) 7 days: 81.4% vs 79.8% (p=0.81) Median: 2 vs 2 (NS)</td>
<td>1 day: 21.7% vs 23.0% (p=0.60) 28 days: 70.1% vs 66.6% (p=0.18) Median: 8 days vs 9 days</td>
</tr>
<tr>
<td><strong>Esomeprazole 40 mg vs omeprazole 20 mg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kahrilas 2000</td>
<td>1 day: 46.6% vs 37.0% (p=0.0006) 7 days: 83.2% vs 79.8% (p=0.12) Median: 2 vs 2 (NS)</td>
<td>1 day: 29.9% vs 23.0% (p=0.01) 28 days: 74.2% vs 66.6% (p=0.003) Median: 5 days vs 9 days</td>
</tr>
<tr>
<td>Kao 2003</td>
<td>1 day: 28.2% vs 26.2% (NS) before 7 days: 56.4% vs 55.6% (NS) Median: 4 days vs 4 days (NS)</td>
<td>7 days: 15.2% vs 15.6% (NS) 14 days: 50% vs 20% (p&lt;0.05) 21 days: 71.7% vs 40% (p=0.01) 28 days: 73.9% vs 51.1% (p&lt;0.05)</td>
</tr>
<tr>
<td>Richter 2001</td>
<td>1 day: 45.3% vs 32% (p≤0.0005) 7 days: 85.6% vs 81.6% (p≤0.0005) Median: 2 days vs 2 days (NS)</td>
<td>1 day: 29.3% vs 19.5% (p≤0.0005) 14 days: 67.6% vs 62.5% (p≤0.0005) Median: 5 days vs 8 days (p≤0.0005)</td>
</tr>
<tr>
<td>Chen 2005</td>
<td>1 day: 77.3% vs 65% (NS)</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

*Esomeprazole vs lansoprazole*. In three studies comparing esomeprazole 40 mg to lansoprazole 30 mg, results were mixed and outcomes were reported differently (Table 5). Overall, results did not favor one drug over another.

### Table 5. Time to symptom relief in trials of esomeprazole vs. lansoprazole in erosive GERD

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Time to first resolution of heartburn</th>
<th>Time to sustained resolution of heartburn (7 consecutive days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Esomeprazole 40 vs lansoprazole 30 mg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Castell 2002</td>
<td>Median: 2 days vs. 2 days (NS)</td>
<td>Median: 7 days vs 8 days (p&lt;0.01)</td>
</tr>
<tr>
<td>Fennerty 2005</td>
<td>NR</td>
<td>7 days: 54.2% vs 51.7% (NS)</td>
</tr>
<tr>
<td>Howden 2002*</td>
<td>1 day: 27.3% vs. 34.5% (p=0.21)</td>
<td>Heartburn-free first 3 days: 37.4% vs 43.8% (NS) Heartburn-free first 7 days: 45.9% vs 51.8% (NS)</td>
</tr>
</tbody>
</table>

*Days or nights without heartburn

*Esomeprazole vs. pantoprazole*. The two trials of esomeprazole versus pantoprazole reported these data differently and found conflicting results. In one trial of esomeprazole 40 mg versus pantoprazole 40 mg, more esomeprazole patients reached the start of sustained resolution...
of heartburn (7 consecutive days) after one day of treatment: 24% vs 20% (p-value not reported). The median time to sustained resolution was 6 days vs 8 days (p<0.001). A second trial of esomeprazole 40 mg versus pantoprazole 40 mg compared the number of days it took for 50% and 75% of patients to achieve relief of heartburn. In both groups, 50% of patients had no heartburn after 2 days, but it took 3 days for 75% of the pantoprazole group to achieve relief of symptoms versus 8 days for the esomeprazole group. Confidence intervals for the number of days overlapped, however (2-7 days for pantoprazole vs. 3-14 days for esomeprazole).

**Lansoprazole vs omeprazole.** Three studies reported time to relief of heartburn symptoms for lansoprazole versus omeprazole. Although lansoprazole improve some symptoms faster at some time points, there was no strong or consistent pattern to suggest that lansoprazole provides faster symptom relief than omeprazole. Time to sustained resolution of heartburn (defined as 3 consecutive days without heartburn) was measured in one study and was similar (median 3 days for both drugs; p=0.285). In another study, daytime and nighttime heartburn were reported separately. After one day of treatment, more lansoprazole-treated patients were free of both day heartburn (48.7% vs 37.6%; p<0.05) and night heartburn (62% vs 52%; p<0.05). The third comparison of these drugs used a visual analogue scale to measure heartburn symptoms and reported the time to relief only for daytime heartburn. After 3 days, there was a significant decrease in VAS score in lansoprazole-treated patients (–20.2 vs –15.3 (p=0.05); the difference was not significant after 7 days (scores not reported).

**Rabeprazole vs omeprazole.** One study reported similar mean time to complete heartburn relief for rabeprazole or omeprazole 20 mg daily; 7.2 and 8.4 days, respectively.

**Esophagitis Healing**

All of the PPIs were effective at healing esophagitis. Healing rates at 4 weeks ranged from 49% to 91%, and at 8 weeks ranged from 71% to 99% (see Evidence Table 1). One small, fair quality study conducted at a single center in China had a lower 8-week healing rate than other studies (64% for esomeprazole 40 mg, 45.5% for omeprazole 20 mg).

To determine an estimate of healing rates for each drug, we pooled data from head-to-head trials, using a random effects model to control for the effect of the study. Table 6 shows results of this analysis. (Note that for lansoprazole 15 mg, pantoprazole 20 mg, and rabeprazole 10 mg, these data are available from only one study). Healing rates were similar and confidence intervals overlapped, indicating no significant differences between PPIs.
**Table 6. Estimated rates of esophagitis healing in head-to-head trials***

<table>
<thead>
<tr>
<th>Drug, dose</th>
<th>Healing rate at 4 weeks (95% CI)</th>
<th>Healing rate at 8 weeks (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole 20 mg</td>
<td>73% (66%-79%)&lt;sup&gt;6, 7&lt;/sup&gt;</td>
<td>87% (84%-91%)&lt;sup&gt;6, 7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Esomeprazole 40 mg</td>
<td>78% (73%-83%)&lt;sup&gt;5, 6, 12, 20, 29, 30, 33&lt;/sup&gt;</td>
<td>90% (88%-92%)&lt;sup&gt;5, 6, 12, 18, 20, 29, 31, 33&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lansoprazole 15 mg</td>
<td>63% (52%-73%)&lt;sup&gt;25&lt;/sup&gt;</td>
<td>73% (63%-82%)&lt;sup&gt;25&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lansoprazole 30 mg</td>
<td>73% (67%-79%)&lt;sup&gt;5, 14, 15, 21, 23, 25, 29&lt;/sup&gt;</td>
<td>86% (83%-90%)&lt;sup&gt;5, 14, 15, 18, 21, 23, 25, 29&lt;/sup&gt;</td>
</tr>
<tr>
<td>Omeprazole 20 mg</td>
<td>70% (64%-76%)&lt;sup&gt;6, 7, 12, 15, 21, 22, 25-27, 33&lt;/sup&gt;</td>
<td>85% (81%-88%)&lt;sup&gt;6, 7, 12, 15, 21, 22, 25-27, 31, 33&lt;/sup&gt;</td>
</tr>
<tr>
<td>Omeprazole 40 mg</td>
<td>68% (59%-78%)&lt;sup&gt;14, 17&lt;/sup&gt;</td>
<td>87% (76%-99%)&lt;sup&gt;14&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pantoprazole 20 mg</td>
<td>67% (54%-81%)&lt;sup&gt;27&lt;/sup&gt;</td>
<td>77% (65%-88%)&lt;sup&gt;27&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pantoprazole 40 mg</td>
<td>71% (65%-78%)&lt;sup&gt;17, 20, 23, 26, 30&lt;/sup&gt;</td>
<td>89% (86%-92%)&lt;sup&gt;20, 23, 26, 30&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rabeprazole 10mg</td>
<td>65% (47%-83%)&lt;sup&gt;22&lt;/sup&gt;</td>
<td>84% (71%-96%)&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rabeprazole 20 mg</td>
<td>69% (59%-79%)&lt;sup&gt;22, 34&lt;/sup&gt;</td>
<td>82% (76%-89%)&lt;sup&gt;22, 34&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*Studies used in calculating pooled estimates are cited after each estimate

We also calculated the percent risk difference for healing in head-to-head comparisons. Figures 1 and 2 show the differences in healing rates at 4 and/or 8 weeks for the 20 trials that provided the number healed/total patients. Seven head-to-head trials are not represented in Figures 1 and 2; three studies (two of rabeprazole vs omeprazole, one of omeprazole vs both lansoprazole and rabeprazole)<sup>19, 28, 35</sup> did not provide number healed/total, and four trials<sup>10, 11, 13, 16</sup> reported only symptom relief, not esophagitis healing. The numbers presented in the figures for one trial of rabeprazole 20 mg compared to omeprazole 20 mg are calculated intention to treat, rather than those presented in the article which are not ITT.<sup>32</sup>

Although some published studies presented results according to life-table analysis, crude rates only are included in figure 1. When a published study did not provide crude rates, we requested and received these data from the manufacturer. Results of life-table analyses cannot be directly compared to crude rates reported in other studies, and using life table analysis may overestimate results by excluding patients who are lost to followup or are withdrawn from the study.

Omeprazole 20mg, the first PPI to be marketed, was the comparator used most often in head-to-head trials. Table 7 summarizes the risk differences in healing rate in eight trials<sup>12, 15, 21, 22, 25-27, 31</sup> comparing omeprazole 20 mg to another PPI.
Table 7. Risk differences of esophagitis healing rates in trials of omeprazole 20 mg vs another PPI*

<table>
<thead>
<tr>
<th>Drug, dose</th>
<th>Difference in healing rate at 4 weeks vs omeprazole 20 mg (95% CI)</th>
<th>Difference in healing rate at 8 weeks vs omeprazole 20 mg (95% CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole 20 mg</td>
<td>3% (-1%, 7%)</td>
<td>3% (0%, 6%)</td>
<td></td>
</tr>
<tr>
<td>Esomeprazole 40 mg</td>
<td>8% (pooled) (6%, 12%)</td>
<td>6% (pooled) (1%, 10%)</td>
<td>NNT=13</td>
</tr>
<tr>
<td>Lansoprazole 30 mg</td>
<td>2% (pooled) (-3%, 6%)</td>
<td>1% (pooled) (-2%, 5%)</td>
<td>NNT=17</td>
</tr>
<tr>
<td>Pantoprazole 20 mg</td>
<td>-4% (-12%, 5%)</td>
<td>-7% (-15%, 0%)</td>
<td></td>
</tr>
<tr>
<td>Pantoprazole 40 mg</td>
<td>-1% (-13%, 11%)</td>
<td>3% (-3%, 10%)</td>
<td></td>
</tr>
<tr>
<td>Rabeprazole 10 mg</td>
<td>-6% (-15%, 3%)</td>
<td>-3% (-10%, 4%)</td>
<td></td>
</tr>
<tr>
<td>Rabeprazole 20 mg</td>
<td>-2% (-8%, 3%)</td>
<td>-3% (-8%, 2%)</td>
<td></td>
</tr>
</tbody>
</table>

*NNTs presented for statistically significant differences

Risk differences at 4 and 8 weeks were non-significant in all comparisons, with the exception of esomeprazole 40 mg versus omeprazole 20 mg.

Two published trials comparing esomeprazole 40 mg to omeprazole 20 mg, found a higher healing rate in the esomeprazole group. A third study found no difference between groups at 4 and 8 weeks. A small study (N=48) found a higher healing rate for esomeprazole at 8 weeks (64% vs 45.5%), but the difference was not statistically significant. Four-week healing rates were not measured. This study may not have had sufficient power to detect a difference between treatment groups; no power calculation was reported. The pooled risk difference for three studies at 4 weeks was 8% and for 4 studies at 8 weeks was 6% (see Table 7). This translates to a number needed to treat to heal one additional patient at 4 weeks of 13, and a NNT at 8 weeks of 17.

Two studies compared esomeprazole 20 mg to omeprazole 20 mg and found no significant difference in healing rate at 4 weeks or 8 weeks.

Table 8 shows results of 3 studies that compared esomeprazole 40 mg to lansoprazole 30 mg. In a large, good quality trial in 5241 patients at multiple centers in the US, healing rates were higher in the esomeprazole group at 4 weeks (risk difference 4%; 95% CI 2%, 6%) and at 8 weeks (risk difference 3%, 95% CI 1%, 5%).
Table 8. Risk differences in head-to-head trials of esomeprazole 40 mg vs lansoprazole 30 mg

<table>
<thead>
<tr>
<th>Study</th>
<th>Difference in Healing at 4 weeks (95% CI)</th>
<th>Difference in Healing at 8 weeks (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castell 2002²</td>
<td>4% (2%, 6%)</td>
<td>3% (1%, 5%)</td>
</tr>
<tr>
<td>Fennerty 2005²⁹</td>
<td>8% (2%, 14%)</td>
<td>4% (-1%, 10%)</td>
</tr>
<tr>
<td>Howden 2002¹⁸</td>
<td>Not reported</td>
<td>-2% (-9%, 5%)</td>
</tr>
<tr>
<td>Pooled estimate Random effects</td>
<td>5% (1%, 9%)</td>
<td>3% (0%, 5%)</td>
</tr>
<tr>
<td>Pooled estimate Fixed effects</td>
<td>5% (2%, 7%)</td>
<td>3% (1%, 5%)</td>
</tr>
<tr>
<td></td>
<td>NNT=20</td>
<td>NNT=33</td>
</tr>
</tbody>
</table>

A second, smaller, fair-quality trial of lansoprazole 30mg versus esomeprazole 40 mg¹⁸ in patients with mostly mild to moderate esophagitis found the two to have equivalent healing rates at 8 weeks. Results at 4 weeks are not reported.

The third study, rated good quality,²⁹ was conducted in patients with moderate to severe esophagitis (LA Grade C and D). At 4 weeks, the esomeprazole group had a higher healing rate, but at 8 weeks the difference was not significant.

Pooled estimates show a 5% higher healing rate at 4 weeks and 3% at 8 weeks for esomeprazole 40 mg. Using a random effects analysis, the difference at 8 weeks was not significant (95% CI 0%, 5%). In a fixed effects analysis, the difference is significant (risk difference 3%, 95% CI 2%, 5%). These estimates translate to a NNT to heal one additional patient at 4 weeks of 20; and at 8 weeks a NNT of 33.

Two trials compared esomeprazole 40 mg to pantoprazole 40 mg.²⁰,³⁰ In one,³⁰ healing at 4 weeks was 6% higher at 4 weeks in the esomeprazole group (95% CI 3%, 9%). At 8 weeks, the difference was smaller but statistically significant (risk difference 3%; 95% CI 1%, 5%). We rated this study fair to poor quality. Data on baseline characteristics excludes 19 patients randomized but excluded from analysis due to intake of an unknown study drug or protocol violations. No data on excluded patients is presented. In addition, randomization and allocation concealment methods are not reported, and there were some differences in baseline esophagitis grade at baseline (grade B: 42.6% esomeprazole vs 45.1% pantoprazole; grade D: 4.5% esomeprazole, 5.8% pantoprazole).

In the other (fair-quality) comparison of esomeprazole 40 mg to pantoprazole 40 mg, healing rates are reported at “early” (4-6 weeks) and “late” (8-10 weeks) time points. Healing rates were equivalent at early and late time points. It was not possible to pool these studies because of the different manner of reporting results. Also, Gillessen included only patients with grade B (84%) and C (16%) esophagitis, whereas Labenz enrolled patients grade A through D.
Analysis of healing rates by baseline severity of esophagitis

Eighteen head-to-head trials reported information about esophagitis healing rates separately by baseline severity of esophagitis. These results are shown in Evidence Table 1. Nine trials reported the number healed/total by baseline severity (Figures 4 and 5) Another reported a combined outcome of either healed or improvement by two grades. To estimate healing rates for each drug at 4 and 8 weeks for patients with moderate to severe esophagitis (i.e., grade C-D or 3-4; see Appendix F for scales used), we conducted a random effects meta-analysis of data from the 9 studies reporting the number healed/total by baseline severity (Table 9).

Table 9. Estimated healing rates in patients with moderate to severe esophagitis at baseline*

<table>
<thead>
<tr>
<th>Drug, dose</th>
<th>Healing rate at 4 weeks (95% CI)</th>
<th>Healing rate at 8 weeks (95% CI)</th>
</tr>
</thead>
</table>
| Esomeprazole 20 mg | 49% (37%-61%)
6, 7                                  | 77% (70%-85%)
6, 7                                  |
| Esomeprazole 40 mg | 64% (57%-71%)
6, 12, 29, 30, 33                     | 85% (81%-89%)
6, 12, 29, 33 |
| Lansoprazole 30 mg | 56% (48%-64%)
15, 25, 29                                        | 77% (71%-82%)
15, 25, 29                                        |
| Omeprazole 20 mg  | 52% (45%-59%)
7, 12, 15, 25, 33                                           | 74% (68%-80%)
15, 25, 33, 29; Kahrilas, 2000 #233; Richter, 2001 #1253 |

*Studies used in calculating estimates are cited after each estimate.

*Esomeprazole versus omeprazole.* Three studies of esomeprazole 40 mg versus omeprazole 20 mg reported healing rates in patients with moderate to severe esophagitis at baseline (Figures 4 and 5). The pooled risk difference at 4 weeks was 16% (95% CI 11%, 22%) and at 8 weeks was 13% (95% CI 9%, 17%).

In two studies comparing esomeprazole 20 mg to omeprazole 20 mg there was no difference in healing rate at 4 weeks (pooled risk difference 2%; 95% CI –5%, 10%) or 8 weeks (pooled risk difference 4%; 95% CI –3%, 10%). Estimates of healing rates in esomeprazole 20 mg are similar to omeprazole 20 mg (see Table 9). There are no comparisons of esomeprazole at any dose to omeprazole 40 mg.

*Esomeprazole versus lansoprazole.* Two studies of esomeprazole 40 mg versus lansoprazole 30 mg reported healing rates in patients with moderate to severe esophagitis at baseline. The pooled risk difference at 4 weeks was 8% (95% CI 4%, 12%) and at 8 weeks was 9% (95% CI 5%, 12%). This corresponds to a NNT of 13 at 4 weeks and 11 at 8 weeks.

A third study, published by the maker of lansoprazole, reported only the combined outcome of healing or improvement of at least 2 grades in the subgroup of patients with moderate to severe esophagitis. In this study, there was a trend for a higher healing/improved rate in the lansoprazole group at 8 weeks (results at 4 weeks are not reported). The number of subjects in this subanalysis was comparatively small (N=109), and the difference was not statistically significant (10%, 95% CI –2%, 22%).
**Esomeprazole versus pantoprazole.** In one study, patients with moderate (Grade C) esophagitis at baseline taking pantoprazole 40 mg had a higher healing rate at “later” time points (8-10 weeks) than those taking esomeprazole 40 mg (67% vs 45%). Among patients diagnosed with grade C at baseline, 100% of pantoprazole and 91% of esomeprazole improved to Grade A or B at the final visit (10 weeks). Rates at 4 weeks are not reported, and no patients with Grade D esophagitis were enrolled.

In the other comparison of esomeprazole 40 mg and pantoprazole 40 mg in patients with moderate to severe esophagitis, there was a 14% risk difference favoring esomeprazole after 4 weeks (95% CI 7%, 21%); 8-week data are not reported.

**Lansoprazole versus omeprazole.** Three studies comparing lansoprazole with omeprazole reported rates in patients with moderate to severe (Grades 3 and 4) esophagitis. Two of these compared lansoprazole 30 mg to omeprazole 20 mg. There was no difference in healing rate at 4 weeks (pooled risk difference 1%; 95% CI –13%, 16%) or 8 weeks (pooled risk difference 3%; 95% CI –4%, 10%). The third study compared lansoprazole 30 mg to omeprazole 40 mg and reported healing rates as percentages only. The number of patients with moderate to severe esophagitis in each group is not reported. There was no significant difference between groups at 4 or 8 weeks.

**Non-erosive or empirically treated GERD**

**Direct Evidence**

We identified 3 fair-quality head-to-head trials in patients with endoscopy negative reflux disease (ENRD, Table 10). They all compared esomeprazole to another PPI (omeprazole, rabeprazole, or pantoprazole). A fourth head-to-head trial of lansoprazole versus omeprazole included patients with both erosive and nonerosive esophagitis, but did not report results separately by these patient populations.

| Table 10. Number of head-to-head trials, short-term treatment of non-erosive/ empirically treated GERD |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| **Omeprazole**                                  | **Lansoprazole**                                | **Rabeprazole**                                 | **Pantoprazole**                                | **Esomeprazole**                                |
| Omeprazole                                      | **********                                     |                                                 |                                                 |                                                 |                                                 |
| Lansoprazole                                    | 0                                               | **********                                     |                                                 |                                                 |                                                 |
| Rabeprazole                                     | 0                                               | 0                                              | **********                                     |                                                 |                                                 |
| Pantoprazole                                    | 0                                               | 0                                              | 0                                              | **********                                     |                                                 |
| Esomeprazole                                    | 1                                               | 0                                              | 1                                              | 1                                              | **********                                     |
The three studies used different outcome measures, but all found esomeprazole to be similar in efficacy to the comparator (Evidence Table 3).

Three 4-week trials of omeprazole 20 mg versus esomeprazole 20 or 40 mg with identical designs were conducted simultaneously and are described in one publication. There was no difference on the outcome of complete resolution of heartburn at 14 days (secondary outcome) or 28 days (primary outcome) between patients taking esomeprazole 20 mg or 40 mg, or omeprazole 20 mg. At 2 weeks, proportions of patients with complete resolution ranged from 34.6% to 44.3%, and at 4 weeks ranged from 56.7% to 70.3%. Results for adequate control of symptoms were similar, with no significant differences between drugs.

A head-to-head trial of pantoprazole 20 mg versus esomeprazole 20 mg measured time to first and sustained symptom relief. This trial was designed to test the non-inferiority of pantoprazole compared with esomeprazole. The non-inferiority margin was set at –2 days for the primary outcome of time to first symptom relief (i.e., a lower boundary of the 95% confidence interval greater than 2 days would indicate non-inferiority). Symptom assessment was based on patient self-report using a validated questionnaire (ReQuest). The questionnaire includes the items on seven dimensions of GERD (general well-being, acid complaints, upper abdominal/stomach complaints, lower abdominal/digestive complaints, nausea, sleep disturbances, and other complaints). Results showed that pantoprazole was not inferior to esomeprazole for first and sustained symptom relief.

A 4-week trial of rabeprazole 10 mg compared to esomeprazole 20 mg was conducted in 134 patients in Singapore. The primary outcome was time to achieve first 24-hour interval with no symptoms of heartburn or regurgitation. There was no difference between groups on this endpoint (8.5 days for rabeprazole vs 9.0 days for esomeprazole for heartburn; 6.0 days for rabeprazole vs 7.5 days for esomeprazole for regurgitation; p=NS). There were also no significant differences between groups on secondary outcomes, including complete and satisfactory relief of heartburn symptoms at week 1 and week 4, and symptom severity score in the first 5 days.

Indirect Evidence

A good-quality Cochrane systematic review addressed the efficacy of PPIs, H2RAs, and prokinetics in adults with endoscopy negative or empirically treated reflux disease. Literature searches were conducted through December 2003. This review was not designed to compare the efficacy of different PPIs, and included trials comparing PPIs to prokinetics, H2RAs, or placebo. The primary efficacy variable of the review was heartburn remission, defined as no more than one day with mild heartburn per week. PPIs were superior to placebo for heartburn remission and overall symptom improvement. PPIs were more effective than H2RAs for heartburn remission in empirically treated patients (pooled RR 0.69; 95% CI 0.61, 0.77), but not in patients with ENRD (pooled RR 0.74; 95% CI 0.53, 1.03). However, only 3 trials compared PPIs to H2RAs in ENRD.

Another systematic review evaluated the efficacy of PPIs for heartburn resolution in patients with ENRD. Searches for this review were conducted through 2002 and included the FDA web site. Seven placebo-controlled trials (three published and four unpublished) were included; 2 rabeprazole, 2 esomeprazole, and 3 omeprazole. In patients with ENRD, the risk difference versus placebo for complete resolution of heartburn at 4 weeks was 25% (95% CI
This review does not provide evidence about comparative efficacy of different PPIs in patients with ENRD.

Table 11 shows the heartburn remission rates and rates of complete symptom relief calculated from data provided in the Cochrane review. Similar proportions of patients experienced heartburn resolution or complete symptom relief across studies, with some exceptions in individual studies.

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Drug, dose</th>
<th>ENRD Patients with heartburn resolution (95% CI)</th>
<th>Patients with complete symptom resolution (95% CI)</th>
<th>Patients with heartburn resolution (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armstrong, 2004 (Study A)</td>
<td>Esomeprazole 20 mg</td>
<td>60.5% (51.8% to 65.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Armstrong, 2004 (Study C)</td>
<td>Esomeprazole 20 mg</td>
<td>61.9% (56.5% to 67.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Armstrong, 2004 (Study A)</td>
<td>Esomeprazole 40 mg</td>
<td>56.7% (51.8% to 61.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Armstrong, 2004 (Study B)</td>
<td>Esomeprazole 40 mg</td>
<td>70.3% (65.2% to 75.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnson, 2003</td>
<td>Esomeprazole 40 mg</td>
<td></td>
<td></td>
<td>83.7% (74.7% to 90.0%)</td>
</tr>
<tr>
<td>Bardhan, 1999</td>
<td>Omeprazole 10 mg or 20 mg</td>
<td></td>
<td></td>
<td>73.8% (67.7% to 79.1%)</td>
</tr>
<tr>
<td>Carlsson, 1998</td>
<td>Omeprazole 10 mg or 20 mg</td>
<td>73.3% (63.0% to 81.5%)</td>
<td>60.0% (47.4% to 67.8%)</td>
<td></td>
</tr>
<tr>
<td>Lind, 1997</td>
<td>Omeprazole 10 mg or 20 mg</td>
<td>76.2% (67.1% to 83.4%)</td>
<td>68.6% (59.1% to 76.7%)</td>
<td></td>
</tr>
<tr>
<td>Richter 2000a</td>
<td>Omeprazole 10 mg or 20 mg</td>
<td>95.1% (89.6% to 97.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venables, 1997</td>
<td>Omeprazole 10 mg or 20 mg</td>
<td>55.7% (48.9% to 62.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bate, 1997</td>
<td>Omeprazole 20 mg</td>
<td></td>
<td></td>
<td>68.8% (59.5% to 76.8%)</td>
</tr>
<tr>
<td>Armstrong, 2004 (Study A)</td>
<td>Omeprazole 20 mg</td>
<td>58.1% (53.4% to 62.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Armstrong, 2004 (Study B)</td>
<td>Omeprazole 20 mg</td>
<td>67.9% (62.8% to 72.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Armstrong, 2004 (Study C)</td>
<td>Omeprazole 20 mg</td>
<td>59.6% (54.2% to 64.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venables, 1997</td>
<td>Omeprazole 20 mg</td>
<td></td>
<td></td>
<td>59.8% (54.4% to 65.0%)</td>
</tr>
</tbody>
</table>
We identified one additional placebo-controlled\textsuperscript{42} and one active-controlled (vs. ranitidine) trial\textsuperscript{43} published more recently and not included in this review (Evidence Table 3). In a fair-quality trial of empirical treatment of patients with symptoms of GERD, more patients taking pantoprazole 20 mg than ranitidine 300 mg were free of GERD symptoms (heartburn, acid eructation, and pain on swallowing) at 4 weeks (68.3% vs 43.3%).\textsuperscript{43} In a fair to poor quality 8-week placebo-controlled trial of endoscopy-negative patients whose primary symptom was upper abdominal discomfort, patients taking lansoprazole 15 mg had fewer days with upper abdominal discomfort and reduced average daily pain severity.\textsuperscript{42} Patients whose predominant symptom was heartburn were not included. It is not clear what proportion of patients was analyzed; patients were excluded from analysis for a specific endpoint if there were no data available for that endpoint.

**Prevention of Relapse**

**Patients with Erosive Esophagitis**

Four randomized controlled trials compared one PPI to another for long-term (6 months or more) maintenance therapy for esophagitis relapse prevention in patients with endoscopically-proven GERD (Evidence Table 4)\textsuperscript{44-46, 47, Labenz, 2005 \#4528}. Two of these found no differences in endoscopic or symptomatic relapse rates for lansoprazole versus omeprazole after 48 weeks of treatment,\textsuperscript{45} or rabeprazole versus omeprazole after 13 weeks, 26 weeks, one year, and five years.\textsuperscript{44, 47} Two similar 6-month trials conducted by the same investigators compared esomeprazole 20 mg a day (an FDA approved dose for healing or maintenance of erosive esophagitis) to
lansoprazole 15 mg a day (FDA approved dose for maintenance of healed erosive esophagitis)\textsuperscript{46} or pantoprazole 20 mg a day (lower than the FDA approved dose for maintenance of healed erosive esophagitis).\textsuperscript{48} These studies randomized patients who had been healed after 4 to 8 weeks of treatment and compared relapse rates at 6 months. According to life-table analysis, a higher proportion of patients in the esomeprazole groups remained healed over 6 months: 83\% vs 74\% and 87\% vs 74.9\% esomeprazole vs lansoprazole and esomeprazole vs pantoprazole, respectively. The authors also present data by baseline severity. More patients in the esomeprazole groups remained healed across all grades of disease severity in both studies. The efficacy of lansoprazole and pantoprazole decreased with increasing severity of disease, while in only 1 study\textsuperscript{48} the efficacy of esomeprazole in preventing relapse was lower in grade D patients compared to lower severity grades. No crude rates or numbers of patients remaining healed were presented. Crude rates provide a more conservative estimate of effectiveness due to the manner in which drop-outs are handled in life-table analyses. Because all patients enrolled in the study of esomeprazole and lansoprazole\textsuperscript{46} had responded to esomeprazole for initial healing of esophagitis, the study may be biased towards esomeprazole. Both studies were funded by the manufacturer of esomeprazole and the publications were co-authored by representatives of the company.

A shorter-term trial of 36 patients with severe (Savary-Miller Grade 4) esophagitis compared omeprazole, lansoprazole, and pantoprazole for the prevention of relapse at 4 weeks.\textsuperscript{49} Before randomization, all of the patients were treated with omeprazole. Six patients did not heal after 6 to 8 weeks of omeprazole; the rest (83\%) were randomized to omeprazole, lansoprazole, or pantoprazole. After 4 weeks, patients taking omeprazole had a lower rate of endoscopic relapse (10\%) than those randomized to either lansoprazole (80\%) or pantoprazole (70\%). The relapse rates in the lansoprazole and pantoprazole groups are very high compared with other studies and, as in the esomeprazole versus lansoprazole study discussed above, had a selection bias in that all subjects had responded well to one of the study drugs before enrollment in the maintenance phase.

A Cochrane systematic review estimated that the relative risk of relapse of healed esophagitis with a healing dose of a PPI compared with placebo was 0.26 (95\% CI 0.19 to 0.36; NNT=1.7).\textsuperscript{50} For maintenance of remission of symptoms, the relative risk was 0.34 (95\% CI 0.25 to 0.46; NNT=2.0). For maintenance doses, the relative risk for remission of esophagitis was 0.46 (95\% CI 0.38 to 0.57; NNT=2.4), and for remission of symptoms, the relative risk was 0.54 (95\% CI 0.42 to 0.69; NNT=3.0). This review did not compare different PPIs.

**Patients with non-erosive or empirically-treated GERD**

We identified only one head-to-head trial of maintenance treatment in patients with non-erosive GERD.\textsuperscript{51} We also included two placebo-controlled trials of on-demand rabeprazole\textsuperscript{52} and esomeprazole,\textsuperscript{53} and a placebo-controlled trial of continuous omeprazole.\textsuperscript{54} Details of these trials are shown in Evidence Table 5. Three other trials included patients with both endoscopy negative GERD and erosive esophagitis, but did not report results separately by group.\textsuperscript{34, 55, 56}

A head-to-head trial compared esomeprazole 20 mg on-demand to continuous lansoprazole 15 mg for 6 months in patients with ENRD who had experienced complete relief of heartburn with esomeprazole 20 mg during an acute treatment phase (2 to 4 weeks).\textsuperscript{51} Patients were not blinded to treatment, and the primary outcome measure was time to discontinuation from the maintenance phase due to unwillingness to continue. Patients also recorded heartburn
and other symptoms on diary cards and were asked about their satisfaction with treatment during scheduled clinic visits. By 6 months, significantly more patients receiving continuous lansoprazole 15 mg were unwilling to continue compared to those receiving esomeprazole 20 mg on-demand (13% vs 6%, p=0.001). More patients in the lansoprazole group said they discontinued because of adverse events (7.4% vs 2.3%; p=0.0028), but discontinuations because of heartburn were not significantly different between treatment groups (2.9% vs 4.8% for esomeprazole and lansoprazole, respectively; P not reported, but NS). At 1 month, more esomeprazole patients were satisfied with their treatment, but at 3 and 6 months, there was no difference between treatment groups on this measure. During the maintenance phase, the mean frequency of heartburn symptoms was higher in the esomeprazole on-demand group compared with the continuous lansoprazole group.

Two 6-month placebo-controlled studies reported efficacy of on-demand therapy with rabeprazole 10 mg\textsuperscript{52} or esomeprazole 20 mg\textsuperscript{53} in patients with ENRD. In both studies, only patients who experienced complete symptom relief during an acute treatment phase were enrolled in the maintenance phase. In the study of rabeprazole 10 mg, rates of discontinuation due to inadequate heartburn control were 20% for placebo versus 6% for rabeprazole (p<0.00001). Although mean duration of heartburn-free periods was similar between groups, the time required for symptom resolution during a heartburn episode was significantly shorter with rabeprazole than placebo. In the study of esomeprazole 20 mg, 14% of patients taking esomeprazole versus 51% of those taking placebo discontinued, mainly due to inadequate control of heartburn (p<0.0001).\textsuperscript{53}

In a placebo-controlled trial of continuous omeprazole 10 mg, 27% of patients taking omeprazole versus 52% of those taking placebo discontinued due to inadequate control of heartburn over 6 months.\textsuperscript{54}

**Systematic reviews of head-to-head trials in patients with erosive esophagitis**

Four recent systematic reviews comparing PPIs for esophagitis healing and symptom relief have been published.\textsuperscript{57-60} Three of the four included studies of esomeprazole, and all concluded that esomeprazole was superior to other PPIs for GERD, based on the same studies included in this report.\textsuperscript{58-60} One of these concludes that better healing rates in patients taking esomeprazole 40 mg compared with those taking omeprazole 20 mg or lansoprazole 30 mg is attributable to increased efficacy of esomeprazole in patients with more severe grades of esophagitis.\textsuperscript{58} The other was designed to compare the efficacy of esomeprazole versus lansoprazole, and concluded that esomeprazole provided an additional benefit of 5% at 4 weeks and 4% at 8 weeks compared with lansoprazole 30 mg.\textsuperscript{60} Both of these were funded by the manufacturer of esomeprazole.

A third systematic review,\textsuperscript{59} in which the funding source is not reported, concluded that esomeprazole 40 mg was superior to omeprazole 20 mg for GERD healing after 4 weeks (RR 1.18, 95% CI 1.14-1.23), but that this result was due to the non-equivalent, higher dose of esomeprazole used. There were no differences among the other PPIs.

A systematic review conducted in 2001\textsuperscript{57} found that lansoprazole, rabeprazole, and pantoprazole had similar efficacy to omeprazole for healing. No study of esomeprazole had been done at the time.
**Key Question 1b. Comparisons of PPIs and H2-RAs**

In comparisons of PPIs and H2-RAs, what is the comparative efficacy of different PPIs in healing esophagitis, reducing symptoms, and preventing relapse of GERD?

Comparisons of PPIs across studies are difficult because patient populations and baseline healing rates are dissimilar.

**Esophagitis Healing**

In the systematic review mentioned above, five PPIs were better than ranitidine at healing esophagitis, but there were no differences among them. No study of esomeprazole was included. We reviewed 22 randomized controlled trials published through 2001 that compared a PPI with an H2-RA for GERD healing. Figure 2 shows the rates of esophagitis healing at 8 weeks. These trials compared an H2-RA to omeprazole (11 studies), lansoprazole (five studies), pantoprazole (five studies), and rabeprazole (1 study). We did not create evidence tables of these studies or rate their quality, because after graphing their results we found no indication that the PPIs differed. If an obvious difference in healing rates were seen in an individual study or studies, investigation of study quality would have been undertaken. In our meta-analysis, PPIs were more effective at healing than H2-RAs, but there were no differences in healing rates among the PPIs for any comparison. Healing rates ranged from 71.2% to 85.6%.

**Relief of Symptoms**

In the Caro systematic review, the pooled relative risk of studies that reported heartburn resolution at 4 weeks was 1.02 (95% CI, 0.94-1.11) for newer PPIs (pantoprazole, rabeprazole, lansoprazole) compared with omeprazole. For all 4 PPIs versus ranitidine, the pooled relative risk was 1.53 (95% CI, 1.37-1.72).

**Prevention of Relapse**

A fair-quality trial compared pantoprazole 10mg, 20 mg, or 40 mg to ranitidine 150 mg for prevention of relapse of healed esophagitis in 371 patients. After 12 months, more patients remained healed on pantoprazole at all doses than those taking ranitidine, and the rate of relapse was related to the dose of pantoprazole (60%, 32%, and 18% relapsed in 10mg, 20 mg, and 40 mg groups, respectively).

A second study of the same doses of pantoprazole and ranitidine found similar results. During the first 12 months of maintenance treatment, 78% of patients treated with pantoprazole 40 mg, 55% of patients treated with pantoprazole 20 mg, 46% of patients treated with
A 2001 systematic review identified 15 studies of relapse prevention. Only three of them compared one PPI to another, and all three were abstracts rather than full-text reports. Seven compared a PPI to placebo, and five compared a PPI to ranitidine. The review found similar remission rates for lansoprazole, rabeprazole, and omeprazole over 12 months of treatment. Relapse rates at 6 months were 6% to 29% with lansoprazole, 9% with rabeprazole, and 7% to 42% with omeprazole.

A more recent 6-month study evaluated on-demand esomeprazole 20 mg, continuous esomeprazole 20 mg daily, or ranitidine 150 mg twice daily to prevent relapse among patients previously healed using esomeprazole 40 mg daily. 1902 patients enrolled in the open-label study, and after 6 months 82% on continuous esomeprazole had no symptoms, while 75.4% using on-demand esomeprazole and 33.5% taking ranitidine had no symptoms. Similarly, the percentage of patients experiencing any relapse over 6 months was lowest in the continuous PPI group (7%) compared to 10.9% in the on-demand PPI group and 34.4% in the H2-antagonist group. Using the Quality of Life in Reflux and Dyspepsia scale, the continuous PPI regimen was again better than the on-demand or H2-antagonist regimens, although the difference was greatest between either PPI regimen and the H2-antagonist regimen.

**Children**

There are no head-to-head trials of PPIs in children. Placebo- and active-controlled trials in children are shown in Evidence Table 6.

A fair quality placebo-controlled trial of omeprazole (10 to 20 mg/day) in infants (3 to 12 months) with gastroesophageal reflux defined as a pH <4 for 5% of the monitoring time (unspecified) and/or abnormal esophageal histology found no difference in the cry/fuss time or visual analog scale scores of parent assessment of infant irritability between placebo and omeprazole. Histologic and pH measures improved significantly with omeprazole but not placebo.

A poor quality trial of omeprazole (40 mg/day per 1.73 squared meters) compared to high dose ranitidine (20 mg/Kg/day) in children with reflux refractory to standard dose ranitidine found both drugs to be effective, but a high drop out rate (19%), lack in intention to treat analysis and inadequate baseline characteristics make these results unreliable.

**Key Question 2. Efficacy in peptic ulcer and NSAID-induced ulcer?**

*What is the comparative efficacy of different PPIs in patients with peptic ulcer and NSAID-induced ulcer?*

**Summary of the Evidence**

*Duodenal ulcer:*

- The data regarding comparative effectiveness of various PPIs for treating duodenal ulcer are good, with nine head-to-head trials.
- Omeprazole 20mg daily is typically the comparator drug.
- The evidence is good for omeprazole and lansoprazole having similar effectiveness in both endoscopic healing and symptom relief. The pooled risk difference for five trials of lansoprazole 30mg versus omeprazole 20mg once daily is -0.2 (95% CI, -3.0 to +2.6).
- The evidence for pantoprazole, rabeprazole and esomeprazole is less strong, because there are only single studies for each drug compared to another PPI (all compared to omeprazole).
- No study found significant differences in healing rate. Data from studies comparing PPIs to H2-RAs also indicate that there are no significant differences between the four PPIs studied (there are no studies of esomeprazole).
- Symptom relief is an important measure in ulcer diseases, and does not always correspond to endoscopic healing. Method for assessment of symptom relief was not consistent across the studies, and reporting of findings was often limited to early time periods and just a few outcome measures (of many measured). Few studies found a difference in any of the many measures of symptom relief, and the lack of reported data at later time-points may indicate that symptom relief was equivalent.

**Gastric ulcer:**
- Comparative data about PPIs for the treatment of gastric ulcer is very limited, with 2 studies of rabeprazole versus omeprazole. No significant differences in healing rates were found.
- Data from studies of omeprazole, lansoprazole and pantoprazole compared to H2-RAs indicate no significant difference in the rate of healing at 4 weeks.
- Symptom relief was better in 3 of 12 measures for rabeprazole compared to omeprazole at 3 weeks or two measures and 6 weeks for a third measure (the measures significantly different at 3 weeks were not different at 6 weeks). Symptom relief was difficult to compare for the other drugs, with no head-to-head studies. No important difference was clear from the PPI versus H2-RA studies.

**NSAID-induced ulcer:**
- There are no head-to-head trials.
- Only 4 trials compared a PPI to another drug, two with omeprazole one each with esomeprazole and lansoprazole. No important differences between PPIs could be discerned from these studies, with the confidence intervals for healing rates overlapping. However, the treatment success rates for all treatments varied widely among the trials, so confidence in this finding is low.

**Prevention of NSAID-induced ulcer:**
- There are no head-to-head trials.
- A good quality systematic review and seven subsequently published trials compared PPIs to placebo or other drugs. Only one trial included outcome measures for serious ulcer complications, and for some of the endoscopic ulcer findings, patients were asymptomatic.
- Based on development of new ulcers or serious erosions and on symptoms, there did not appear to be differences in the PPIs studied (omeprazole, lansoprazole and pantoprazole). However, because of the differences in patient populations, comparison groups, and outcome measure definitions, confidence in this finding is low.
Eradication of *H. pylori*:
- The evidence regarding comparative effectiveness of various PPIs is fair, with five systematic reviews, and 25 recent head-to-head trials. The significant heterogeneity among studies based on design, participants, and method of measuring outcomes lessen the strength of the evidence.
- These studies generally did not find a difference in eradication rate between the PPIs, with the exception of lower dose pantoprazole when compared to high dose pantoprazole or high dose omeprazole, pantoprazole compared to esomeprazole in one study, and rabeprazole when compared to lansoprazole in one study.
- Symptom resolution was not assessed in these studies.
- In children, evidence is extremely limited with only 2 trials of lansoprazole versus placebo. Neither trial found the addition of lansoprazole to result in higher eradication rates than antibiotic therapy alone.

**Detailed Assessment**

**Key Question 2a. In head-to-head comparisons, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in patients with duodenal ulcer?**

Nine randomized controlled trials compared one PPI to another.\(^{35, 89-96}\) The details of these studies are summarized in Evidence Table 7. Six of these trials compared lansoprazole 30mg to omeprazole 20mg\(^{89-93, 96}\). One study each compared pantoprazole 40mg and rabeprazole 20mg to omeprazole 20mg\(^{35, 94}\) and one study comparing esomeprazole 40mg to omeprazole 40mg.\(^{95}\) All of these dose comparisons are fair based on equipotency.

The studies were fair quality. These studies were generally similar with respect to design, demographics and other population characteristics, with the following exceptions. One study was unusual in that as a part of a *H. pylori* eradication regimen, patients with active duodenal ulcer were given esomeprazole plus antibiotics for only 1 week, while omeprazole patients received antibiotics plus omeprazole for 1 week, then continued omeprazole for another 3 weeks.\(^{95}\)

As shown in Figure 3, there was no difference between omeprazole 20mg, lansoprazole 30mg, and rabeprazole 20mg in the percentage of patients healed by 4 weeks. Results from a large multicenter trial of esomeprazole 20mg twice daily versus omeprazole 20mg twice daily also showed no difference in healing rates.\(^{95}\) The pooled risk difference for lansoprazole 30mg versus omeprazole 20mg once a day was -0.2 (95% CI, -3.0 to +2.6). The risk differences found between esomeprazole 40mg, pantoprazole 40mg and rabeprazole 20mg and omeprazole were approximately −0.97%, 6% and 5%, respectively, however these are based on single studies and were not statistically significant. The results for healing at 2 weeks were similar.

Symptoms (pain, nausea, vomiting, antacid use, or overall well-being) were assessed by investigators at visits and through patient diaries in seven studies. Only one found a significant difference between PPIs.\(^{35}\) This study found that daytime pain was ‘improved’ in 92% on rabeprazole and 83% on omeprazole at 4 weeks (p=0.038), however no difference was found in
nighttime pain or in the number of patients who were pain-free. Antacid use, GI symptoms, and overall well-being were not different in any of the studies.

Only one head-to-head study addressed maintenance, comparing lansoprazole 15mg, lansoprazole 30mg and omeprazole 20mg for up to 12 months (see Evidence Table 8). At 6 months post-healing, recurrence rates were 4.5%, 0%, and 6.3%, respectively. At 12 months the recurrence rates were 3.3%, 0%, and 3.5%, respectively. These differences were not statistically significant.

Three other studies listed in Evidence Table 8 compared lansoprazole to placebo or ranitidine. Relapse rates at 12 months in the lansoprazole 15mg groups ranged from 23 to 30%, in the single lansoprazole 30mg group the rate was 15%, compared to placebo rates of 39 to 100%. One study reported relapse rates with no maintenance treatment following healing with omeprazole, ranitidine or placebo. Relapse rates were not significantly different between the groups.

**Key Question 2b. In comparisons of PPIs and H2-RAs, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in patients with duodenal ulcer?**

Twenty-five randomized controlled trials compared a PPI with an H2-RA. Of these, 22 papers were reviewed. Since these studies can only be used to make indirect comparisons of the effectiveness of the various PPIs, a limited analysis is presented. Individual study quality assessments for these studies will not be presented. If an obvious difference in healing rate were seen in an individual study or studies, investigation of study quality would have been undertaken.

The most common H2-RA used as a comparator was ranitidine 300mg per day, with ten studies comparing omeprazole 20mg, four studies comparing pantoprazole 40mg, two studies comparing lansoprazole (doses varying from 15 to 60mg per day), and one study comparing rabeprazole 20mg. Two compared omeprazole 20mg to cimetidine (doses varying from 800mg to 1200mg per day), two compared omeprazole 20mg with famotidine 40mg, and 1 compared omeprazole with nizatidine 300mg. There are no studies comparing esomeprazole to an H2-RA.

Figure 4 shows the rates of duodenal ulcer healing at 4 weeks in 21 studies of a PPI versus an H2-RA PPIs were more effective at healing than H2-RAs, but there were no significant differences in healing rates among the PPIs. Duodenal ulcer healing rate at 4 weeks with omeprazole and lansoprazole was dependent on H2-RAs healing. That is, as the healing rate in the H2-RA group increased, PPI healing rate increased. One comparison showed pantoprazole to have a significantly higher healing rate than rabeprazole (risk difference 11.3%), but this comparison is based on only one study, and the confidence interval is large (95% CI, 2.4%-23.2%).

Another study examined the added benefit of continuing omeprazole 20 mg for 3 additional weeks after 1 week of eradication therapy with omeprazole 20mg combined with amoxicillin 1000 mg and clarithromycin 500 mg. At 4 weeks, there was no difference in healing rates in patients assigned to omeprazole (89%) versus placebo (87%). An additional four trials were found in updating the original review. These studies were consistent with the studies reported above and are not added to figure 4. One of these studies reported symptom relief only.
Key Question 2c. In head-to-head comparisons, what is the comparative efficacy different PPIs in reducing symptoms and improving endoscopic healing in patients with gastric ulcer?

Three studies compared PPIs directly in treating gastric ulcer. A fair quality study of 227 patients compared rabeprazole 20mg to omeprazole 20mg (Evidence Table 9). Healing was assessed at 3 and 6 weeks, while most other studies of gastric ulcer healing use 4 and 8 weeks. The percent risk difference in the rate of healing at 3 weeks is -3% (95% CI, -16, 9.7), and reported as the same in both groups at 6 weeks. Symptoms were assessed by investigators at visits and through patient diaries. Twelve different comparisons of symptom resolution or improvement were made. No significant differences were found in the reporting of pain resolution or improvement (frequency, severity, night or daytime) at 3 or 6 weeks for nine of these comparisons. Rabeprazole was statistically superior in three comparisons: improvement of severity of pain at 3 weeks and improvement in the frequency of daytime pain and resolution of nighttime pain at 6 weeks. No difference in changes in overall well-being or reduction in antacid use was found.

A smaller fair quality study (n = 80) compared rabeprazole 10 mg a day and omeprazole 20 mg a day, and evaluated the impact of CYP2C19 genotype on healing rates. The overall healing rate comparison at 8 weeks (risk difference 1.94%, 95% CI -1.34% to 1.71%) did not show a difference between the drugs.

A poor quality trial compared lansoprazole 30 mg/day to omeprazole 20 mg/day. This study did not conduct intent to treat analysis and more patients were excluded from the omeprazole (15%) analysis than the lansoprazole group (7%). Although the authors state there were no differences between groups at baseline, 4% of patients in the omeprazole group were smokers, compared to 1% in the lansoprazole group. The results of this study found lansoprazole superior in cumulative healing rate at 8 weeks (93% vs 82%, p=0.04); the difference at 4 weeks was not statistically significant. It is not clear from the publication which patients were included in this analysis, and our statistical analyses based on differing assumptions did not result in statistically significant differences between the groups at either time point. Differences in symptom relief were not found to be statistically significant.

Key Question 2d. In comparisons of PPIs and H2-RAs, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in patients with gastric ulcer?

Fifteen studies compared a PPI to an H2-RA for treatment of gastric ulcer (Evidence Table 9). There were two studies of maintenance therapy and one followup study of relapse rates in patients healed in one of the above studies. One of the maintenance studies included patients with either gastric or duodenal ulcer, all of which were resistant to H2-RA therapy. One study evaluated esomeprazole versus ranitidine in healing ulcers in patient who continued to take a NSAID. This study is examined below, in key question 2f. No study compared rabeprazole to a H2-RA. Five trials compared omeprazole to ranitidine; three compared lansoprazole to ranitidine; one compared pantoprazole to ranitidine; two, lansoprazole to famotidine; three, omeprazole to cimetidine, and one, lansoprazole to cimetidine.
The total followup times varied, but healing rates at 4 weeks were available from all studies. Differences in the percentages of patients healed with different PPIs at 4 weeks are plotted in Figure 5. The pooled risk differences range from 1.09 to 62.5%, with the smallest studies showing larger effects. The confidence intervals for PPIs compared to H2-RAs all overlap.

Symptoms were assessed by investigators at visits and through patient diaries in 13 studies. One did not report symptoms. Pain was the most commonly assessed symptom. The scales used were not consistent across the studies (0 to 3 in some, 0 to 4 in others), or were not described. Most found the PPI relieved symptoms somewhat faster, with no difference later on. However, only three studies found statistically significant differences, and then only in some of the many measures assessed.

One study reported maintenance therapy of lansoprazole 15 or 30 mg compared to placebo. Lansoprazole was effective for preventing endoscopic recurrence and eliminating symptoms and reducing antacid use. Omeprazole 20 mg every day was more effective than ranitidine in preventing relapse in patients with refractory ulcer (not healed after 8 weeks of H2-RA treatment) in one 6-month open study. Only 12 patients of 102 enrolled were assigned to ranitidine in this study, and patients with both gastric and duodenal ulcer were included. A 6-month followup study without treatment of patients who had healed after 6 weeks of treatment with omeprazole or cimetidine found no significant difference in relapse rates. All of these studies had high or differential dropout rates.

**Key Question 2e. In head-to-head comparisons, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in patients with NSAID-induced ulcer?**

No study compared one PPI to another.

**Key Question 2f. In comparisons of PPIs and misoprostol or H2-RAs, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in patients with NSAID-induced ulcer?**

Four studies assessed PPIs (omeprazole, esomeprazole, and lansoprazole) compared to another drug in healing ulcers induced by NSAIDs. The details of these studies are summarized in Evidence Table 10. A good quality systematic review of prevention and treatment of NSAID-induced ulcers was also found.

Comparisons of ranitidine 150 mg twice daily to omeprazole 20 and 40 mg daily, lansoprazole 15 and 30 mg daily and esomeprazole 20 and 40 mg once daily resulted in higher rates of healed ulcer at 8 weeks for the PPI. The difference in percent healed ranged from 14 to 22% favoring the PPI, but in all comparisons the difference was statistically significant. While there is no direct comparison of the PPIs, all confidence intervals overlap. A single study found that 20 mg of omeprazole was superior to misoprostol in healing rates at 8 weeks, but that 40 mg was not superior.

One study assessed quality of life using the Gastrointestinal Symptom Rating Scale and the Nottingham Health Profile. Based on the Gastrointestinal Symptom Rating Scale,
omeprazole was better than misoprostol in the changes in scores for the total scale, as well as scores for reflux and diarrhea. Although the improvement in score was greater with 20mg omeprazole than 40mg, these were not statistically significant. Only the sleep score of the Nottingham Health Profile was reported, which also showed omeprazole 20mg to be superior to misoprostol, but the change in score for omeprazole 40mg was not reported.

**Key Question 2g. In head-to-head comparisons, what is the comparative efficacy of different PPIs in preventing NSAID-induced ulcer?**

There are no head-to-head comparison studies.

**Key Question 2h. In comparisons of PPIs, other drugs, or placebo what is the comparative efficacy of different PPIs in preventing NSAID-induced ulcer?**

One recent, good quality systematic review addressed this question. The search for literature covered 1966 to 2000 (MEDLINE search from 1966 to January 2000, Current Contents for 6 months prior to January 2000, EMBASE to February 1999, and a search of the Cochrane Controlled Trials Register from 1973 to 1999). This review found five randomized trials, which assessed omeprazole 20 to 40mg in prevention of NSAID-induced gastroduodenal toxicity. None of the studies were designed to evaluate the effectiveness of PPIs in preventing serious ulcer complications (hemorrhage, perforation or death). The review showed that omeprazole is superior to the H2-RAs but provided no data on any other PPI.

Five trials published more recently are presented in Evidence Table 11, along with two of the treatment studies that included a prevention phase. None of these studies was a head-to-head comparison and there were important differences in treatment regimens and followup, making comparisons across studies impossible. All enrolled patients who were regular users of NSAIDs. One study included only patients who were H. pylori negative and randomized to placebo, misoprostol 800mcg, lansoprazole 15mg or 30mg with followup at 1,2 and 3 months, another randomized patients to pantoprazole 40mg or placebo for 3 months. The third study included patients who were H.pylori positive and had ulcer complications after using low-dose aspirin continuously for more than one month. After ulcers were healed and H. pylori eradicated, patients were randomized to lansoprazole 30 mg or placebo, in addition to 100 mg of aspirin daily. In the last study, H.pylori positive patients with no past or current ulcer were assigned to one of 4 treatment groups: omeprazole 20 mg plus clarithromycin 500 mg and amoxicillin 1 gram for one week, followed by placebo or omeprazole 20 mg daily for 4 weeks; omeprazole 20 mg once daily for five weeks; or placebo for 5 weeks.

In the study of H. pylori negative patients, lansoprazole was inferior to misoprostol in preventing gastric ulcers. At 3 months, the gastric ulcer rate (failure rate) was 7% for misoprostol, 20% for lansoprazole 15mg, and 18% for lansoprazole 30mg, with no significant difference between lansoprazole doses. However, when adverse effects were included as failures, the failure rate for all 3 treatment groups was 31%. A post-hoc subgroup analysis of patients taking NSAIDs and low dose aspirin found no significant differences were found among the groups of drug treatments at 12 weeks.

In the study of pantoprazole versus placebo, a life-table analysis is presented, rather than simple proportions of patients without ulcer, making comparison to other PPI versus
placebo studies unclear. At 4 weeks, the risk difference is 17% fewer ulcers in the pantoprazole group, and 27% at 12 weeks. These numbers include those who dropped out due to adverse effects as treatment failures.

In the study of H. pylori positive patients with ulcer complications,\textsuperscript{153} the primary endpoint was prevention of ulcer complications and the secondary endpoint was recurrence. The rate of recurrence of ulcer complications at a median followup of 12 months was 1.6% in the lansoprazole group, compared with 14.8% in the placebo group. Two patients in the placebo group were also taking NSAIDS.

In patients with H. pylori but no history of ulcer, all 3 active treatment regimens were better than placebo in reducing the occurrence of ulcer and dyspeptic symptoms requiring therapy, and there were no significant differences between the treatment groups.

Symptom assessment and reporting varied among these studies. The pantoprazole versus placebo study did not describe methods or scales used to assess symptoms, but reported “GI symptoms.”\textsuperscript{152} GI symptoms were not the same at baseline in the two groups; 43% in the pantoprazole versus 18% in placebo group complained of GI symptoms. At 4 and 12 weeks the pantoprazole group improved (17% and 20%, respectively), while the placebo group remained stable (20% and 19%, respectively). In the lansoprazole versus misoprostol study, symptoms (day and nighttime abdominal pain and antacid use) were assessed by patient diary and were found to be significantly better in the lansoprazole groups versus misoprostol, but comparisons between the two lansoprazole doses were not made.\textsuperscript{151}

**Key Question 2i. In head-to-head comparisons, what is the comparative efficacy of different PPIs in improving eradication rates in patients with Helicobacter pylori?**

A good-quality meta-analysis reviewed 14 head-to-head trials of PPIs combined with antibiotics in triple-therapy regimens for h. pylori eradication.\textsuperscript{157} Using omeprazole as the reference for comparison, no difference was found in eradication rates among any of the PPIs. In addition, a fair quality systematic review addressed this question.\textsuperscript{158} The search for literature covered 1986 to 1998 (MEDLINE search from 1986 to 1997, and hand searches from 1986 to January 1998). This meta-analysis included 666 studies overall. Although the number of studies evaluating a PPI is unclear, there were nine different regimens that included a PPI. The PPIs included in these studies were omeprazole, lansoprazole, and pantoprazole. Using a meta-regression analysis, no difference in cure rate was found between the three PPIs in any of the antibiotic combinations studied. Another recent fair quality systematic review focused on lansoprazole in eradication of H. pylori.\textsuperscript{159} This review found no difference between lansoprazole and omeprazole in eradication rate.

Since these reviews, 25 studies were published that directly compared one PPI to another in combination with the same antibiotic(s).\textsuperscript{95, 96, 160-179} They made the following comparisons:

- Rabeprazole 20mg versus omeprazole 40mg, plus amoxicillin (one study)\textsuperscript{171}
- Lansoprazole 60mg versus omeprazole 40mg, plus amoxicillin and metronidazole (one study)\textsuperscript{164}
- Omeprazole 40mg versus pantoprazole 40mg, plus clarithromycin and metronidazole (one study)\textsuperscript{160}
- Omeprazole 20mg versus lansoprazole 30mg, plus clarithromycin and tinidazole (one study) 96
- Various doses of lansoprazole, rabeprazole, pantoprazole and esomeprazole versus omeprazole, plus clarithromycin and amoxicillin (ten studies)76, 95, 161, 163, 167-169, 174, 177, 180-182
- Omeprazole 20 mg, lansoprazole 30 mg, or rabeprazole 10 mg (all twice daily) each combined with amoxicillin and clarithromycin (one study),165
- Rabeprazole 10 mg or 20 mg or lansoprazole 30 mg twice daily, each combined with amoxicillin and clarithromycin (three studies),136, 166, 170, 172
- Lansoprazole 30 mg or omeprazole 20 mg twice daily combined with amoxicillin alone, versus lansoprazole 30 mg twice daily combined with amoxicillin and clarithromycin (one study).173
- Lansoprazole 30 mg once a day vs omeprazole 20 mg twice a day combined with amoxicillin and clarithromycin. (1 study).176
- Lansoprazole 30 mg or omeprazole 20 mg (both twice daily) plus amoxicillin and clarithromycin (1 study).162
- Lansoprazole 30 mg or omeprazole 20 mg (both twice daily) plus amoxicillin alone (1 study).183
- Esomeprazole 40 mg versus omeprazole 40 mg, plus clarithromycin and metronidazole (one study)184
- Esomeprazole 40 mg daily, esomeprazole 40 mg twice daily, or omeprazole 20 mg twice daily plus amoxicillin and clarithromycin (1 study).178
- Esomeprazole 40 mg or pantoprazole 40 mg (both once daily) plus amoxicillin and clarithromycin (w study).179

These studies were fair quality, with the exception of 5 poor quality studies that were not blinded. 171, 176, 178, 182, 184  This is a heterogeneous group of studies. Some of the PPI comparisons did not use what would be considered equivalent doses (e.g., rabeprazole 20 mg versus omeprazole 40 mg or omeprazole 40 mg versus pantoprazole 40 mg) and one used a dose of omeprazole that is not standard in the US (60 mg).167  In addition, the doses of clarithromycin, amoxicillin and metronidazole also varied. Some of the studies were assessing short durations of treatment; while others were evaluating the use of lower doses of PPIs in Asian patients (see Key Question 3). The methods of assessing H. pylori eradication also varied among the studies, as did other treatments during the study period. Hence, direct comparison across all studies is not possible.

Twelve studies included patients with documented ulcer. 95, 96, 161, 162, 164-166, 169, 171, 172, 175-177, 182  Nine studies included patients with ulcers or non-ulcer dyspepsia. The proportion of non-ulcer patients ranged from 12%170 to 71%.174  One study conducted in a low-income population in Colombia included patients with “gastritis” and did not check for ulcer,167 and two included both patients with previous or present recurrent ulcer.173

As would be expected based on these differences, eradication rates varied in these studies, from a low of 42% (lansoprazole 30 mg with only amoxicillin) 175 to a high of 100% (pantoprazole 40 mg).160  One study found a significantly lower eradication rate for pantoprazole (40 mg) than for higher relative doses of omeprazole (40 mg) or high-dose pantoprazole (80 mg). Another study found a lower eradication rate for pantoprazole 40 mg compared to esomeprazole 40 mg daily.179  Rabeprazole (20 mg or 40 mg) had lower rates of eradication than lansoprazole
30 mg in another comparison. No other study found a significant difference regardless of dose or specific PPI. A study evaluating the effect of age found that older patients (> 50 years) had higher eradication rates than younger patients.

**Key Question 2j.** In comparisons of PPIs and H2-RAs, what is the comparative efficacy of different PPIs in improving eradication rates in patients with *Helicobacter pylori*?

**Adults**

Four fair quality systematic reviews assessed PPIs compared to H2-RA-based eradication regimens. All found similar eradication rates for the PPIs compared to H2-RAs.

**Children**

Two trials evaluated lansoprazole in eradication of *H. pylori* in children. Both studies used antibiotic regimens of amoxicillin and tinidazole, given for 6 or 7 days, in combination with lansoprazole or placebo. The 2 protocols were very similar, but not identical; in one the dose of lansoprazole was 30 mg per day with children 10 to 21 years eligible for enrollment, while in the other dosing was based on weight (<20 Kg: 15 mg and >/= 20 Kg: 30 mg per day) and the age range enrolled was 8 to 14 years. However, the mean age for participants in both trials was 11 years. Neither trial resulted in significantly different eradication rates between placebo (58% and 71%) and lansoprazole (67% and 68%).

**Key Question 3. Adverse effects**

*What are the comparative incidence and nature of complications (serious or life-threatening or those that may adversely effect compliance) of different PPIs in patients being treated for symptoms of gastroesophageal reflux, peptic ulcer, and NSAID-induced ulcer?*

**Summary of the Evidence**

- The comparative evidence on long-term adverse effects is limited. There are no long-term head-to-head comparative studies (clinical or observational) specifically designed to monitor adverse effects.
- Two long-term (48 weeks to 5 years) maintenance studies found no difference between omeprazole and lansoprazole in adverse events or withdrawals due to adverse events, and a 6-month study of esomeprazole 20 mg versus lansoprazole 15 mg found no differences in adverse event rates.
In long-term followup studies of individual drugs, no important differences in long-term findings were apparent, but comparisons across these studies are not clear.

Short-term head-to-head comparative studies indicate that the incidence of all and serious adverse events, and the drop out rate due to adverse events for all the PPIs is low. No consistent differences between the PPIs were seen in these trials.

All PPIs share drug interactions based on elevated gastric pH altering absorption of a small number of drugs. Omeprazole is known to have drug interactions with a small number of drugs metabolized by the CYP2C19 and CYP3A4 enzyme systems. The action required is monitoring to see if dose adjustment of the other drug(s) is necessary. Lansoprazole may possibly interact with theophylline. Pantoprazole, rabeprazole, and esomeprazole have no documented drug interactions deemed clinically significant.

**Detailed Assessment**

There are no head-to-head long-term comparison studies designed to assess adverse events between PPIs. In three long-term (6 months or longer) maintenance studies of patients with GERD, there was no difference in the number of adverse events reported or number of withdrawals due to adverse events in the different PPI treatment groups. In one study of GERD patients, 9 of 248 (3.6%) patients withdrew for adverse events over 48 weeks of treatment, 4% in the lansoprazole group and 3.3% in the omeprazole group. In another study, comparing rabeprazole 10 or 20mg to omeprazole 20mg 13 of 243 (5.3%) patients withdrew because of adverse events at 52 weeks, and 26 of 243 (11%) withdrew at 5 years; the numbers in each group did not differ significantly. In the third long-term maintenance study, 29 of 617 (4.7%) patients in the esomeprazole 20 mg group and 32/614 (5.2%) of those in the lansoprazole 15 mg group withdrew due to adverse effects. There are no head-to-head maintenance studies of ulcer, but three 12-month studies of duodenal ulcer maintenance compared a PPI to placebo or other anti-ulcer medications. In two of the studies, the withdrawal rates for placebo were higher than any of the drug arms. In one study, the withdrawal rates due to adverse events were high, 17% for lansoprazole 15mg, 5.3% for lansoprazole 30mg and 21.5% for placebo over a 12-month period.

Several reports of long-term (ranging from 1 year up to 11 years) followup of individual PPIs (omeprazole, lansoprazole, pantoprazole, and rabeprazole) have been published. Potential adverse events studied include hypergastrinemia related enterochromaffin-like cell (ECL) hyperplasia and ECL carcinoids, atrophic gastritis and intestinal metaplasia, overgrowth of gastric bacteria and N-nitrosamine formation, enteric infections, potential malabsorption syndromes, and diarrhea. Of these, the risk of enteric infections may be increased with sustained acid suppression. This is a rare event, however. The other concerns have not been proven in these long-term, non-comparative studies. While ECL hyperplasia occurs, no increased risk of ECL carcinoids has been found. Likewise, atrophic gastritis is increased with long term PPI therapy, but progression to intestinal metaplasia and gastric cancer has not been shown. Gastric bacterial overgrowth does occur, but a related higher rate of gastric adenocarcinoma has not been found. Long-term studies assessing the risk of esophageal cancer were not found.

A nested case-control study of 10,008 lansoprazole users followed for 4 years found a trend for diarrhea to be dose related, reported in 5%, 3.7%, and 2.5% of patients using 60 mg or more, 30 mg, and 15 mg or less, respectively (p=0.08). In 42.1% of patients reporting diarrhea...
the lansoprazole dosage was reduced or discontinued due to this event. Cases had a higher current use of oral antibiotics than controls with no diarrhea (adjusted OR 2.7, 95% CI 1.0-6.9). There are no long-term studies of esomeprazole or rabeprazole.

Reports of adverse effects in head-to-head comparisons of PPIs for short-term treatment of GERD and ulcer are shown in Evidence Table 12. The proportion of patients withdrawing due to adverse events in these studies was very low, with most studies reporting 1% to 3%. No study found significant differences among treatment groups in the rate of withdrawals for adverse effects. Reports of serious adverse events were low, and generally balanced among the drugs. Many of these incidences could be associated with pre-existing diseases.

Serum gastrin levels were monitored in several studies, and found to be significantly elevated compared to baseline although the magnitude of increase was small and generally not considered clinically significant. A dose-related difference was found in some studies, but no differences between drugs. Likewise, when studied, the effect of the individual PPIs on H. pylori-related gastritis was similar, worsening gastritis in the corpus, and improving gastritis in the antrum.207

Also in Evidence Table 12 is a head-to-head study designed to determine patient preferences about switching from one PPI to another.208 The study included patients who had been taking a PPI for any indication for at least 56 days before the start of the study. All patients took omeprazole 20 mg and rabeprazole 20 mg daily for 4 weeks in a crossover design, with the order of medication randomized. A double-dummy presentation was used to blind patients to treatment assignment. At the end of each 4-week treatment phase patients were asked to name any unwanted or welcome side effects from the medication. The two PPIs maintained similar relief of symptoms, and the tolerability was similar.

**Children**

Reporting of adverse events in children is limited to short-term trials and 1 open-label uncontrolled study with longer term follow up.87, 88, 188, 189, 209-212 In a before-after study of omeprazole for esophageal reflux, 15 children were followed for a mean of 12 months. Seven (47%) had elevations of liver enzymes. Eleven (73%) had hypergastrinemia.213 In short-term trials of omeprazole no serious adverse events were reported.87, 209, 214

A short-term before-after study of pantoprazole reported elevated liver enzymes in 1 of 18 children exposed for 28 days and 5 of 18 (28%) had hypergastrinemia.211 In a 2-week study of lansoprazole in children (mean age 11 years) only mild gastric adverse events were reported.212

**Drug Interactions**

There are no head-to-head comparative studies of drug interactions with PPIs in patients with acid-related diseases. Drug interaction studies in healthy adults have been done with individual PPIs, and are summarized in Table 12, below. All of the PPIs reduce the absorption of drugs that require an acidic gastric pH for maximal absorption, such as ketoconazole. With all of the PPIs, the dose of these drugs may need to be increased, or the drug combination avoided (e.g., delavirdine and PPIs). All of the PPIs are metabolized by the CYP2C19 and CYP3A4
enzyme systems, and have some potential for interacting with other drugs that are also metabolized through this pathway. As can be seen in the table, omeprazole interacts with several drugs, but only four require any action (carbamazepine, phenytoin, diazepam and trovafloxacin). The recommended action is to monitor the patient for signs of adverse effects due to increased levels of these drugs. The newer PPIs have fewer studies of drug interactions, but in the studies that have been done, no clinically significant drug interactions have been found. The one possible exception to this is the decreased clearance of theophylline with lansoprazole. Since these studies have been done in healthy people, the external validity of the judgment of no clinical significance is unknown.

### Table 12. Clinically significant drug interactions

<table>
<thead>
<tr>
<th>Drugs with pH dependent absorption (e.g. ketoconazole, iron,itraconazole, delavirdine, indinivir, enteric coated salicylates)</th>
<th>Omeprazole</th>
<th>Esomeprazole</th>
<th>Rabeprazole</th>
<th>Lansoprazole</th>
<th>Pantoprazole</th>
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</thead>
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<tr>
<td>Carbamazepine</td>
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<td></td>
<td></td>
<td>No significant interaction (3)</td>
</tr>
<tr>
<td>Clarithromycin</td>
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<td>No significant interaction (2)</td>
<td></td>
<td></td>
<td>No significant interaction (3)</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>No specific action required (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>No specific action required (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>Monitor (1)</td>
<td>No significant interaction (2)</td>
<td>No significant interaction (4)</td>
<td>No significant interaction (4)</td>
<td>No significant interaction (3)</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>No specific action required (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Monitor (1)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
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<td></td>
<td></td>
<td></td>
<td>No significant interaction (3)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Monitor (1)</td>
<td>No significant interaction (2)</td>
<td>No significant interaction (4)</td>
<td>No significant interaction (4)</td>
<td>No significant interaction (4)</td>
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<tr>
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</tr>
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<td>Trovafloxacin</td>
<td>Monitor (1)</td>
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<tr>
<td>Warfarin</td>
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<td>No significant interaction (2)</td>
<td>No significant interaction (4)</td>
<td>No significant interaction (4)</td>
<td>No significant interaction (3)</td>
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<td>No significant interaction (4)</td>
<td>No significant interaction (4)</td>
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<td>Omeprazole</td>
<td>Esomeprazole</td>
<td>Rabeprazole</td>
<td>Lansoprazole</td>
<td>Pantoprazole</td>
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<tr>
<td>Glyburide</td>
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<td></td>
<td>No significant interaction (3)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>No significant interaction (3)</td>
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<td>Metronidazole</td>
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<td>No significant interaction (3)</td>
</tr>
<tr>
<td>Prednisone</td>
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<td></td>
<td></td>
<td></td>
<td>No significant interaction (4)</td>
</tr>
<tr>
<td>Atazanavir</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Monitor (5)</td>
</tr>
</tbody>
</table>

(A) These interactions could occur with any of the PPIs due to acid reduction

Refs: (1) Drug Interactions, Facts and Comparisons; (2) esomeprazole manufacturer submission; (3) pantoprazole manufacturer submission; (4) Review of PPI drug interactions by Humphries (employee of manufacturer of rabeprazole); (5) manufacturer comments

Key Question 4. Subgroups

Are there subgroups of patients based on demographics, other medications, or co-morbidities for which one medication or preparation is more effective or associated with fewer adverse effects?

Summary of the Evidence

- Head-to-head comparison studies did not adequately describe or analyze subgroups for differences in effectiveness, although two assessed differences in adverse effects based on age, gender and race with no differences found.
- There are studies which suggest that a lower dose of PPI may be equally effective in patients who are older or are deficient in the CYP2C19 liver enzyme (3% of whites and African Americans and 17-25% of Asians). Only one of these studies was a head-to-head comparison, omeprazole versus lansoprazole, but no difference was found between the two.
- While there may be differing effects of the PPIs based on demographics, there are inadequate data to identify any difference between them.

Detailed Assessment

Age and Sex

In included head-to-head studies, the populations included were middle aged, with mean ages ranging from a low of 43,97 to a high of 70.153 From 38% to 89% of the patients enrolled were male. The ethnicity of participants was only stated in five trials,5, 25, 46, 97, 128. In these studies (3 conducted in the US, one46 in Europe and South Africa), the patients enrolled ranged from 76% to 98% white. Of the remaining studies, 25 were conducted in European countries (including five in Italy), five in Japan, two in the US, and two in Taiwan. The effect of co-morbidities, or other medications were not studied in these trials.

There is one small, 12-month, placebo-controlled trial in which pantoprazole 20 mg was effective for maintenance treatment of GERD in patients age 65 or older.215 An age-based
analysis of healing or prevention was not possible in most head-to-head trials, due to the small numbers of older patients. However, two trials did assess the impact of age, gender and race on the incidence of adverse effects. There were no differences between PPIs (omeprazole, rabeprazole, esomeprazole) based on these characteristics. In addition, the effect of age on eradication rates was evaluated. This study found higher eradication rates among patients older than 50 years compared to patients younger than 50, but comparison of PPIs was made.

In trials comparing a PPI to another drug, the same general statements can be made, but a few findings deserve comment. Studies of healing NSAID-induced ulcer, and prevention of NSAID-induced ulcer included more women than men with the proportion of women ranging from 62 to 67%, and 64 to 83%, respectively. This is most likely due to the greater prevalence of women in the diseases requiring long-term NSAID treatment. However, no gender-based analyses were presented.

**Genotype**

The PPIs are all metabolized, largely by the CYP2C19 and CYP3A4 liver enzymes. This enzyme is estimated to be deficient in 3% of white and African Americans, and 17-25% of Asians. This results in a significantly longer half-life, although clinically significant accumulation of these drugs has not been shown. While dose adjustments are not required, and adverse effect profiles of the drugs do not differ, there is some evidence that lower doses may be effective in these populations, and that rapid metabolizers may have a higher failure rate in eradicating H. pylori and esophagitis healing. Results of subgroup analysis found no effect by race in one study of esomeprazole and lansoprazole in healing erosive esophagitis. A small study (n = 80) found no statistically significant differences in ulcer healing rate at 8 weeks between rabeprazole 10 mg a day and omeprazole 20 mg a day among patients with differing CYP2C19 genotypes. Adverse events were few and were not analyzed by genotype. A trial of omeprazole in Japanese patients with recurrent esophagitis found no differences in efficacy or safety by genotype.

Older patients also metabolize PPIs more slowly, resulting in significantly higher drug levels and half-lives. However, accumulation has not been shown, and dose adjustments are not recommended. One re-analysis of data from two trials of omeprazole versus either ranitidine or cimetidine for reflux esophagitis examined differences in effects in those age 65 or older compared to under age 65. In this analysis, there were no differences in healing rate or in symptom resolution at 4 and 8 weeks, with slightly higher proportion of older patients both healed and symptom-free. Withdrawals due to adverse events were higher in the older group, 7.6% versus 2.5%. This was not a comparative trial, and similar data are not available for other PPIs.

**Pregnancy**

A multicenter, prospective cohort study enrolled 410 pregnant women who had sought counseling after exposure to omeprazole (N=295), lansoprazole (N=62), or pantoprazole (N=53) between 1992 and 2001. Details of exposure were collected during pregnancy before pregnancy outcome was known, and followup was performed in the neonatal period. A control
group of 868 women who had been counseled during pregnancy in regard to exposures known to be non-teratogenic served as a control group. There were some differences between control and treatment groups at baseline (e.g., number of children was larger in treatment vs control groups), and confounders were not controlled for in the analysis. There was a higher rate of elective terminations of pregnancy in the omeprazole and lansoprazole groups compared with the control group. Two of these terminations in the omeprazole group, one in the lansoprazole group, none in the pantoprazole group, and five in the control group were because of prenatal diagnosis of anomalies. There were no differences in the rate of major anomalies between each of the three groups compared to the control group. The relative risk was 0.95 (95% CI 0.46 to 1.98) for omeprazole, 1.04 (0.25 to 4.21) for lansoprazole, and 0.55 (0.08 to 3.95) for pantoprazole. There was a reduction of 60 grams in median birth weight in omeprazole exposed versus control groups, but no differences in median gestational age at delivery, rate of preterm births, rate of miscarriages, ectopic pregnancies, or stillbirths in exposed versus control groups.

OVERALL SUMMARY

Results for the key questions are summarized in Table 13. In general, there is very little evidence that there are any important differences in the effectiveness or safety of the five PPIs in the general population, or in relevant subgroups. The majority of the studies had fair internal validity, but poor external validity with highly selected patient populations.
**Table 13. Summary of evidence**

<table>
<thead>
<tr>
<th>Key Question 1: GERD, short-term efficacy</th>
<th>Quality of Evidence</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erosive GERD: Symptoms</td>
<td>Good for omeprazole, lansoprazole, pantoprazole, and rabeprazole. Good for esomeprazole vs lansoprazole. Good for esomeprazole 40mg vs omeprazole 20mg Fair for esomeprazole 40 mg vs lansoprazole 30 mg, Fair for esomeprazole 40 mg vs pantoprazole 40 mg and lansoprazole 30 mg</td>
<td>There is good evidence that there is no comparative difference between omeprazole, lansoprazole, pantoprazole, and rabeprazole for relief of GERD symptoms. In 14 head-to-head trials, there was no difference between lansoprazole, omeprazole, pantoprazole, and rabeprazole on the outcome of complete symptom relief at 4 weeks. A significant difference on this outcome was found in the comparison of esomeprazole 40 mg to omeprazole 20 mg. The pooled risk difference in three trials was 10% (95% CI 6%-14%). Esomeprazole 40 mg was also compared to lansoprazole 30 mg and to pantoprazole 40 mg for complete symptom relief at 4 weeks with no significant differences. Time to relief of heartburn was similar for all PPIs in head-to-head trials, but the methods used to measure and report this outcome varied.</td>
</tr>
<tr>
<td>Erosive GERD: Esophagitis healing</td>
<td>Good for omeprazole, lansoprazole, pantoprazole, and rabeprazole. Good for esomeprazole vs lansoprazole. Good for esomeprazole 40mg vs omeprazole 20mg. Fair for esomeprazole vs pantoprazole</td>
<td>There is good evidence from 14 head-to-head trials and 3 good quality systematic reviews that there is no comparative difference between omeprazole, lansoprazole, pantoprazole, and rabeprazole for esophagitis healing. Esomeprazole 40mg had higher 4- and 8-week healing rates than omeprazole 20mg. Three trials compared esomeprazole 40 mg to lansoprazole 30 mg. The pooled healing rate for esomeprazole was 5% higher at 4 weeks (NNT = 20). One of three studies found a significantly higher healing rate for esomeprazole at 8 weeks (NNT=33). Two others found healing rates equivalent at 8 weeks, and the pooled estimate from 3 studies was not significant. <strong>Moderate to severe esophagitis</strong> Esomeprazole 40 mg was more effective at healing esophagitis at 4 and 8 weeks than omeprazole 20 mg (3 studies) and lansoprazole 30 mg (2 studies). Pantoprazole 40 mg had a higher healing rate at 8 weeks than esomeprazole 40 mg in patients with moderate (Grade C) esophagitis (1 study). Lansoprazole and omeprazole had equivalent healing rates in patients with moderate to severe esophagitis (3 studies).</td>
</tr>
<tr>
<td>Non-erosive or empirically-treated GERD: Symptoms</td>
<td>Fair for esomeprazole vs omeprazole, pantoprazole, and rabeprazole. Poor for other comparisons.</td>
<td>Three head-to-head trials in patients with endoscopy-negative GERD found no difference between esomeprazole 20 mg and omeprazole 20 mg, pantoprazole 20 mg, and rabeprazole 10 mg. These studies used different outcome measures. Limited indirect evidence from placebo- and active-controlled trials suggests similar efficacy for heartburn resolution and complete symptom relief for the five PPIs.</td>
</tr>
<tr>
<td>GERD: Evidence in Children</td>
<td>Poor</td>
<td>There are no direct comparisons of PPIs for reflux esophagitis in children. A fair quality placebo-controlled trial in infants did not find omeprazole to be superior to placebo.</td>
</tr>
<tr>
<td>Key Question 2: Ulcer, H. pylori eradication</td>
<td>Quality of Evidence</td>
<td>Conclusion</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>--------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Duodenal Ulcer</td>
<td>Good for (l) vs (o) Fair for (p), (r), (e) versus (o)</td>
<td>All newer PPIs have been compared to omeprazole. No significant differences were found. Data from trials comparing PPIs to H2-RAs support this finding. The evidence suggests no difference between the PPIs in healing rates or symptom relief.</td>
</tr>
<tr>
<td>Gastric Ulcer</td>
<td>Fair for (r) vs (o) Poor for others</td>
<td>Only two head-to-head studies were found, comparing rabeprazole to omeprazole. No significant differences in healing rate, minor improvements in symptom relief with rabeprazole.</td>
</tr>
<tr>
<td>NSAID-induced ulcer</td>
<td>Poor</td>
<td>No head-to-head studies. In trials of omeprazole and lansoprazole vs ranitidine, no difference in healing rates or symptom resolution were apparent.</td>
</tr>
<tr>
<td>Prevention of NSAID induced ulcer</td>
<td>Poor</td>
<td>No head-to-head studies. In other studies, significant heterogeneity in study design and outcome measure definitions make this evidence insufficient to identify any differences between PPIs.</td>
</tr>
<tr>
<td>Eradication of H. pylori</td>
<td>Fair</td>
<td>Two fair quality systematic reviews and 25 more recent trials indicate that eradication rates among the PPIs do not differ significantly. Differences between the antibiotic regimens, participants and study designs limit the strength of this evidence. In children, evidence is extremely limited, with only 2 trials of lansoprazole versus placebo. Neither trial found the addition of lansoprazole to result in higher eradication rates than antibiotic therapy alone.</td>
</tr>
</tbody>
</table>

Key Question 3: Adverse events

<table>
<thead>
<tr>
<th>Quality of Evidence</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-term studies</td>
<td>Poor</td>
</tr>
<tr>
<td><strong>Short-term studies</strong></td>
<td><strong>Quality of Evidence</strong></td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td><em>Fair</em></td>
<td>Evidence from short-term head-to-head comparison trials does not indicate a difference in the rate of overall adverse events, serious adverse events or the rate of dropouts due to adverse events. These studies are very short-term and include highly selected patient populations; evidence may not be generalizable to patients with co-morbidities and longer-term treatment.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Drug Interactions</strong></th>
<th><strong>Quality of Evidence</strong></th>
<th><strong>Conclusion</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Fair</em></td>
<td>No head-to-head trials assessing clinically important drug interactions of PPIs in patients with acid-related diseases were found. Based on primarily uncontrolled studies in healthy subjects, omeprazole has more drug interactions than the newer drugs. However, the numbers of drugs with clinically significant interactions are few and monitoring for needed dose adjustments is the only action required.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Key Question 4: Subpopulations</strong></th>
<th><strong>Quality of Evidence</strong></th>
<th><strong>Conclusion</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Poor</em></td>
<td>No head-to-head trials of two PPIs assessing the impact of race, age, gender, co-morbidities or other drugs were found. One head-to-head trial of lansoprazole and omeprazole in rapid and slow metabolizers (all Japanese patients) found no difference between these drugs in H. pylori eradication rates. There is insufficient evidence to indicate a difference between the PPIs based on subpopulation characteristics.</td>
<td></td>
</tr>
</tbody>
</table>
REFERENCES


152. Bianchi Porro G, Lazzaroni M, Imbesi V, Montrone F, Santagada T. Efficacy of pantoprazole in the prevention of peptic ulcers, induced by non-steroidal anti-


166. Kawabata H, Habu Y, Tomioka H, et al. Effect of different proton pump inhibitors, differences in CYP2C19 genotype and antibiotic resistance on the eradication rate of


**Figure 1** Esophagitis healing rates at 4 weeks in head-to-head trials of PPIs (risk difference, 95% CI)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Drug A n/N</th>
<th>Drug B n/N</th>
<th>RD (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 esomeprazole 20 mg vs omeprazole 20 mg</td>
<td>390/587</td>
<td>386/588</td>
<td>0.01 [-0.05, 0.06]</td>
</tr>
<tr>
<td>A-Z Study #174</td>
<td>436/656</td>
<td>399/650</td>
<td>0.05 [0.00, 0.10]</td>
</tr>
<tr>
<td>Kahrilas 2000</td>
<td>393/576</td>
<td>379/572</td>
<td>0.02 [-0.03, 0.07]</td>
</tr>
<tr>
<td>02 esomeprazole 40 mg vs omeprazole 20 mg</td>
<td>465/654</td>
<td>399/650</td>
<td>0.10 [0.05, 0.15]</td>
</tr>
<tr>
<td>A-Z Study #173</td>
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<td>805/1209</td>
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</tr>
<tr>
<td>Richter 2001</td>
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<td>1877/2617</td>
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</tr>
<tr>
<td>Castell 2002 (#267)</td>
<td>278/498</td>
<td>238/501</td>
<td>0.08 [0.02, 0.14]</td>
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<tr>
<td>03 esomeprazole 40 mg vs lansoprazole 30 mg</td>
<td>1231/1562</td>
<td>1157/1589</td>
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<td>Fennerty (#322)</td>
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<td>55/113</td>
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<td>343/431</td>
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</tr>
<tr>
<td>04 esomeprazole 40 mg vs pantoprazole 40 mg</td>
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<td>343/431</td>
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<td>73/112</td>
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</tr>
<tr>
<td>Hatlebakk 1993</td>
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<td>172/304</td>
<td>0.05 [-0.02, 0.13]</td>
</tr>
<tr>
<td>Mee 1996</td>
<td>91/104</td>
<td>83/103</td>
<td>0.07 [-0.03, 0.17]</td>
</tr>
<tr>
<td>05 lansoprazole 15 mg vs omeprazole 20 mg</td>
<td>128/166</td>
<td>130/161</td>
<td>-0.04 [-0.12, 0.05]</td>
</tr>
<tr>
<td>Castell 1996</td>
<td>261/337</td>
<td>248/332</td>
<td>0.03 [-0.04, 0.09]</td>
</tr>
<tr>
<td>06 lansoprazole 30 mg vs omeprazole 20 mg</td>
<td>81/120</td>
<td>83/121</td>
<td>-0.01 [-0.13, 0.11]</td>
</tr>
<tr>
<td>Castell 1996</td>
<td>184/226</td>
<td>189/235</td>
<td>0.01 [-0.06, 0.08]</td>
</tr>
<tr>
<td>Hatlebakk 1993</td>
<td>261/337</td>
<td>248/332</td>
<td>0.03 [-0.04, 0.09]</td>
</tr>
<tr>
<td>Mee 1996</td>
<td>88/103</td>
<td>94/103</td>
<td>-0.06 [-0.15, 0.03]</td>
</tr>
<tr>
<td>07 lansoprazole 30 mg vs omeprazole 40 mg</td>
<td>92/104</td>
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<td>Mulder 1996</td>
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<td>-0.02 [-0.09, 0.05]</td>
</tr>
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<td>08 pantoprazole 20 mg vs omeprazole 20 mg</td>
<td>212/283</td>
<td>213/277</td>
<td>-0.02 [-0.09, 0.05]</td>
</tr>
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<td>Bardhan 2001</td>
<td>261/337</td>
<td>248/332</td>
<td>0.03 [-0.04, 0.09]</td>
</tr>
<tr>
<td>Corinaldesi 1995</td>
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<td>189/235</td>
<td>0.01 [-0.06, 0.08]</td>
</tr>
<tr>
<td>09 pantoprazole 40 mg vs omeprazole 20 mg</td>
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<td>Korne 2003</td>
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<tr>
<td>10 pantoprazole 40 mg vs omeprazole 40 mg</td>
<td>92/104</td>
<td>94/103</td>
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</tr>
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<td>Delcier 2000</td>
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<td>11 pantoprazole 40 mg vs lansoprazole 30 mg</td>
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<td>213/277</td>
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<td>12 rabeprazole 10 mg vs omeprazole 20 mg</td>
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<td>94/103</td>
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<td>13 rabeprazole 20 mg vs omeprazole 20 mg</td>
<td>212/283</td>
<td>213/277</td>
<td>-0.02 [-0.09, 0.05]</td>
</tr>
</tbody>
</table>

Favors Drug B  Favors Drug A
Figure 2. Esophagitis healing rates at 8 weeks in head-to-head trials of PPIs (risk difference, 95% CI)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Drug A</th>
<th>Drug B</th>
<th>RD (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 esomeprazole 20 mg vs omeprazole 20 mg</td>
<td>508/587</td>
<td>484/588</td>
<td>0.04 [0.00, 0.08]</td>
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<tr>
<td>Kahrilas 2000</td>
<td>550/656</td>
<td>529/650</td>
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<td>02 Esomeprazole 40 mg vs omeprazole 20 mg</td>
<td>501/576</td>
<td>491/572</td>
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<td>Chen 2005</td>
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</tr>
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<td>96/111</td>
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<td>Mee 1996</td>
<td>226/300</td>
<td>216/304</td>
<td>0.04 [-0.03, 0.11]</td>
</tr>
<tr>
<td>06 Lansoprazole 30 mg vs omeprazole 20 mg</td>
<td>134/166</td>
<td>142/161</td>
<td>-0.07 [-0.15, 0.00]</td>
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<tr>
<td>07 Lansoprazole 30 mg vs omeprazole 40 mg</td>
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<td>08 Pantoprazole 20 mg vs omeprazole 20 mg</td>
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<td>231/277</td>
<td>-0.03 [-0.09, 0.04]</td>
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</table>
Figure 3. Rates of complete resolution of symptoms at 4 weeks in head-to-head trials of PPIs (risk difference, 95% CI)

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug A</th>
<th>Drug B</th>
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<th>Risk Difference (random)</th>
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<td></td>
</tr>
<tr>
<td>Kahrilas 2000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>03 esomeprazole 40 mg vs lansoprazole 30 mg</td>
<td>1575/2617</td>
<td>1575/2617</td>
<td>0.03 [0.00, 0.05]</td>
<td></td>
</tr>
<tr>
<td>Castell 2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>04 esomeprazole 40 mg vs pantoprazole 40 mg</td>
<td>507/483</td>
<td>307/483</td>
<td>0.08 [0.03, 0.14]</td>
<td></td>
</tr>
<tr>
<td>Finney 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>05 lansoprazole 30 mg vs omeprazole 20 mg</td>
<td>80/112</td>
<td>80/112</td>
<td>-0.01 [-0.13, 0.11]</td>
<td></td>
</tr>
<tr>
<td>Molider 2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>06 lansoprazole 30 mg vs omeprazole 40 mg</td>
<td>75/103</td>
<td>75/103</td>
<td>-0.06 [-0.15, 0.03]</td>
<td></td>
</tr>
<tr>
<td>Molider 1996</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>07 lansoprazole 30 mg vs pantoprazole 40 mg</td>
<td>129/154</td>
<td>129/154</td>
<td>-0.06 [-0.14, 0.03]</td>
<td></td>
</tr>
<tr>
<td>Dupas 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>08 pantoprazole 20 mg vs omeprazole 20 mg</td>
<td>110/131</td>
<td>110/131</td>
<td>-0.07 [-0.17, 0.02]</td>
<td></td>
</tr>
<tr>
<td>Bardhan 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>09 pantoprazole 40 mg vs omeprazole 20 mg</td>
<td>83/101</td>
<td>83/101</td>
<td>0.06 [-0.04, 0.16]</td>
<td></td>
</tr>
<tr>
<td>Corinaldesi 1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 pantoprazole 40 mg vs omeprazole 40 mg</td>
<td>127/151</td>
<td>127/151</td>
<td>0.00 [-0.09, 0.08]</td>
<td></td>
</tr>
<tr>
<td>Molider 2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 rabeprazole 20 mg vs omeprazole 20 mg</td>
<td>27/102</td>
<td>27/102</td>
<td>0.03 [-0.09, 0.16]</td>
<td></td>
</tr>
<tr>
<td>Dekkers 1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 4. Healing at 4 weeks in patients with moderate to severe esophagitis (risk difference, 95% CI)

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug A Number healed/Total</th>
<th>Drug B Number healed/Total</th>
<th>RD (random) 95% CI</th>
<th>Risk Difference (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 esomeprazole 20 mg vs omeprazole 20 mg</td>
<td>79/158</td>
<td>71/154</td>
<td>0.04 [-0.07, 0.15]</td>
<td></td>
</tr>
<tr>
<td>AstraZeneca Study #174 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kahrilas 2000</td>
<td>79/165</td>
<td>85/182</td>
<td>0.01 [-0.09, 0.12]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>323</td>
<td>336</td>
<td>0.02 [-0.05, 0.10]</td>
<td></td>
</tr>
<tr>
<td>02 esomeprazole 40 mg vs omeprazole 20 mg</td>
<td>115/189</td>
<td>81/169</td>
<td>0.13 [0.03, 0.23]</td>
<td></td>
</tr>
<tr>
<td>Lightdale 20065</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kahrilas 2000</td>
<td>98/166</td>
<td>85/182</td>
<td>0.12 [0.02, 0.23]</td>
<td></td>
</tr>
<tr>
<td>Richter 2001</td>
<td>216/317</td>
<td>153/320</td>
<td>0.20 [0.13, 0.28]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>672</td>
<td>671</td>
<td>0.16 [0.11, 0.22]</td>
<td></td>
</tr>
<tr>
<td>03 esomeprazole 40 mg vs lansoprazole 30 mg</td>
<td>401/640</td>
<td>351/646</td>
<td>0.08 [0.03, 0.14]</td>
<td></td>
</tr>
<tr>
<td>Castell 2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fennerty 2005</td>
<td>278/498</td>
<td>238/501</td>
<td>0.08 [0.02, 0.14]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1138</td>
<td>1147</td>
<td>0.08 [0.04, 0.12]</td>
<td></td>
</tr>
<tr>
<td>04 omeprazole 20 mg vs lansoprazole 30 mg</td>
<td>97/139</td>
<td>111/151</td>
<td>-0.04 [-0.14, 0.07]</td>
<td></td>
</tr>
<tr>
<td>Castell 1996</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mee 1996</td>
<td>24/42</td>
<td>18/40</td>
<td>0.12 [-0.09, 0.34]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>181</td>
<td>191</td>
<td>0.01 [-0.13, 0.16]</td>
<td></td>
</tr>
<tr>
<td>05 esomeprazole 40 mg vs pantoprazole 40 mg</td>
<td>259/374</td>
<td>219/395</td>
<td>0.14 [0.07, 0.21]</td>
<td></td>
</tr>
<tr>
<td>Labenz 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>374</td>
<td>395</td>
<td>0.14 [0.07, 0.21]</td>
<td></td>
</tr>
</tbody>
</table>
Figure 5. Healing at 8 weeks in patients with moderate to severe esophagitis (risk difference, 95% CI)

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug A Number healed/Total</th>
<th>Drug B Number healed/Total</th>
<th>Risk Difference 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 esomeprazole 20 mg vs omeprazole 20 mg</td>
<td>AstraZeneca Study #174</td>
<td>122/158</td>
<td>110/154</td>
</tr>
<tr>
<td></td>
<td>Kahrilas 2000</td>
<td>125/165</td>
<td>135/182</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>323</td>
<td>336</td>
</tr>
<tr>
<td>02 esomeprazole 40 mg vs omeprazole 20 mg</td>
<td>Lightdale 2006</td>
<td>167/189</td>
<td>131/169</td>
</tr>
<tr>
<td></td>
<td>Kahrilas 2000</td>
<td>137/166</td>
<td>155/182</td>
</tr>
<tr>
<td></td>
<td>Richter 2001</td>
<td>272/317</td>
<td>220/320</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>672</td>
<td>671</td>
</tr>
<tr>
<td>03 esomeprazole 40 mg vs lansoprazole 30 mg</td>
<td>Castell 2002</td>
<td>534/640</td>
<td>461/646</td>
</tr>
<tr>
<td></td>
<td>Fennerty 2005</td>
<td>386/498</td>
<td>367/501</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>1138</td>
<td>1147</td>
</tr>
<tr>
<td>04 omeprazole 20 mg vs lansoprazole 30 mg</td>
<td>Castell 1996</td>
<td>118/133</td>
<td>128/150</td>
</tr>
<tr>
<td></td>
<td>Mee 1996</td>
<td>27/38</td>
<td>26/37</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>171</td>
<td>187</td>
</tr>
</tbody>
</table>

Favors Drug B Favors Drug A
Figure 6. PPI vs. H2 Receptor antagonists for esophagitis healing at 8 weeks: results of 22 randomized controlled trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Estimated Healing Rate Mean</th>
<th>95% CrI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lansoprazole</td>
<td>78.8%</td>
<td>69.7%</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>79.3%</td>
<td>72.2%</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>71.2%</td>
<td>59.0%</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>85.6%</td>
<td>67.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Difference between PPIs</th>
<th>Mean Difference</th>
<th>95% CrI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lansoprazole vs Omeprazole</td>
<td>-0.5%</td>
<td>-11.6%</td>
</tr>
<tr>
<td>Lansoprazole vs Pantoprazole</td>
<td>7.5%</td>
<td>-5.9%</td>
</tr>
<tr>
<td>Lansoprazole vs Rabeprazole</td>
<td>-6.9%</td>
<td>-20.5%</td>
</tr>
<tr>
<td>Omeprazole vs Pantoprazole</td>
<td>8.1%</td>
<td>-4.3%</td>
</tr>
<tr>
<td>Omeprazole vs Rabeprazole</td>
<td>-6.4%</td>
<td>-18.9%</td>
</tr>
<tr>
<td>Pantoprazole vs Rabeprazole</td>
<td>-14.4%</td>
<td>-30.4%</td>
</tr>
</tbody>
</table>
Figure 7. Duodenal ulcer healing at 4 weeks: PPI vs PPI (% risk difference)

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk difference (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lansoprazole 30mg vs omeprazole 20mg once daily</td>
<td></td>
</tr>
<tr>
<td>Ekstrom 1995</td>
<td>0.96 (-3.80, 6.15)</td>
</tr>
<tr>
<td>Chang 1995</td>
<td>2.55 (-9.62, 15.5)</td>
</tr>
<tr>
<td>Chang 1995</td>
<td>6.14 (-7.0, 20)</td>
</tr>
<tr>
<td>Dobrilla 1999</td>
<td>-3.57 (-8.84, 3.14)</td>
</tr>
<tr>
<td>Capruso 1995</td>
<td>-0.34 (-11.41, 10.32)</td>
</tr>
<tr>
<td>Pooled risk difference = -0.2 (95% CI -3.0, 2.6)</td>
<td></td>
</tr>
<tr>
<td>Pantoprazole 40mg vs omeprazole 20mg once daily</td>
<td></td>
</tr>
<tr>
<td>Beker 1995</td>
<td>5.85 (-0.84, 12.95)</td>
</tr>
<tr>
<td>Rabeprazole 20mg vs omeprazole 20mg once daily</td>
<td></td>
</tr>
<tr>
<td>Dekkers 1999</td>
<td>4.84 (-0.96, 11.70)</td>
</tr>
<tr>
<td>Esomeprazole 40mg vs omeprazole 40mg once daily</td>
<td></td>
</tr>
<tr>
<td>Tullassy 2001</td>
<td>-0.97 (-6.4, 4.35)</td>
</tr>
</tbody>
</table>
Figure 8. PPI vs. H2 Receptor antagonists for duodenal ulcer healing at 4 weeks
Figure 8. PPI vs. H2 Receptor antagonists for duodenal ulcer healing at 4 weeks (continued)

Duodenal ulcer healing rate at 4 weeks

<table>
<thead>
<tr>
<th>Estimated healing rate</th>
<th>when H2 healing is...</th>
<th>Mean</th>
<th>95% CrI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lansoprazole</td>
<td>60%</td>
<td>73.3%</td>
<td>55.8%</td>
</tr>
<tr>
<td></td>
<td>73%</td>
<td>89.6%</td>
<td>85.0%</td>
</tr>
<tr>
<td></td>
<td>80%</td>
<td>93.9%</td>
<td>89.5%</td>
</tr>
<tr>
<td></td>
<td>90%</td>
<td>97.0%</td>
<td>92.6%</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>60%</td>
<td>82.6%</td>
<td>75.5%</td>
</tr>
<tr>
<td></td>
<td>73%</td>
<td>90.9%</td>
<td>88.7%</td>
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<tr>
<td></td>
<td>80%</td>
<td>93.7%</td>
<td>91.9%</td>
</tr>
<tr>
<td></td>
<td>90%</td>
<td>96.3%</td>
<td>94.5%</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>—</td>
<td>93.9%</td>
<td>90.9%</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>—</td>
<td>82.6%</td>
<td>70.9%</td>
</tr>
</tbody>
</table>

Difference between PPIs

<table>
<thead>
<tr>
<th>Difference between PPIs</th>
<th>when H2 healing is...</th>
<th>Mean difference</th>
<th>95% CrI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lansoprazole vs Omeprazole</td>
<td>60%</td>
<td>-9.3%</td>
<td>-28.1%</td>
</tr>
<tr>
<td></td>
<td>80%</td>
<td>0.2%</td>
<td>-4.6%</td>
</tr>
<tr>
<td></td>
<td>90%</td>
<td>0.8%</td>
<td>-4.0%</td>
</tr>
<tr>
<td>Lansoprazole vs Pantoprazole</td>
<td>80%</td>
<td>0.0%</td>
<td>-5.0%</td>
</tr>
<tr>
<td>Lansoprazole vs Rabeprazole</td>
<td>73%</td>
<td>7.0%</td>
<td>-2.5%</td>
</tr>
<tr>
<td>Omeprazole vs Pantoprazole</td>
<td>80%</td>
<td>-0.2%</td>
<td>-3.1%</td>
</tr>
<tr>
<td>Omeprazole vs Rabeprazole</td>
<td>73%</td>
<td>8.3%</td>
<td>-0.2%</td>
</tr>
<tr>
<td>Pantoprazole vs Rabeprazole</td>
<td>—</td>
<td>11.3%</td>
<td>2.4%</td>
</tr>
</tbody>
</table>
Figure 9. Gastric ulcer: PPI vs H2-Antagonist healing at 4 weeks (% risk difference)

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk difference (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooperative Study 1990 (o40) vs (r)</td>
<td>22.92% (-7.50%, 47.83%)</td>
</tr>
<tr>
<td>Walan 1989 (o40) vs (r)</td>
<td>21.02% (11.31%, 30.37%)</td>
</tr>
<tr>
<td>Walan 1989 (o20) vs (r)</td>
<td>9.97% (-0.19%, 19.92%)</td>
</tr>
<tr>
<td>Rossini 1989 (o20) vs (r)</td>
<td>22.22% (-22.28%, 59.36%)</td>
</tr>
<tr>
<td>Classen 1985 (o20) vs (r)</td>
<td>1.09% (-10.66%, 12.83%)</td>
</tr>
<tr>
<td>Bardhan 1994 (l30) vs (r)</td>
<td>17.82% (2.82%, 32.26%)</td>
</tr>
<tr>
<td>Michel 1994 (l30) vs (r)</td>
<td>12.66% (-2.53%, 27.31%)</td>
</tr>
<tr>
<td>Capurso1 995 (l30) vs (r)</td>
<td>2.43% (-12.18%, 16.36%)</td>
</tr>
<tr>
<td>Bardhan 1994 (l60) vs (r)</td>
<td>23.22% (8.78%, 37.08%)</td>
</tr>
<tr>
<td>Tsuji 1995 (l30) vs (f)</td>
<td>62.50% (12.85%, 87.18%)</td>
</tr>
<tr>
<td>Okai 1995 (l30) vs (f)</td>
<td>40.00% (-4.08%, 71.22%)</td>
</tr>
<tr>
<td>Hotz 1995 (p40) vs (r)</td>
<td>24.67% (12.15%, 37.01%)</td>
</tr>
<tr>
<td>Bate 1989 (o20) vs (c800)</td>
<td>15.08% (1.45%, 28.38%)</td>
</tr>
<tr>
<td>Aoyama 1995 (l30) vs (c800)</td>
<td>24.06% (-0.38%, 47.17%)</td>
</tr>
<tr>
<td>Lauritsen 1988 (o30) vs (c1000)</td>
<td>8.56% (-4.24%, 21.27%)</td>
</tr>
<tr>
<td>Danish Omeprazole Study Group 1989 (o30) vs (c1000mg)</td>
<td>19.07% (3.49%, 33.82%)</td>
</tr>
</tbody>
</table>
Appendix A. Search Strategy

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2005>

Search Strategy:

1. (gastroesophageal reflux or gerd).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1077)
2. (gastroesophageal reflux or gord).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (87)
3. 1 or 2 (1094)
4. (peptic ulcer$ or stomach ulcer$ or gastric ulcer$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (3038)
5. 3 or 4 (4097)
6. (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (2632)
7. (proton pump$ adj3 (antagon$ or inhibit$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (616)
8. 6 or 7 (2729)
9. 5 and 8 (917)
10. from 9 keep 1-917 (917)

Database: Ovid MEDLINE(R) <1996 to November Week 3 2005>

Search Strategy:

1. Gastroesophageal reflux/ or "gerd".mp. (7177)
2. exp peptic ulcer/ or "peptic ulcer".mp. (11820)
3. 1 or 2 (18234)
4. Proton pump/ai (2118)
5. proton pump inhibitor$.mp. (2872)
6. (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. (4884)
7. 4 or 5 or 6 (6850)
8. 3 and 7 (3592)
9. limit 8 to (humans and english language) (2806)
10. limit 9 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial) (947)
11. exp clinical trials/ or clinical trial$.mp. (115736)
12. exp epidemiologic research design/ (288078)
13. observational stud$.mp. (9134)
14. 11 or 12 or 13 (394813)
15. 9 and 14 (784)
16. 10 or 15 (1303)
17. limit 16 to yr="2004 - 2006" (249)
18. from 17 keep 1-249 (249)
Database: Ovid MEDLINE(R) <1996 to November Week 3 2005>
Search Strategy:

1   Gastroesophageal reflux/ or "gerd".mp. (7177)
2   exp peptic ulcer/ or "peptic ulcer".mp. (11820)
3   1 or 2 (18234)
4   Proton pump/ai (2118)
5   proton pump inhibitor$.mp. (2872)
6   (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. (4884)
7   4 or 5 or 6 (6850)
8   3 and 7 (3592)
9   limit 8 to (humans and english language) (2806)
10  limit 9 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial) (947)
11  exp clinical trials/ or clinical trial$.mp. (115736)
12  exp epidemiologic research design/ (288078)
13  observational stud$.mp. (9134)
14  11 or 12 or 13 (394813)
15  9 and 14 (784)
16  10 or 15 (1303)
17  limit 16 to yr="2005 - 2006" (107)
18  from 17 keep 1-107 (107)

Database: Ovid MEDLINE(R) <1996 to November Week 3 2005>
Search Strategy:

1   Gastroesophageal reflux/ or "gerd".mp. (7177)
2   exp peptic ulcer/ or "peptic ulcer".mp. (11820)
3   1 or 2 (18234)
4   Proton pump/ai (2118)
5   proton pump inhibitor$.mp. (2872)
6   (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. (4884)
7   4 or 5 or 6 (6850)
8   3 and 7 (3592)
9   limit 8 to (humans and english language) (2806)
10  limit 9 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial) (947)
11  exp clinical trials/ or clinical trial$.mp. (115736)
12  exp epidemiologic research design/ (288078)
13  observational stud$.mp. (9134)
14  11 or 12 or 13 (394813)
15  9 and 14 (784)
16  10 or 15 (1303)
17  limit 16 to yr="2003 - 2006" (107)
18  from 17 keep 1-409 (409)
Appendix B. Quality assessment methods for drug class reviews for DERP

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well-documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on Undertaking Systematic Reviews of Research on Effectiveness: CRD’s Guidance for Carrying Out or Commissioning Reviews (2nd edition, 2001) and “The Database of Abstracts of Reviews of Effects (DARE)” in Effectiveness Matters, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of “good”, “fair” or “poor”. Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are rated fair quality. As the “fair quality” category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are likely to be valid, while others are only probably valid. A “poor quality” trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
   Adequate approaches to sequence generation:
   - Computer-generated random numbers
   - Random numbers tables
   Inferior approaches to sequence generation:
   - Use of alternation, case record numbers, birth dates or week days
   - Not reported

2. Was the treatment allocation concealed?
   Adequate approaches to concealment of randomization:
   - Centralized or pharmacy-controlled randomization
   - Serially-numbered identical containers
   - On-site computer based system with a randomization sequence that is not readable until allocation
Other approaches sequence to clinicians and patients

Inferior approaches to concealment of randomization:
- Use of alternation, case record numbers, birth dates or week days
- Open random numbers lists
- Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)
For Studies Reporting Complications/Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?

2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there non-biased and accurate ascertainment of events (independent ascertainer; validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

Systematic Reviews:

1. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making,
i.e., how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

3. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results and adverse events.

5. Are the primary studies summarized appropriately?

The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (e.g., according to sample size, or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.
Appendix C. Placebo-controlled randomized trials of PPIs (not included)


Appendix D. Abstract-only studies (not included)

1. Andersson, T, Bredberg, E, Sunzel, M, et al. Pharmacokinetics (PK) and effect on pentagastrin stimulated peak acid output (PAO) of omeprazole (O) and its 2 optical isomers, S-omeprazole/esomeprazole (E) and R-omeprazole (R-O). *Gastroenterology*. 2000;118:A1210.


115. Rohss, K., et al., Esomeprazole 40mg o.m. provides faster and more effective acid control than rabeprazole 20 mg o.m. in patients with symptoms of GERD. *Gut* 2001; 49(Suppl III): p. Abs 1956.


128. Thjodleifson, B, Dekkers, CPM, Beker, JA. Rabeprazole sodium once daily is similar to omeprazole 20 mg once daily in the treatment of erosive or ulcerative GERD. *Gastroenterology*. 1997;112:A312.


148. Wilder-Smith, C, Rohss, K, Claar-Nilsson, C. Esomeprazole 40 mg provides more effective acid control than rabeprazole 20 mg. *In: 8th United European Gastroenterology Week; 2000; Brussels, Belgium; 2000.*


Appendix E. Results of search and selection of included articles

3073 citations

580 retrieved for full-text evaluation

2493 excluded at title/abstract level

Update #4: 52 excluded at full-text level
Reasons for exclusion include not English language, wrong outcome, drug not included, population not included, wrong publication type, wrong study design, insufficient duration

Update #4: 39 publications included
- 11 head-to-head trials
- 8 active controlled trials or combination therapy
- 7 placebo-controlled trials
- 1 other
- 8 observational studies
- 4 systematic reviews
Appendix F. Esophagitis grading scales used in randomized controlled trials

**Savary-Miller**

Grade I: one or more supravestibular, non-confluent reddish spots, with or without exudate.

Grade II: erosive and exudative lesions in the distal esophagus which may be confluent, but not

Grade III: circumferential erosions in the distal esophagus, covered by hemorrhagic and pseudomembranous exudates.

Grade IV: presence of chronic complications such as deep ulcers, stenosis, or scarring with Barrett's metaplasia.

**Modified Hetzel-Dent**

Grade 0: Normal mucosa, no abnormalities found

Grade 1: No macroscopic erosions, but presence of erythema, hyperemia, and/or friability of the esophageal mucosa.

Grade 2: Superficial ulceration or erosions involving less than 10% of the mucosal surface area of the last 5 cm of esophageal squamous mucosa.

Grade 3: Superficial ulceration or erosions involving greater than or equal to 10% but less than 50% of the mucosal surface area of the last 5 cm of esophageal squamous mucosa.

Grade 4: Deep ulceration anywhere in the esophagus or confluent erosion of more than 50% of the mucosal surface area of the last 5 cm of esophageal squamous mucosa.

Grade 5: Stricture, defined as a narrowing of the esophagus that does not allow easy passage of the endoscope without dilation.

**Los Angeles Classification**

Not present: No breaks (erosions) in the esophageal mucosa (edema, erythema, or friability may be present)

Grade A: One or more mucosal breaks confined to the mucosal folds, each not more than 5 mm in maximum length.

Grade B: One or more mucosal breaks more than 5 mm in maximum length, but not continuous between the tops of two mucosal folds.

Grade C: Mucosal breaks that are continuous between the tops of two or more mucosal folds, but which involve less than 75% of the esophageal circumference.
Grade D: Mucosal breaks which involve at least 75% of the esophageal circumference.

The presence or absence of strictures, ulcers, and/or Barrett’s esophagus much be noted separately, e.g., “Grade B with stricture”.

**Criteria used in Hatlebakk, 1993:**

Grade 1: red streaks or spots along the ridge of the folds in the distal esophagus, covered or not by fibrinous exudate

Grade 2: Broader lesions, each involving the entire width of a fold or coalescing into fields or erythema, covered or not with fibrinous exudates

Grade 3: Stricture or endoscopically visible ulcer in distal esophagus.

**Criteria used in Castell, 1996, Howden, 2002, Richter 2001b:**

Grade 0: normal-appearing mucosa

Grade 1: mucosal edema, hyperemia, and/or friability

Grade 2: one or more erosions/ulcerations involving <10% of the distal 5 cm of the esophagus

Grade 3: erosions/ulcerations involving 10-50% of the distal 5 cm of the esophagus or an ulcer 3-5 mm in diameter. In cases of Barrett’s esophagus, the area 5 cm proximal to the squamocolumnar junction was evaluated

Grade 4: multiple erosions involving >50% of the distal 5 cm of the esophagus or a single ulcer > 5mm in diameter.
Appendix G. Studies Currently Under Review / In-Process

Published After Search Dates for Update 4
These citations will be included in any future update of this review.

GERD Maintenance


GERD
