Drug Class Review
on
Proton Pump Inhibitors

Final Report Update 4

July 2006

Original Report Date: November 2002
Update 1 Report Date: April 2003
Update 2 Report Date: April 2004
Update 3 Report Date: May 2005

A literature scan of this topic is done periodically

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.

Marian S. McDonagh, PharmD
Susan Carson, MPH

Oregon Evidence-based Practice Center
Oregon Health & Science University
Mark Helfand, MD, MPH, Director

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.

TABLE OF CONTENTS

TABLES

FIGURES

APPENDICES

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").[1] 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-RAs 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[5, 6] and one trial[7] 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).[2, 3] 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.[8]

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

	Omeprazole	Lansoprazole	Rabeprazole	Pantoprazole	Esomeprazole
Omeprazole	*********				
Lansoprazole	**6**	**********			
Rabeprazole	**4**	**0**	**********		
Pantoprazole	**3**	**1**	**0**	**********	
Esomeprazole	**6**	**4**	**0**	**4**	**********

Three studies[5, 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,[10, 11, 13, 16] and 14 reported symptoms as a secondary outcome.[5, 6, 12, 14, 15, 17, 21-26, 30, 32] 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.[5, 6, 10, 12-14, 16, 17, 20, 23, 24, 26, 27, 29] 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

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

Figure 3 shows risk differences in rates of complete symptom resolution at 4 weeks in these trials.[5, 6, 10, 12-14, 16, 17, 20, 23, 24, 26, 27, 29] 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 20mg, 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

Study	Patients with complete symptom relief at 4 weeks	Risk difference (95% CI)
Esomeprazole 40 mg vs omeprazole 20 mg		
Kahrilas 2000[6]	65% vs 57%	8% (2%, 13%)
Kao 2003[16]	74% vs 51%	23% (3%, 42%)
Richter 2001[12]	68% vs 58%	10% (6%, 14%)
Pooled estimate		**10% (6%, 14%) NNT=10**
Esomeprazole 40 mg vs lansoprazole 30 mg		
Castell 2002[5]	63% vs 60%	3% (0%, 5%)
Fennerty 2005 (ITT*)	69% vs 61%	8% (2%-14%)
Pooled estimate		**5% (0%, 9%)**
Esomeprazole 40 mg vs pantoprazole 40 mg		
Gillessen 2004[20]	35% vs 37%	-2% (-16%, 11%)
Scholten 2003[10]	70% vs 71%	-1% (-13%, 11%)
Pooled estimate		**-2% (-11%, 7%)**

*ITT calculated by the reviewers.

A single study reported complete resolution of symptoms after 1 week of therapy,[32] 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.[10]

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.

<u>*Esomeprazole vs omeprazole*</u>. 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).[6, 12, 16] 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,[12] non-significant in two others[16, 31], and not assessed in the fourth.[6] The time to *sustained* resolution of

heartburn was statistically superior with esomeprazole 40mg compared to omeprazole 20mg at 14 days in 2 studies.[12, 16] The differences at other time points were mixed or not statistically assessed.

In a comparison of esomeprazole 20 mg to omeprazole 20 mg,[6] 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

Study, year	Time to first resolution of heartburn	Time to sustained resolution of heartburn (7 consecutive days)
Esomeprazole 20 mg vs omeprazole 20 mg		
Kahrilas 2000	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)	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
Esomeprazole 40 mg vs omeprazole 20 mg		
Kahrilas 2000	**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)	**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
Kao 2003	1 day: 28.2% vs 26.2% (NS) before 7 days: 56.4% vs 55.6% (NS) Median: 4 days vs 4 days (NS)	7 days: 15.2% vs 15.6% (NS) 14 days: 50% vs 20% (p<0.05) 21 days: 71.7% vs 40% (p<0.01) 28 days: 73.9% vs 51.1% (p<0.05)
Richter 2001	**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)	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)
Chen 2005	1 day: 77.3% vs 65% (NS)	Not reported

<u>*Esomeprazole vs lansoprazole*</u>. 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

Study, year	Time to first resolution of heartburn	Time to sustained resolution of heartburn (7 consecutive days)
Esomeprazole 40 vs lansoprazole 30 mg		
Castell 2002	Median: 2 days vs. 2 days (NS)	**Median: 7 days vs 8 days (p≤0.01)**
Fennerty 2005	NR	7 days: 54.2% vs 51.7% (NS)
Howden 2002*	1 day: 27.3% vs. 34.5% (p=0.21)	Heartburn-free first 3 days: 37.4% vs 43.8% (NS) Heartburn-free first 7 days: 45.9% vs 51.8% (NS)

*Days or nights without heartburn

<u>*Esomeprazole vs. pantoprazole.*</u> 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).[30] 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.[10] 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.[14, 15, 25] 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).[14] In another study, daytime and nighttime heartburn were reported separately.[25] 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.[15] 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.[32]

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).[31]

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*

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

*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.[12, 14, 15, 17, 18, 20-23, 25-27, 30-32] 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)[19, 28, 35] did not provide number healed/total, and four trials[10, 11, 13, 16] 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.[32]

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[12, 15, 21, 22, 25-27, 31] comparing omeprazole 20 mg to another PPI.

Table 7. Risk differences of esophagitis healing rates in trials of omeprazole 20 mg vs another PPI*

Drug, dose	Difference in healing rate at 4 weeks vs omeprazole 20 mg (95% CI)	Difference in healing at 8 weeks vs omeprazole 20 mg (95% CI)
Esomeprazole 20 mg	3% (-1%, 7%)	3% (0%, 6%)
Esomeprazole 40 mg	8% (pooled) (6%, 12%)[6, 12, 33] **NNT=13**	6% (pooled) (1%, 10%)[6, 12, 31, 33] **NNT=17**
Lansoprazole 30 mg	2% (pooled) (-3%, 6%)[15, 21, 25]	1% (pooled) (-2%-5%)[15, 21, 25]
Pantoprazole 20 mg	-4% (-12%, 5%)[27]	-7% (-15%, 0%)[27]
Pantoprazole 40 mg	-1% (-13%, 11%)[26]	3% (-3%, 10%)[26]
Rabeprazole 10 mg	-6% (-15%, 3%)[22]	-3% (-10%, 4%)[22]
Rabeprazole 20 mg	-2% (-8%, 3%)[22, 32]	-3% (-8%, 2%)[22, 32]

*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 40mg to omeprazole 20mg, found a higher healing rate in the esomeprazole group.[6, 12] A third study[33] 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.[31] 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 20mg to omeprazole 20 mg[6, 7] 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,[5] 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

Study	Difference in Healing at 4 weeks (95% CI)	Difference in Healing at 8 weeks (95% CI)
Castell 2002[5]	4% (2%, 6%)	3% (1%, 5%)
Fennerty 2005[29]	8% (2%, 14%)	4% (-1%, 10%)
Howden 2002[18]	Not reported	-2% (-9%, 5%)
Pooled estimate **Random effects** **Fixed effects**	**5%** **(1%, 9%)** **5%** **(2%, 7%)** **NNT=20**	**3%** **(0%, 5%)** **3%** **(1%, 5%)** **NNT=33**

A second, smaller, fair-quality trial of lansoprazole 30mg versus esomeprazole 40 mg[18] 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.[5-7, 12-15, 18-23, 25, 27, 29, 30, 33] 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.[18]

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[5-7, 12, 15, 25, 29, 30, 33] reporting the number healed/total by baseline severity (Table 9).

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

Drug, dose	Healing rate at 4 weeks (95% CI)	Healing rate at 8 weeks (95% CI)
Esomeprazole 20 mg	49% (37%-61%)[6, 7]	77% (70%-85%)[6, 7]
Esomeprazole 40 mg	64% (57%-71%)[5, 6, 12, 29, 30, 33]	85% (81%-89%)[5, 6, 12, 29, 33]
Lansoprazole 30 mg	56% (48%-64%)[5, 15, 25, 29]	77% (71%-82%)[5, 15, 25, 29]
Omeprazole 20 mg	52% (45%-59%)[6, 7, 12, 15, 25, 33]	74% (68%-80%)[7, 15, 25, 33]; 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[6, 12, 33] 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[6, 7] 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.[5, 29] 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.[18] 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%).[20] 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.[14, 15, 25] Two of these compared lansoprazole 30 mg to omeprazole 20 mg.[14, 15, 25] 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.[14] 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,[36] rabeprazole,[37] or pantoprazole[38]). 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.[39]

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.[36] 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.[38] 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.[37] 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.[40] 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.[41] 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

18% to 31%). 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.[40] Similar proportions of patients experienced heartburn resolution or complete symptom relief across studies, with some exceptions in individual studies.

Table 11. Outcomes at 4 weeks, endoscopy negative/ empirically treated patients

		Endoscopy Negative Reflux Disease		Empirical Treatment
Study, year	Drug, dose	ENRD Patients with heartburn resolution (95% CI)	Patients with complete symptom resolution (95% CI)	Patients with heartburn resolution (95% CI)
Armstrong, 2004 (Study A)	Esomeprazole 20 mg	60.5% (51.8% to 65.5%)		
Armstrong, 2004 (Study C)	Esomeprazole 20 mg	61.9% (56.5% to 67.1%)		
Armstrong, 2004 (Study A)	Esomeprazole 40 mg	56.7% (51.8% to 61.5%)		
Armstrong, 2004 (Study B)	Esomeprazole 40 mg	70.3% (65.2% to 75.1%)		
Johnson, 2003	Esomeprazole 40 mg			83.7% (74.7% to 90.0%)
Bardhan, 1999	Omeprazole 10 mg or 20 mg			73.8% (67.7% to 79.1%)
Carlsson, 1998	Omeprazole 10 mg or 20 mg	73.3% (63.0% to 81.5%)	60.0% (47.4% to 67.8%)	
Lind, 1997	Omeprazole 10 mg or 20 mg	76.2% (67.1% to 83.4%)	68.6% (59.1% to 76.7%)	
Richter 2000a	Omeprazole 10 mg or 20 mg	95.1% (89.6% to 97.8%)		
Venables, 1997	Omeprazole 10 mg or 20 mg	55.7% (48.9% to 62.2%)		
Bate, 1997	Omeprazole 20 mg			68.8% (59.5% to 76.8%)
Armstrong, 2004 (Study A)	Omeprazole 20 mg	58.1% (53.4% to 62.6%)		
Armstrong, 2004 (Study B)	Omeprazole 20 mg	67.9% (62.8% to 72.6%)		
Armstrong, 2004 (Study C)	Omeprazole 20 mg	59.6% (54.2% to 64.7%)		
Venables, 1997	Omeprazole 20 mg			59.8% (54.4% to 65.0%)

		Endoscopy Negative Reflux Disease		Empirical Treatment
Study, year	Drug, dose	ENRD Patients with heartburn resolution (95% CI)	Patients with complete symptom resolution (95% CI)	Patients with heartburn resolution (95% CI)
Bate, 1996	Omeprazole 20 mg	83.8% (75.7% to 89.5%)		
Bate, 1997	Omeprazole 20 mg	66.0% (52.0% to 77.7%)		
Hatlebakk, 1999	Omeprazole 20 mg			69.8% (62.2% to 76.4%)
Schenk, 1997	Omeprazole 40 mg		85.7% (67.6% to 94.5%)	
Watson, 1997	Omeprazole 40 mg	94.7% (70.6% to 99.3%)		
Richter, 2000b	Lansoprazole 15 mg or 30 mg		78.1% (72.8% to 82.6%)	
Talley, 2002	Pantoprazole 20 mg			81.0% (74.1% to 86.4%)
Armstrong, 2001	Pantoprazole 40 mg	57.1% (42.0% to 71.1%)		66.1% (56.7% to 74.3%)
Miner, 2002	Rabeprazole 10 mg or 20 mg	97.7% (91.4% to 99.4%)	67.6% (55.7% to 77.7%)	

We identified one additional placebo-controlled[42] and one active-controlled (vs. ranitidine) trial[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%).[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.[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).[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,[45] or rabeprazole versus omeprazole after 13 weeks, 26 weeks, one year, and five years.[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) [46] or pantoprazole 20 mg a day (lower than the FDA approved dose for maintenance of healed erosive esophagitis).[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[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[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.[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).[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.[51] We also included two placebo-controlled trials of on-demand rabeprazole[52] and esomeprazole,[53] and a placebo-controlled trial of continuous omeprazole.[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.[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).[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[52] or esomeprazole 20 mg[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).[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.[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.[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.[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.[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.[60] Both of these were funded by the manufacturer of esomeprazole.

A third systematic review,[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[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,[57] four PPIs were better than ranitidine at healing esophagitis, but there were no differences among them. No study of esomeprazole was included.[57]

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[61-71] lansoprazole (five studies),[72-76] pantoprazole (five studies),[77-81] and rabeprazole (1 study).[82]

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,[57] 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.[83] 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.[84] 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

pantoprazole 10 mg, and 21% of those treated with ranitidine remained healed. This study is planned for 3 years, but only the first 12 months have been reported so far.

A 2001 systematic review identified 15 studies of relapse prevention.[57] 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. [85, 86] 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. [85]

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.[87] 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.[88]

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).[92] 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[97, 98] or ranitidine.[99] 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.[100-121] 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[122] 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[121, 123-125] These studies were consistent with the studies reported above and are not added to figure 4. One of these studies reported symptom relief only.[121]

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.[126-128] A fair quality study of 227 patients compared rabeprazole 20mg to omeprazole 20mg (Evidence Table 9).[126] 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.[128] 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 and 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).[93, 100, 129-141] There were two studies of maintenance therapy and one followup study of relapse rates in patients healed in one of the above studies.[98, 142, 143] One of the maintenance studies included patients with either gastric or duodenal ulcer, all of which were resistant to H2-RA therapy.[143] One study evaluated esomeprazole versus ranitidine in healing ulcers in patient who continued to take a NSAID.[129] 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.[132] 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[144] reported maintenance therapy of lansoprazole 15 or 30mg 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.[143] 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[142] of patients who had healed after 6 weeks of treatment with omeprazole or cimetidine[131] 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.[129, 145-147] 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.[148]

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.[129, 145, 147] 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.[146]

One study[146, 149] 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.[150] 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[151-155] are presented in Evidence Table 11, along with two of the treatment studies that included a prevention phase.[146, 147] 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[151] 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[152] randomized patients to pantoprazole 40mg or placebo for 3 months. The third study[153]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,[154] 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,[151] 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.[156]

In the study of pantoprazole versus placebo,[152] 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,[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."[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.[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.[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.[158] The search for literature covered 1986 to1998 (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.[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).[95, 96, 160-179] They made the following comparisons:

- Rabeprazole 20mg versus omeprazole 40mg, plus amoxicillin (one study)[171]
- Lansoprazole 60mg versus omeprazole 40mg, plus amoxicillin and metronidazole (one study)[164]
- Omeprazole 40mg versus pantoprazole 40mg, plus clarithromycin and metronidazole (one study)[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 10mg (all twice daily) each combined with amoxicillin and clarithromycin (one study),[165]
- Rabeprazole 10 mg or 20mg or lansoprazole 30mg 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 30mg 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 40mg versus omeprazole 40mg, plus clarithromycin and metronidazole (one study)[184]
- Esomeprazole 40 mg daily, esomeprazole 40 mg twice daily, or omeprazole 20 mg twice daily plus amoxacillin 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 20mg versus omeprazole 40mg or omeprazole 40mg versus pantoprazole 40mg) and one used a dose of omeprazole that is not standard in the US (60mg).[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[76, 160, 163, 168, 170, 174, 181, 184] 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 30mg with only amoxicillin)[175] to a high of 100% (pantoprazole 40mg).[160] One study found a significantly lower eradication rate for pantoprazole (40mg) than for higher relative doses of omeprazole (40mg) or high-dose pantoprazole (80mg). 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.[172] 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.[175]

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.[158, 185-187] All found similar eradication rates for the PPIs compared to H2-RAs.

Children

Two trials evaluated lanzoprazole in eradication of H. pylori in children.[188, 189] 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,[188] while in the other dosing was based on weight (<20 Kg: 15 mg and >/= 20 Kg: 30 mg per day)[189] 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%[189] and 71%[188]) and lansoprazole (67%[189] and 68%[188]).

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,[45, 47, 190] 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,[45] 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,[44] and 26 of 243 (11%) withdrew at 5 years;[47] the numbers in each group did not differ significantly. In the third long-term maintenance study,[190] 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.[98]

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.[191-206] 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., delaviridine 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

	Omeprazole	Esomeprazole	Rabeprazole	Lansoprazole	Pantoprazole
Drugs with pH dependent absorption (e.g. ketoconazole, iron, itraconazole, delaviridine, indinivir, enteric coated salicylates)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)
Carbamazepine	Monitor (1)				No significant interaction (3)
Clarithromycin	No specific action required (1)	No significant interaction (2)			No significant interaction (3)
Clorazepate	No specific action required (1)				
Cyclosporine	No specific action required (1)				
Diazepam	Monitor (1)	No significant interaction (2)	No significant interaction (4)	No significant interaction (4)	No significant interaction (3)
Disulfiram	No specific action required (1)				
Methotrexate	Monitor (1)				
Nifedipine	No specific action required (1)				No significant interaction (3)
Phenytoin	Monitor (1)	No significant interaction (2)	No significant interaction (4)		No significant interaction (4)
Tacrolimus	No specific action required (1)				
Tolbutamide	No specific action required (1)				
Trovafloxacin	Monitor (1)				
Warfarin	No specific action required (1)	No significant interaction (2)	No significant interaction (4)	No significant interaction (4)	No significant interaction (3)
Quinidine		No significant interaction (2)			
Amoxicillin		No significant interaction (2)			No significant interaction (3)
Oral contraceptives		No significant interaction (2)		No significant interaction (4)	No significant interaction (3)
Midazolam					No significant interaction (3)
Metoprolol					No significant interaction (3)
Diclofenac					No significant interaction (3)
Theophylline			No significant interaction (4)	Decreased Clearance (4)	No significant interaction (3)

	Omeprazole	Esomeprazole	Rabeprazole	Lansoprazole	Pantoprazole
Glyburide					No significant interaction (3)
Antipyrene					No significant interaction (3)
Metronidazole					No significant interaction (3)
Prednisone				No significant interaction (4)	
Atazanavir		Monitor (5)			

(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, one[46] 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.[6, 126] There were no differences between PPIs (omeprazole, rabeprazole, esomeprazole) based on these characteristics. In addition, the effect of age on eradication rates was evaluated.[175] 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,[168, 216] and that rapid metabolizers may have a higher failure rate in eradicating H. pylori[163, 171, 217] and esophagitis healing.[218] Results of subgroup analysis found no effect by race in one study of esomeprazole and lansoprazole in healing erosive esophagitis[5]. 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.[128] 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.[219]

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.[220] 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.[221] 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

Key Question 1: GERD, short-term efficacy	Quality of Evidence	Conclusion
Erosive GERD: Symptoms	Good for omeprazole, lansoprazole, pantoprazole, and rabeprazole. Good for esomeprazole vs lansoprazole. Good for esomeprazole 40mg vs omeprazole 20mg Fair for omeprazole 40 mg)vs l lansoprazole 30 mg, Fair for esomeprazole 40 mg vs pantoprazole 40 mg and lansoprazole 30 mg	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.
Erosive GERD: Esophagitis healing	Good for omeprazole, lansoprazole, pantoprazole, and rabeprazole. Good for esomeprazole vs lansoprazole. Good for esomeprazole 40mg vs omeprazole 20mg. Fair for esomeprazole vs pantoprazole	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. **Moderate to severe esophagitis** 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).
Non-erosive or empirically-treated GERD: Symptoms	Fair for esomeprazole vs omeprazole, pantoprazole, and rabeprazole. Poor for other comparisons.	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.
GERD: Evidence in Children	Poor	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.

Erosive GERD: Prevention of relapse	Good for omeprazole, lansoprazole, and rabeprazole Fair for esomeprazole and pantoprazole	One head-to-head trial of esomeprazole 20 mg or lansoprazole 15 mg found higher remission rates for esomeprazole (83% vs 74%) over 6 months, using life table analysis. Esomeprazole group had higher remission rates across all grades of disease severity, whereas the efficacy of lansoprazole decreased with increasing severity of disease. 2 head-to-head trials found no differences in endoscopic or symptomatic relapse rates for lansoprazole versus omeprazole after 48 weeks and rabeprazole versus omeprazole after 13, 26, 1 year and 5 years. A systematic review found, in studies comparing PPIs to placebo or ranitidine, similar remission rates for lansoprazole, rabeprazole, and omeprazole over 12 months of treatment. Pantoprazole at 10, 20, and 40 mg had lower 12-month relapse rates than ranitidine in one trial.
Non-erosive or empirically-treated GERD: Prevention of relapse	Fair to Poor	In a 6-month head-to-head trial of on-demand esomeprazole vs continuous lansoprazole 15 mg, more patients discontinued lansoprazole.. 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.
Key Question 2: Ulcer, H. pylori eradication	**Quality of Evidence**	**Conclusion**
Duodenal Ulcer	Good for (l) vs (o) Fair for (p), (r), (e) versus (o)	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.
Gastric Ulcer	Fair for (r) vs (o) Poor for others	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.
NSAID-induced ulcer	Poor	No head-to-head studies. In trials of omeprazole and lansoprazole vs ranitidine, no difference in healing rates or symptom resolution were apparent.
Prevention of NSAID induced ulcer	Poor	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.
Eradication of H. pylori	Fair	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.
Key Question 3: Adverse events	**Quality of Evidence**	**Conclusion**
Long-term studies	Poor	Three comparative trials. Evidence from single-drug followup studies indicates no differences between the PPIs.

Short-term studies	Fair	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.
Drug Interactions	Fair	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.
Key Question 4: Subpopulations	**Quality of Evidence**	**Conclusion**
	Poor	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.

REFERENCES

1. Anonymous. Heartburn (http://www.gastro.org/wmspage.cfm?parm1=848#Tips): American Gastrological Association.

2. Anonymous. *Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews CRD Report Number 4 (2nd edition).* York, UK: NHS Centre for Reviews and Dissemination; CR 2001. 4 (2nd edition).

3. Harris RP, Helfand M, Woolf SH, et al. Current methods of the third U.S. Preventive Services Task Force. *Am J Prev Med.* CR 2001;20(3S):21-35.

4. Mulrow CD, Oxman AD. How to conduct a Cochrane systematic review. Version 3.0.2. Paper presented at: Cochrane Collaboration; CR, 1997; San Antonio, TX.

5. Castell DO, Kahrilas PJ, Richter JE, et al. Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. *American Journal of Gastroenterology.* CR 2002;97(3):575-583.

6. Kahrilas PJ, Falk GW, Johnson DA, et al. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial. The Esomeprazole Study Investigators. *Alimentary Pharmacology & Therapeutics.* CR 2000;14(10):1249-1258.

7. AstraZeneca. Clinical Study #174. CR 2005.

8. *WinBUGS Version 1.2 User Manual* [computer program]. Version 1.2. Cambridge: MRC Biostatistics Unit; 1999.

9. FDA. Medical Review of Nexium (Esomeprazole Magnesium) Delayed-Release Capsules. CR] Application # 21-153/21-154:http://www.fda.gov/cder/foi/nda/2001/21154_Nexium.htm. Accessed 4/29/2004, 2004.

10. Scholten T, Gatz G, Hole U. Once-daily pantoprazole 40 mg and esomeprazole 40 mg have equivalent overall efficacy in relieving GERD-related symptoms. *Alimentary Pharmacology & Therapeutics.* 2003;18(6):587-594.

11. Richter JE, Kahrilas PJ, Sontag SJ, Kovacs TO, Huang B, Pencyla JL. Comparing lansoprazole and omeprazole in onset of heartburn relief: results of a randomized, controlled trial in erosive esophagitis patients.[comment]. *American Journal of Gastroenterology.* 2001;96(11):3089-3098.

12. Richter JE, Kahrilas PJ, Johanson J, et al. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. *American Journal of Gastroenterology.* 2001;96(3):656-665.

13. Mulder CJ, Westerveld BD, Smit JM, et al. A double-blind, randomized comparison of omeprazole Multiple Unit Pellet System (MUPS) 20 mg, lansoprazole 30 mg and pantoprazole 40 mg in symptomatic reflux oesophagitis followed by 3 months of omeprazole MUPS maintenance treatment: a Dutch multicentre trial. *European Journal of Gastroenterology & Hepatology.* 2002;14(6):649-656.

14. Mulder CJ, Dekker W, Gerretsen M. Lansoprazole 30 mg versus omeprazole 40 mg in the treatment of reflux oesophagitis grade II, III and IVa (a Dutch multicentre trial). Dutch Study Group. *European Journal of Gastroenterology & Hepatology.* 1996;8(11):1101-1106.

15. Mee AS, Rowley JL. Rapid symptom relief in reflux oesophagitis: a comparison of lansoprazole and omeprazole. *Alimentary Pharmacology & Therapeutics.* 1996;10(5):757-763.
16. Kao AW, Sheu BS, Sheu MJ, et al. On-demand therapy for Los Angeles grade A and B reflux esophagitis: esomeprazole versus omeprazole. *Journal of the Formosan Medical Association.* 2003;102(9):607-612.
17. Korner T, Schutze K, van Leendert RJ, et al. Comparable efficacy of pantoprazole and omeprazole in patients with moderate to severe reflux esophagitis. *Digestion.* 2003;67(1-2):6-13.
18. Howden CW, Ballard EDI, Robieson W. Evidence for therapeutic equivalence of lansoprazole 30mg and esomeprazole 40mg in the treatment of erosive oesophagitis. *Clinical Drug Investigation.* 2002;22(2):99-109.
19. Holtmann G, Bytzer P, Metz M, Loeffler V, Blum AL. A randomized, double-blind, comparative study of standard-dose rabeprazole and high-dose omeprazole in gastro-oesophageal reflux disease. *Alimentary Pharmacology & Therapeutics.* 2002;16(3):479-485.
20. Gillessen A, Beil W, Modlin IM, Gatz G, Hole U. 40 mg pantoprazole and 40 mg esomeprazole are equivalent in the healing of esophageal lesions and relief from gastroesophageal reflux disease-related symptoms. *Journal of Clinical Gastroenterology.* 2004;38(4):332-340.
21. Hatlebakk JG, Berstad A, Carling L, et al. Lansoprazole versus omeprazole in short-term treatment of reflux oesophagitis. Results of a Scandinavian multicentre trial. *Scandinavian Journal of Gastroenterology.* 1993;28(3):224-228.
22. Delchier JC, Cohen G, Humphries TJ. Rabeprazole, 20 mg once daily or 10 mg twice daily, is equivalent to omeprazole, 20 mg once daily, in the healing of erosive gastrooesophageal reflux disease. *Scandinavian Journal of Gastroenterology.* 2000;35:1245-1250.
23. Dupas JL, Houcke P, Samoyeau R, French Collaborative Pantaprazole Study G. Pantoprazole versus lansoprazole in French patients with reflux esophagitis. *Gastroenterologie Clinique et Biologique.* 2001;25(3):245-250.
24. Dekkers CPM, Beker JA, Thjodleifsson B, et al. Double-blind, placebo-controlled comparison of rabeprazole 20 mg vs. omeprazole 20 mg in the treatment of erosive or ulcerative gastro-oesophageal reflux disease. *Alimentary Pharmacology & Therapeutics.* 1999;13(1):49-57.
25. Castell DO, Richter JE, Robinson M, Sontag SJ, Haber MM. Efficacy and safety of lansoprazole in the treatment of erosive reflux esophagitis. *American Journal of Gastroenterology.* 1996;91(9):1749-1757.
26. Corinaldesi R, Valentini M, Belaiche J, Colin R, Geldof H, Maier C. Pantoprazole and omeprazole in the treatment of oesophagitis: a European multicenter study. *Alimentary Pharmacology & Therapeutics.* 1995;9:667-671.
27. Bardhan KD, Van Rensburg C. Comparable clinical efficacy and tolerability of 20 mg pantoprazole and 20 mg omeprazole in patients with grade I reflux oesophagitis. *Alimentary Pharmacology & Therapeutics.* 2001;15(10):1585-1591.
28. Adachi K, Hashimoto T, Hamamoto N, et al. Symptom relief in patients with reflux esophagitis: comparative study of omeprazole, lansoprazole, and rabeprazole. *Journal of Gastroenterology & Hepatology.* 2003;18(12):1392-1398.

29. Fennerty MB, Johanson JF, Hwang C, Sostek M. Efficacy of esomeprazole 40 mg vs. lansoprazole 30 mg for healing moderate to severe erosive oesophagitis. *Alimentary Pharmacology & Therapeutics.* 15 2005;21(4):455-463.

30. Labenz J, Armstrong D, Lauritsen K, et al. A randomized comparative study of esomeprazole 40 mg versus pantoprazole 40 mg for healing erosive oesophagitis: the EXPO study. *Alimentary Pharmacology & Therapeutics.* 2005;21(6):739-746.

31. Chen C-Y, Lu C-L, Luo J-C, Chang F-Y, Lee S-D, Lai Y-L. Esomeprazole tablet vs omeprazole capsule in treating erosive esophagitis. *World Journal of Gastroenterology.* May 28 2005;11(20):3112-3117.

32. Pace F, Annese V, Prada A, et al. Rabeprazole is equivalent to omeprazole in the treatment of erosive gastro-oesophageal reflux disease. A randomised, double-blind, comparative study of rabeprazole and omeprazole 20 mg in acute treatment of reflux oesophagitis, followed by a maintenance open-label, low-dose therapy with rabeprazole. *Digestive & Liver Disease.* 2005;37(10):741-750.

33. Lightdale C, Schmitt C, Hwang C, Hamelin B. A Multicenter, Randomized, Double-Blind, 8-Week Comparative Trial of Low-Dose Esomeprazole (20 mg) and Standard-Dose Omeprazole (20 mg) in Patients with Erosive Esophagitis. *Dig Dis Sci.* 2006:1-6.

34. Pace F, Negrini C, Wiklund I, Rossi C, Savarino V, The Italian One Investigators Study G. Quality of life in acute and maintenance treatment of non-erosive and mild erosive gastro-oesophageal reflux disease. *Alimentary pharmacology & therapeutics.* Aug 15 2005;22(4):349-356.

35. Dekkers CP, Beker JA, Thjodleifsson B, Gabryelewicz A, Bell NE, Humphries TJ. Comparison of rabeprazole 20 mg versus omeprazole 20 mg in the treatment of active duodenal ulcer: a European multicentre study. *Alimentary Pharmacology & Therapeutics.* 1999;13(2):179-186.

36. Armstrong D, Talley NJ, Lauritsen K, et al. The role of acid suppression in patients with endoscopy-negative reflux disease: the effect of treatment with esomeprazole or omeprazole. *Alimentary pharmacology & therapeutics.* 2004;20(4):413-421.

37. Fock KM, Teo EK, Ang TL, Chua TS, Ng TM, Tan YL. Rabeprazole vs esomeprazole in non-erosive gastro-esophageal reflux disease: a randomized, double-blind study in urban Asia. *World journal of gastroenterology : WJG.* 2005;11(20):3091-3098.

38. Monnikes H, Pfaffenberger B, Gatz G, Hein J, Bardhan KD. Novel measurement of rapid treatment success with ReQuest: first and sustained symptom relief as outcome parameters in patients with endoscopy-negative GERD receiving 20 mg pantoprazole or 20 mg esomeprazole. *Digestion.* 2005;71(3):152-158.

39. Vivian E, Morreale A, Boyce E, Lowry K, Ereso O, Hlavin P. Efficacy and cost effectiveness of lansoprazole versus omeprazole in maintenance treatment of symptomatic gastroesophageal reflux disease. *American Journal of Managed Care.* 1999;5(7):881-886.

40. van Pinxteren B, Numans ME, Bonis PA, Lau J. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease.[update of Cochrane Database Syst Rev. 2001;(4):CD002095; PMID: 11687139]. *Cochrane Database of Systematic Reviews.* 2004(4):CD002095.

41. Dean BB, Gano Jr. AD, Knight K, Ofman JJ, Fass R. Effectiveness of proton pump inhibitors in nonerosive reflux disease. *Clinical Gastroenterology and Hepatology.* 2004;2(8):656-664.
42. Peura DA, Kovacs TO, Metz DC, Siepman N, Pilmer BL, Talley NJ. Lansoprazole in the treatment of functional dyspepsia: two double-blind, randomized, placebo-controlled trials.[see comment]. *American Journal of Medicine.* 2004;116(11):740-748.
43. Van Zyl J, Van Rensburg C, Vieweg W, Fischer R. Efficacy and Safety of Pantoprazole versus Ranitidine in the Treatment of Patients with Symptomatic Gastroesophageal Reflux Disease. *Digestion.* 2004;70(1):61-69.
44. Thjodleifsson B, Beker JA, Dekkers C, Bjaaland T, Finnegan V, Humphries TJ. Rabeprazole versus omeprazole in preventing relapse of erosive or ulcerative gastroesophageal reflux disease: a double-blind, multicenter, European trial. The European Rabeprazole Study Group. *Digestive Diseases & Sciences.* 2000;45(5):845-853.
45. Carling L, Axelsson CK, Forssell H, et al. Lansoprazole and omeprazole in the prevention of relapse of reflux oesophagitis: a long-term comparative study. *Alimentary Pharmacology & Therapeutics.* 1998;12(10):985-990.
46. Lauritsen K, Deviere J, Bigard MA, et al. Esomeprazole 20 mg and lansoprazole 15 mg in maintaining healed reflux oesophagitis: Metropole study results. *Alimentary Pharmacology & Therapeutics.* 2003;17(3):333-341.
47. Thjodleifsson B, Rindi G, Fiocca R, et al. A randomized, double-blind trial of the efficacy and safety of 10 or 20 mg rabeprazole compared with 20 mg omeprazole in the maintenance of gastro-oesophageal reflux disease over 5 years.[comment]. *Alimentary Pharmacology & Therapeutics.* 2003;17(3):343-351.
48. Labenz J, Armstrong D, Lauritsen K, et al. Esomeprazole 20 mg vs. pantoprazole 20 mg for maintenance therapy of healed erosive oesophagitis: results from the EXPO study. *Alimentary Pharmacology & Therapeutics.* Nov 1 2005;22(9):803-811.
49. Jaspersen D, Diehl KL, Schoeppner H, Geyer P, Martens E. A comparison of omeprazole, lansoprazole and pantoprazole in the maintenance treatment of severe reflux oesophagitis. *Alimentary Pharmacology & Therapeutics.* 1998;12:49-52.
50. Donnellan C, Sharma N, Preston C, Moayyedi P. Medical treatments for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease. *Cochrane Database of Systematic Reviews.* 2005(2):CD003245.
51. Tsai HH, Chapman R, Shepherd A, et al. Esomeprazole 20 mg on-demand is more acceptable to patients than continuous lansoprazole 15 mg in the long-term maintenance of endoscopy-negative gastro-oesophageal reflux patients: the COMMAND Study. *Alimentary pharmacology & therapeutics.* 2004;20(6):657-665.
52. Bytzer P, Blum A, De Herdt D, Dubois D. Six-month trial of on-demand rabeprazole 10 mg maintains symptom relief in patients with non-erosive reflux disease. *Aliment Pharmacol Ther.* 2004;20(2):181-188.
53. Talley NJ, Lauritsen K, Tunturi-Hihnala H, et al. Esomeprazole 20 mg maintains symptom control in endoscopy-negative gastro-oesophageal reflux disease: a controlled trial of 'on-demand' therapy for 6 months. *Alimentary Pharmacology & Therapeutics.* 2001;15(3):347-354.
54. Venables TL, Newland RD, Patel AC, Hole J, Copeman MB, Turbitt ML. Maintenance treatment for gastro-oesophageal reflux disease. A placebo-controlled evaluation of 10

milligrams omeprazole once daily in general practice. *Scandinavian Journal of Gastroenterology.* 1997;32(7):627-632.

55. Bate CM, al. e. Omeprazole is more effective than cimetidine in the prevention of recurrence of GERD-associated heartburn and the occurrence of underlying oesophagitis. *Alimentary Pharmacology & Therapeutics.* 1998;12(1):41-47.

56. Bardhan KD, Muller-Lissner S, Bigard MA, et al. Symptomatic gastro-oesophageal reflux disease: double blind controlled study of intermittent treatment with omeprazole or ranitidine. The European Study Group. *Bmj.* 1999;318(7182):502-507.

57. Caro JJ, Salas M, Ward A. Healing and relapse rates in gastroesophageal reflux disease treated with the newer proton-pump inhibitors lansoprazole, rabeprazole, and pantoprazole compared with omeprazole, ranitidine, and placebo: Evidence from randomized clinical trials. *Clinical Therapeutics.* 2001;23(7):998-1017.

58. Vakil N, Fennerty MB. Direct comparative trials of the efficacy of proton pump inhibitors in the management of gastro-oesophageal reflux disease and peptic ulcer disease. *Alimentary Pharmacology & Therapeutics.* 2003;18(6):559-568.

59. Klok RM, Postma MJ, van Hout BA, Brouwers JR. Meta-analysis: comparing the efficacy of proton pump inhibitors in short-term use. *Alimentary Pharmacology & Therapeutics.* 2003;17(10):1237-1245.

60. Raghunath AS, Green JRB, Edwards SJ. A review of the clinical and economic impact of using esomeprazole or lansoprazole for the treatment of erosive esophagitis. *Clinical Therapeutics.* 2003;25(7):2088-2101.

61. Bate CM, Keeling PW, O'Morain C, et al. Comparison of omeprazole and cimetidine in reflux oesophagitis: symptomatic, endoscopic, and histological evaluations. *Gut.* 1990;31(9):968-972.

62. Dehn TC, Shepherd HA, Colin-Jones D, Kettlewell MG, Carroll NJ. Double blind comparison of omeprazole (400 mg qd) in the treatment of symptomatic erosive reflux oesophagitis, assessed endoscopically, histologically and by 24 h pH monitoring. *Gut.* 1990;31:509-513.

63. Havelund T, Laursen LS, Skoubo Kristensen E, al. e. Omeprazole and ranitidine in treatment of reflux oesophagitis: double blind comparative trial. *British Medical Journal (Clinical Research Edition).* 1988;296:89-92.

64. Klinkenberg-Knol EC, Jansen JM, Festen HP, Meuwissen SG, Lamers CB. Double-blind multicentre comparison of omeprazole and ranitidine in the treatment of reflux oesophagitis. *Lancet.* 1987;1(8529):349-351.

65. Lundell L, Backman L, Ekstrom P, et al. Omeprazole or high-dose ranitidine in the treatment of patients with reflux oesophagitis not responding to 'standard doses' of H2-receptor antagonists. *Alimentary Pharmacology & Therapeutics.* 1990;4(2):145-155.

66. Robinson M, Decktor DL, Maton PN, et al. Omeprazole is superior to ranitidine plus metoclopramide in the short-term treatment of erosive oesophagitis. *Alimentary Pharmacology & Therapeutics.* 1993;7(1):67-73.

67. Sandmark S, Carlsson R, Fausa O, Lundell L. Omeprazole or ranitidine in the treatment of reflux esophagitis: results of a double-blind, randomized, Scandinavian multicenter study. *Scandinavian Journal of Gastroenterology.* 1988;23:625-632.

68. Vantrappen G, Rutgeerts L, Schurmans P, Coenegrachts JL. Omeprazole (40 mg) is superior to ranitidine in short-term treatment of ulcerative reflux esophagitis. *Digestive Diseases & Sciences.* 1988;33(5):523-529.

69. Zeitoun P. Comparison of omeprazole with ranitidine in the treatment of reflux oesophagitis. *Scandinavian Journal of Gastroenterology - Supplement.* 1989;166:83-87; discussion 94.
70. Anonymous. Omeprazole produces significantly greater healing of erosive or ulcerative reflux oesophagitis than ranitidine. *European Journal of Gastroenterology & Hepatology.* 1991;3:511-517.
71. Kawano S, Murata H, Tsuji S, et al. Randomized comparative study of omeprazole and famotidine in reflux esophagitis. *Journal of Gastroenterology & Hepatology.* 2002;17(9):955-959.
72. Feldman M, Harford WV, Fisher RS, et al. Treatment of reflux esophagitis resistant to H2-receptor antagonists with lansoprazole, a new H+/K(+)-ATPase inhibitor: a controlled, double-blind study. Lansoprazole Study Group. *American Journal of Gastroenterology.* 1993;88(8):1212-1217.
73. Bardhan KD, Hawkey CJ, Long RG, et al. Lansoprazole versus ranitidine for the treatment of reflux oesophagitis. UK Lansoprazole Clinical Research Group. *Alimentary Pharmacology & Therapeutics.* 1995;9(2):145-151.
74. Jansen JB, Van Oene JC. Standard-dose lansoprazole is more effective than high-dose ranitidine in achieving endoscopic healing and symptom relief in patients with moderately severe reflux oesophagitis. The Dutch Lansoprazole Study Group. *Alimentary Pharmacology & Therapeutics.* 1999;13(12):1611-1620.
75. Umeda N, Miki K, Hoshino E. Lansoprazole versus famotidine in symptomatic reflux esophagitis: a randomized, multicenter study. *Journal of Clinical Gastroenterology.* 1995;20(Suppl 1):S17-23.
76. Sontag SJ, Kogut DG, Fleischmann R, et al. Lansoprazole heals erosive reflux esophagitis resistant to histamine H2-receptor antagonist therapy. *American Journal of Gastroenterology.* 1997;92(3):429-437.
77. Armstrong D, Pare P, Pericak D, Pyzyk M, Canadian Pantoprazole GSG. Symptom relief in gastroesophageal reflux disease: a randomized, controlled comparison of pantoprazole and nizatidine in a mixed patient population with erosive esophagitis or endoscopy-negative reflux disease. *American Journal of Gastroenterology.* 2001;96(10):2849-2857.
78. Dettmer A, Vogt R, Sielaff F, Luhmann R, Schneider A, Fischer R. Pantoprazole 20 mg is effective for relief of symptoms and healing of lesions in mild reflux oesophagitis. *Alimentary Pharmacology & Therapeutics.* 1998;12(9):865-872.
79. Koop H, Schepp W, Dammann HG, Schneider A, Luhmann R, Classen M. Comparative trial of pantoprazole and ranitidine in the treatment of reflux esophagitis. Results of a German multicenter study. *Journal of Clinical Gastroenterology.* 1995;20(3):192-195.
80. Adamek RJ, Behrendt J, Wenzel C. Relapse prevention in reflux oesophagitis with regard to Helicobacter pylori status: a double-blind, randomized, multicentre trial to compare the efficacy of pantoprazole versus ranitidine. *European Journal of Gastroenterology & Hepatology.* 2001;13(7):811-817.
81. Meneghelli UG, Boaventura S, Moraes-Filho JP, et al. Efficacy and tolerability of pantoprazole versus ranitidine in the treatment of reflux esophagitis and the influence of Helicobacter pylori infection on healing rate. *Diseases of the Esophagus.* 2002;15(1):50-56.

82. Farley A, Wruble LD, Humphries TJ. Rabeprazole versus ranitidine for the treatment of erosive gastroesophageal reflux disease a double blind, randomized clinical trial. Raberprazole Study Group. *American Journal of Gastroenterology.* 2000;95:1894-1899.
83. Metz DC. Therapy for gastroesophageal reflux disease: more is not necessarily better. *American Journal of Gastroenterology.* 2003;98(9):1913-1915.
84. Richter JE, Fraga P, Mack M, Sabesin SM, Bochenek W, Pantoprazole USGSG. Prevention of erosive oesophagitis relapse with pantoprazole. *Alimentary pharmacology & therapeutics.* 2004;20(5):567-575.
85. Hansen AN, Bergheim R, Fagertun H, Lund H, Wiklund I, Moum B. Long-term management of patients with symptoms of gastro-oesophageal reflux disease -- a Norwegian randomised prospective study comparing the effects of esomeprazole and ranitidine treatment strategies on health-related quality of life in a general practitioners setting. *International Journal of Clinical Practice.* 2006;60(1):15-22.
86. Hansen AN, Wahlqvist P, Jorgensen E, et al. Six-month management of patients following treatment for gastroesophageal reflux disease symptoms -- a Norwegian randomized, prospective study comparing the costs and effectiveness of esomeprazole and ranitidine treatment strategies in a general medical practitioners setting. *International journal of clinical practice.* Jun 2005;59(6):655-664.
87. Moore DJ, Tao BS, Lines DR, Hirte C, Heddle ML, Davidson GP. Double-blind placebo-controlled trial of omeprazole in irritable infants with gastroesophageal reflux. *Journal of Pediatrics.* 2003;143(2):219-223.
88. Cucchiara S, Minella R, Campanozzi A, et al. Effects of omeprazole on mechanisms of gastroesophageal reflux in childhood. *Digestive Diseases & Sciences.* 1997;42(2):293-299.
89. Chang FY, Chiang CY, Tam TN, Ng WW, Lee SD. Comparison of lansoprazole and omeprazole in the short-term management of duodenal ulcers in Taiwan. *Journal of Gastroenterology & Hepatology.* 1995;10(5):595-601.
90. Chang FY, Lee CT, Chiang CY, Lee SD. Effect of omeprazole and lansoprazole on serum pepsinogen a levels in patients with duodenal ulcer. *Current Therapeutic Research, Clinical & Experimental.* 1995;56(9):887-893.
91. Ekstrom P, Carling L, Unge P, Anker-Hansen O, Sjostedt S, Sellstrom H. Lansoprazole versus omeprazole in active duodenal ulcer. A double-blind, randomized, comparative study. *Scandinavian Journal of Gastroenterology.* 1995;30(3):210-215.
92. Dobrilla G, Piazzi L, Fiocca R. Lansoprazole versus omeprazole for duodenal ulcer healing and prevention of relapse: A randomized, multicenter, double-masked trial. *Clinical Therapeutics.* 1999;21(8):1321-1332.
93. Capurso L, Di Pietro C, Bordi C, et al. Lansoprazole in the treatment of peptic ulcer disease: A multicentre double-blind study. *Gastroenterology International.* 1996;8(3):125-132.
94. Beker JA, Bianchi Porro G, Bigard MA, et al. Double-blind comparison of pantoprazole and omeprazole for the treatment of acute duodenal ulcer. *European Journal of Gastroenterology & Hepatology.* 1995;7(5):407-410.
95. Tulassay Z, Kryszewski A, Dite P, et al. One week of treatment with esomeprazole-based triple therapy eradicates Helicobacter pylori and heals patients with duodenal ulcer disease. *European Journal of Gastroenterology & Hepatology.* 2001;13(12):1457-1465.

96. Fanti L, Ieri R, Mezzi G, Testoni PA, Passaretti S, Guslandi M. Long-term follow-up and serologic assessment after triple therapy with omeprazole or lansoprazole of Helicobacter-associated duodenal ulcer. *Journal of Clinical Gastroenterology.* 2001;32(1):45-48.

97. Lanza F, Goff J, Silvers D, et al. Prevention of duodenal ulcer recurrence with 15 mg lansoprazole: A double-blind placebo-controlled study. *Digestive Diseases & Sciences.* 1997;42(12):2529-2536.

98. Kovacs TO, Campbell D, Richter J, Haber M, Jennings DE, Rose P. Double blind comparison of lansoprazole 15 mg, lansoprazole 30 mg and placebo as maintenance therapy in patients with healed duodenal ulcers resistant to H2 receptor antagonists. *Alimentary Pharmacology & Therapeutics.* 1999;13:959-967.

99. Russo A, Dattilo M. Bedtime administration of lansoprazole does not modify its greater efficacy vs ranitidine in the acute and long term treatment of duodenal ulcer. Results from a multicentre, randomised, double blind clinical trial. *Italian Journal of Gastroenterology & Hepatology.* 1997;29:312-319.

100. Lee FI, Colin-Jones DG, Golding PL, et al. Double blind comparative study of omeprazole and ranitidine in patients with duodenal or gastric ulcer: a multicentre trial. Cooperative study group. *Gut.* 1990;31(6):653-656.

101. Kager L, Lindberg G, Nilsson LH, et al. The effect of omeprazole and ranitidine on ulcer healing, relief of symptoms, and incidence of adverse events in the treatment of duodenal ulcer patients. *Hepato-Gastroenterology.* 1991;38(4):287-290.

102. Chelvam P, Goh KL, Leong YP, et al. Omeprazole compared with ranitidine once daily in the treatment of duodenal ulcer. *Journal of Gastroenterology & Hepatology.* 1989;4(Suppl 2):53-61.

103. Marks IN, Danilewitz MD, Garisch JA. A comparison of omeprazole and ranitidine for duodenal ulcer in South African patients. A multiracial study. *Digestive Diseases & Sciences.* 1991;36(10):1395-1400.

104. McFarland RJ, Bateson MC, Green JR, et al. Omeprazole provides quicker symptom relief and duodenal ulcer healing than ranitidine. *Gastroenterology.* 1990;98(2):278-283.

105. Lanza F, Goff J, Scowcroft C, al. e. Double-blind comparison of lansoprazole, ranitidine and placebo in the treatment of acute duodenal ulcer. *American Journal of Gastroenterology.* 1994;89:1191-1200.

106. Hawkey CJ, Long RG, Bardhan KD, et al. Improved symptom relief and duodenal ulcer healing with lansoprazole, a new proton pump inhibitor, compared with ranitidine. *Gut.* 1993;34(10):1458-1462.

107. Cremer M, Lambert R, Lamers CB, Delle Fave G, Maier C. A double-blind study of pantoprazole and ranitidine in treatment of acute duodenal ulcer. A multicenter trial. European Pantoprazole Study Group. *Digestive Diseases & Sciences.* 1995;40(6):1360-1364.

108. Schepp W, Classen M. Pantoprazole and ranitidine in the treatment of acute duodenal ulcer. A multicentre study. *Scandinavian Journal of Gastroenterology.* 1995;30(6):511-514.

109. Judmaier G, Koelz HR. Comparison of pantoprazole and ranitidine in the treatment of acute duodenal ulcer. Pantoprazole-Duodenal Ulcer-Study Group. *Alimentary Pharmacology & Therapeutics.* 1994;8(1):81-86.

110. Breiter JR, Riff D, Humphries TJ. Rabeprazole is superior to ranitidine in the management of active duodenal ulcer disease: results of a double-blind, randomized North American study. *American Journal of Gastroenterology.* 2000;95(4):936-942.
111. Valenzuela JE, Berlin RG, Snape WJ, et al. U.S. experience with omeprazole in duodenal ulcer. Multicenter double-blind comparative study with ranitidine. The Omeprazole DU Comparative Study Group. *Digestive Diseases & Sciences.* 1991;36(6):761-768.
112. Bardhan KD, Bianchi Porro G, Bose K, Daly MJ, Hinchliffe RF, Jonsson E. A comparison of two different doses of omeprazole versus ranitidine in the treatment of duodenal ulcers. *Journal of Clinical Gastroenterology.* 1986;8:408-413.
113. Ahmed W, Qureshi H, Zuberi SJ, Alam SE. Omeprazole vs ranitidine in the healing of duodenal ulcer. *JPMA - Journal of the Pakistan Medical Association.* 1993;43(6):111-112.
114. Arber N, Avni Y, Eliakim R, et al. A multicenter, double-blind, randomized controlled study of omeprazole versus ranitidine in the treatment of duodenal ulcer in Israel. *Isr J Med Sci.* 1994;30(10):757-761.
115. Crowe JP, Wilkinson SP, Bate CM, Willoughby CP, Peers EM, Richardson PD. Symptom relief and duodenal ulcer healing with omeprazole or cimetidine. Opus (Omeprazole Peptic Ulcer Study) Research Group. *Alimentary Pharmacology & Therapeutics.* 1989;3(1):83-91.
116. Davis RH, Stott NC, Barber JH, Freeling P, Peers EM, Richardson PD. Treatment of peptic ulcer in general practice and in hospital: a comparison of omeprazole and cimetidine. *British Journal of Clinical Practice.* 1990;44(1):13-16.
117. Delle Fave G, Annibale B, Franceschi M, Quatrini M, Cassetta MR, Torsoli A. Omeprazole versus famotidine in the short-term treatment of duodenal ulcer disease. *Alimentary Pharmacology & Therapeutics.* 1992;6(4):469-478.
118. Kumar TR, Naidu MU, Shobha JC, et al. Comparative study of omeprazole and famotidine in the treatment of duodenal ulcer. *Indian J Gastroenterol.* 1992;11(2):73-75.
119. Meneghelli UG, Zaterka S, de Paula Castro L, Malafaia O, Lyra LG. Pantoprazole versus ranitidine in the treatment of duodenal ulcer: a multicenter study in Brazil. *American Journal of Gastroenterology.* 2000;95(1):62-66.
120. Zaterka S, Massuda H, Chinzon D, et al. Treatment of duodenal ulcer with omeprazole or ranitidine in a Brazilian population: a multicenter double-blind, parallel group study. *American Journal of Gastroenterology.* 1993;88(3):397-401.
121. Archambault AP, Hunt RH, Cleator IGM, et al. Comparison of omeprazole with ranitidine for treatment of symptoms associated with gastroesophageal reflux disease and uncomplicated duodenal ulcer. *Canadian Journal of Gastroenterology.* 1996;10(3):156-162.
122. Colin R, The Hepylog Investigator Study G. Duodenal ulcer healing with 1-week eradication triple therapy followed, or not, by anti-secretory treatment: a multicentre double-blind placebo-controlled trial. *Alimentary Pharmacology & Therapeutics.* 2002;16(6):1157-1162.
123. Catalano F, Mangiameli A, Inserra G, et al. Omeprazole vs. ranitidine in short-term treatment of Helicobacter pylori positive duodenal ulcer patients. *Ital J Gastroenterol.* 1991;23(1):9-11.

124. Wang CY, Wang TH, Lai KH, et al. Double-blind comparison of omeprazole 20 mg OM and ranitidine 300 mg NOCTE in duodenal ulcer: a Taiwan multi-centre study. *Journal of Gastroenterology & Hepatology.* 1992;7(6):572-576.
125. Wilairatana S, Kurathong S, Atthapaisalsarudee C, Saowaros V, Leethochawalit M. Omeprazole or cimetidine once daily for the treatment of duodenal ulcers? *Journal of Gastroenterology & Hepatology.* 1989;4(Suppl 2):45-52.
126. Dekkers CP, Beker JA, Thjodleifsson B, Gabryelewicz A, Bell NE, Humphries TJ. Comparison of rabeprazole 20 mg vs. omeprazole 20 mg in the treatment of active gastric ulcer--a European multicentre study. The European Rabeprazole Study Group. *Alimentary Pharmacology & Therapeutics.* 1998;12(8):789-795.
127. Florent C, Audigier JC, Boyer J, et al. Efficacy and safety of lansoprazole in the treatment of gastric ulcer: A multicentre study. *Eur J Gastroenterol Hepatol.* 1994;6(12):1135-1139.
128. Ando T, Kato H, Sugimoto N, et al. A comparative study on endoscopic ulcer healing of omeprazole versus rabeprazole with respect to CYP2C19 genotypic differences. *Digestive Diseases & Sciences.* Sep 2005;50(9):1625-1631.
129. Goldstein JL, Johanson JF, Suchower LJ, Brown KA. Healing of gastric ulcers with esomeprazole versus ranitidine in patients who continued to receive NSAID therapy: a randomized trial. *American Journal of Gastroenterology.* Dec 2005;100(12):2650-2657.
130. Classen M, Dammann HG, Domschke W, et al. Omeprazole heals duodenal, but not gastric ulcers more rapidly than ranitidine. Results of two German multicentre trials. *Hepato Gastroenterology.* 1985;32(5):243-245.
131. Wulff HR, Lauritsen K, Laursen LS, et al. Omeprazole and cimetidine in the treatment of ulcers of the body of the stomach: a double blind comparative trial. Danish Omeprazole Study Group. *Br Med J.* 1989;298(6674):645-647.
132. Tsuji S, Kawano S, Higashi T, et al. Gastric ulcer healing and basic fibroblast growth factor: effects of lansoprazole and famotidine. *Journal of Clinical Gastroenterology.* 1995;20(Suppl 2):S1-4.
133. Okai T, Sawabu N, Songur Y, Motoo Y, Watanabe H. Comparison of lansoprazole and famotidine for gastric ulcer by endoscopic ultrasonography: a preliminary trial. *Journal of Clinical Gastroenterology.* 1995;20(Suppl 2):S32-35.
134. Aoyama N, Kinoshita Y, Misaki F, Himeno S, Kasuga M, Chiba T. Evaluation of gastric ulcer healing by lansoprazole by measurement of ulcer diameter. *Journal of Clinical Gastroenterology.* 1995;20 Suppl 2:S86-89.
135. Rossini FP, Spandre M, Gemme C, et al. Histological aspects and healing rates of gastric ulcers treated with omeprazole 20 mg once daily or ranitidine 150 mg B.I.D. *Panminerva Med.* 1989;31(2):94-96.
136. Walan A, Bader JP, Classen M, Lamers BHW, Piper DW, Rutgersson K. Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. *New England Journal of Medicine.* 1989;320:69-75.
137. Bardhan KD, Ahlberg J, Hislop WS, et al. Rapid healing of gastric ulcers with lansoprazole. *Alimentary Pharmacology & Therapeutics.* 1994;8(2):215-220.
138. Michel P, Lemaire M, Colin R, al. e. Short report: Treatment of gastric ulcer with lansoprazole or ranitidine: a multicentre clinical trial. *Alimentary Pharmacology & Therapeutics.* 1994;6:87-95.

139. Hotz J, Plein K, Schonekas H, Rose K. Pantoprazole is superior to ranitidine in the treatment of acute gastric ulcer. *Scandinavian Journal of Gastroenterology.* 1995;30(2):111-115.
140. Lauritsen K, Rune SJ, Wulff HR, et al. Effect of omeprazole and cimetidine on prepyloric gastric ulcer: double blind comparative trial. *Gut.* 1988;29(2):249-253.
141. Bate CM, Wilkinson SP, Bradby GV, et al. Randomised, double blind comparison of omeprazole and cimetidine in the treatment of symptomatic gastric ulcer. *Gut.* 1989;30(10):1323-1328.
142. Lauritsen K, Laursen LS, Havelund T, et al. Relapse of gastric ulcers after healing with omeprazole and cimetidine. A double-blind follow-up study. Danish Omeprazole Study Group. *Scandinavian Journal of Gastroenterology.* 1989;24(5):557-560.
143. Di Mario F, Battaglia G, Grassi SA, et al. Different doses of omeprazole in the maintenance treatment of patients with peptic ulcers resistant to H2-blockers. *Current Therapeutic Research, Clinical & Experimental.* 1994;55(11):1363-1371.
144. Kovacs TO, Campbell D, Haber M, Rose P, Jennings DE, Richter J. Double blind comparison of lansoprazole 15 mg, lansoprazole 30 mg, and placebo in the maintenance of healed gastric ulcer. *Digestive Diseases & Sciences.* 1998;43:779-785.
145. Agrawal NM, Campbell DR, Safdi MA, Lukasik Nl, Huang B, Haber MM. Superiority of lansoprazole vs ranitidine in healing nonsteroidal anti inflammatory drug associated gastric ulcers results of a double blind, randomized, multicenter study. NSAID Associated Gastric Ulcer Study Group. *Archives of Internal Medicine.* 2000;160:1455-1461.
146. Hawkey CJ, Karrasch JA, Szczepanski L, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. Omeprazole versus Misoprostol for NSAID induced Ulcer Management (OMNIUM) Study Group. [see comments]. *New England Journal of Medicine.* 1998;338:727-734.
147. Yeomans ND, Tulassay Z, Juhasz L, et al. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs. Acid Suppression Trial Ranitidine versus Omeprazole for NSAID associated Ulcer Treatment (ASTRONAUT) Study Group. [see comments]. *New England Journal of Medicine.* 1998;338:719-726.
148. Rostom A, Dube C, Jolicoeur E, Boucher M, Joyce J. Gastroduodenal ulcers associated with the use of non-steroidal anti-inflammatory drugs: a systematic review of preventive pharmacological interventions. *Health Technol Assess.* 2004(12).
149. Yeomans N, Wilson I, Langstrom G, et al. Quality of life in chronic NSAID users: a comparison of the effect of omeprazole and misoprostol. *Scandinavian journal of rheumatology.* 2001;30(6):328-334.
150. Rostom A, Wells G, Tugwell P, Welch V, Dube C, McGowan J. Prevention of NSAID-induced gastroduodenal ulcers. *Cochrane Database of Systematic Reviews [computer file].* 2000(4):CD002296.
151. Graham DY, Agrawal NM, Campbell DR, et al. Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs: results of a double-blind, randomized, multicenter, active- and placebo-controlled study of misoprostol vs lansoprazole. *Archives of Internal Medicine.* 2002;162(2):169-175.
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-

inflammatory drugs: A prospective, placebo-controlled, double-blind, parallel-group study. *Digestive & Liver Disease.* 2000;32(3):201-208.

153. Lai KC, Lam SK, Chu KM, et al. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. *New England Journal of Medicine.* 2002;346(26):2033-2038.

154. Labenz J, Blum AL, Bolten WW, et al. Primary prevention of diclofenac associated ulcers and dyspepsia by omeprazole or triple therapy in Helicobacter pylori positive patients: a randomised, double blind, placebo controlled, clinical trial. *Gut.* 2002;51(3):329-335.

155. Stupnicki T, Dietrich K, Gonzalez-Carro P, et al. Efficacy and tolerability of pantoprazole compared with misoprostol for the prevention of NSAID-related gastrointestinal lesions and symptoms in rheumatic patients. *Digestion.* 2003;68(4):198-208.

156. Goldstein JL, Huang B, Amer F, Christopoulos NG. Ulcer recurrence in high-risk patients receiving nonsteroidalanti-inflammatory drugs plus low-dose aspirin: results of a post HOC subanalysis. *Clinical therapeutics.* 2004;26(10):1637-1643.

157. Vergara M, Vallve M, Gisbert JP, Calvet X. Meta-analysis: comparative efficacy of different proton-pump inhibitors in triple therapy for Helicobacter pylori eradication. *Alimentary Pharmacology & Therapeutics.* 2003;18(6):647-654.

158. Laheij RJ, Rossum LG, Jansen JB, Straatman H, Verbeek AL. Evaluation of treatment regimens to cure Helicobacter pylori infection--a meta-analysis. *Alimentary Pharmacology & Therapeutics.* 1999;13(7):857-864.

159. Bazzoli F, Pozzato P, Zagari M, et al. Efficacy of lansoprazole in eradicating Helicobacter pylori: a meta-analysis. *Helicobacter.* 1998;3(3):195-201.

160. Adamek RJ, Szymanski C, Pfaffenbach B. Pantoprazole versus omeprazole in one-week low-dose triple therapy for curve of H. pylori infection. *American Journal of Gastroenterology.* 1997;92(10):1949-1950.

161. Catalano F, Branciforte G, Catanzaro R, et al. Comparative treatment of Helicobacter pylori-positive duodenal ulcer using pantoprazole at low and high doses versus omeprazole in triple therapy. *Helicobacter.* 1999;4(3):178-184.

162. Eralp Y, Dobrucali A, Bagatur N, et al. A comparison of lansoprazole and omeprazole based triple combinations for the treatment of Helicobacter pylori associated gastritis and peptic ulcer. *Turkish Journal of Gastroenterology.* 2000;11(1):25-29.

163. Furuta T, Shirai N, Takashima M, et al. Effect of genotypic differences in CYP2C19 on cure rates for Helicobacter pylori infection by triple therapy with a proton pump inhibitor, amoxicillin, and clarithromycin. *Clinical Pharmacology & Therapeutics.* 2001;69(3):158-168.

164. Harris AW, Misiewicz JJ, Bardhan KD, et al. Incidence of duodenal ulcer healing after 1 week of proton pump inhibitor triple therapy for eradication of Helicobacter pylori. The Lansoprazole Helicobacter Study Group. *Alimentary Pharmacology & Therapeutics.* 1998;12:741-745.

165. Inaba T, Mizuno M, Kawai K, et al. Randomized open trial for comparison of proton pump inhibitors in triple therapy for Helicobacter pylori infection in relation to CYP2C19 genotype. *Journal of Gastroenterology & Hepatology.* 2002;17(7):748-753.

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

Helicobacter pylori infection by a 1-week regimen of proton pump inhibitor, amoxicillin and clarithromycin. *Alimentary Pharmacology & Therapeutics.* 2003;17(2):259-264.

167. Mera R, Realpe JL, Bravo LE, DeLany JP, Correa P. Eradication of Helicobacter pylori infection with proton pump based triple therapy in patients in whom bismuth based triple therapy failed. *Journal of Clinical Gastroenterology.* 1999;29:51-55.

168. Miwa H, Nagahara A, Sato K, et al. Efficacy of 1 week omeprazole or lansoprazole amoxycillin clarithromycin therapy for Helicobacter pylori infection in the Japanese population. *Journal of Gastroenterology & Hepatology.* 1999;14:317-321.

169. Miwa H, Ohkura R, Murai T, et al. Impact of rabeprazole, a new proton pump inhibitor, in triple therapy for Helicobacter pylori infection comparison with omeprazole and lansoprazole. *Alimentary Pharmacology & Therapeutics.* 1999;13:741-746.

170. Miwa H, Yamada T, Sato K, et al. Efficacy of reduced dosage of rabeprazole in PPI/AC therapy for Helicobacter pylori infection comparison of 20 and 40 mg rabeprazole with 60 mg lansoprazole. *Digestive Diseases & Sciences.* 2000;45:77-82.

171. Miyoshi M, Mizuno M, Ishiki K, et al. A randomized open trial for comparison of proton pump inhibitors, omeprazole versus rabeprazole, in dual therapy for Helicobacter pylori infection in relation to CYP2C19 genetic polymorphism. *Journal of Gastroenterology & Hepatology.* 2001;16(7):723-728.

172. Murakami K, Sato R, Okimoto T, et al. Eradication rates of clarithromycin-resistant Helicobacter pylori using either rabeprazole or lansoprazole plus amoxicillin and clarithromycin. *Alimentary Pharmacology & Therapeutics.* 2002;16(11):1933-1938.

173. Ohlin B, Cederberg A, Kjellin T, et al. Dual versus triple therapy in eradication of Helicobacter pylori. *Hepato-Gastroenterology.* 2002;49(43):172-175.

174. Rinaldi V, Zullo A, De Francesco V, et al. Helicobacter pylori eradication with proton pump inhibitor based triple therapies and re treatment with ranitidine bismuth citrate based triple therapy. *Alimentary Pharmacology & Therapeutics.* 1999;13:163-168.

175. Treiber G, Ammon S, Klotz U. Age-dependent eradication of Helicobacter pylori with dual therapy. *Alimentary pharmacology & therapeutics.* 1997;11(4):711-718.

176. Ungan M, Kulacoglu H, Kayhan B. Cure rates obtained with five different Helicobacter pylori eradication protocols in patients with duodenal ulcer: A prospective, open-label, randomized study in a primary care setting in Turkey. *Current Therapeutic Research, Clinical & Experimental.* 2001;62(6):462-472.

177. Veldhuyzen van Zanten S, Lauritsen K, Delchier JC, et al. One-week triple therapy with esomeprazole provides effective eradication of Helicobacter pylori in duodenal ulcer disease. *Alimentary Pharmacology & Therapeutics.* 2000;14(12):1605-1611.

178. Anagnostopoulos GK, Tsiakos S, Margantinis G, Kostopoulos P, Arvanitidis D. Esomeprazole versus omeprazole for the eradication of Helicobacter pylori infection: results of a randomized controlled study. *Journal of Clinical Gastroenterology.* 2004;38(6):503-506.

179. Hsu P-I, Lai K-H, Lin C-K, et al. A prospective randomized trial of esomeprazole- versus pantoprazole-based triple therapy for Helicobacter pylori eradication.[see comment]. *American Journal of Gastroenterology.* Nov 2005;100(11):2387-2392.

180. Harris A. Treatment of Helicobacter pylori. *World Journal of Gastroenterology.* 2001;7(3):303-307.

181. Vakil N, Lanza F, Schwartz H, Barth J. Seven-day therapy for Helicobacter pylori in the United States. *Alimentary Pharmacology & Therapeutics.* 2004;20(1):99-107.

182. Yang KC, Wang GM, Chen JH, Chen TJ, Lee SC. Comparison of rabeprazole-based four- and seven-day triple therapy and omeprazole-based seven-day triple therapy for Helicobacter pylori infection in patients with peptic ulcer. *Journal of the Formosan Medical Association.* 2003;102(12):857-862.

183. Treiber G, Ammon S, Klotz U. Age dependent eradication of Helicobacter pylori with dual therapy. *Alimentary Pharmacology & Therapeutics.* 1997;11:711-718.

184. Miehlke S, Schneider-Brachert W, Bastlein E, et al. Esomeprazole-based one-week triple therapy with clarithromycin and metronidazole is effective in eradicating Helicobacter pylori in the absence of antimicrobial resistance. *Aliment Pharmacol Ther.* 2003;18(8):799-804.

185. Van Oijen AH, Verbeek AL, Jansen JB, De Boer WA. Review article: treatment of Helicobacter pylori infection with ranitidine bismuth citrate- or proton pump inhibitor-based triple therapies. *Alimentary Pharmacology & Therapeutics.* 2000;14(8):991-999.

186. Gisbert JP, Gonzalez L, Calvet X, Roque M, Gabriel R, Pajares JM. Proton pump inhibitors versus H2-antagonists: a meta-analysis of their efficacy in treating bleeding peptic ulcer. *Alimentary Pharmacology & Therapeutics.* 2001;15(7):917-926.

187. Graham DY, Hammoud F, El-Zimaity HM, Kim JG, Osato MS, El-Serag HB. Meta-analysis: proton pump inhibitor or H2-receptor antagonist for Helicobacter pylori eradication. *Alimentary Pharmacology & Therapeutics.* 2003;17(10):1229-1236.

188. Oderda G, Marinello D, Lerro P, et al. Dual vs. triple therapy for childhood Helicobacter pylori gastritis: A double-blind randomized multicentre trial. *Helicobacter.* 2004;9(4):293-301.

189. Tindberg Y, Casswall TH, Blennow M, Bengtsson C, Granstrom M, Sorberg M. Helicobacter pylori eradication in children and adolescents by a once daily 6-day treatment with or without a proton pump inhibitor in a double-blind randomized trial. *Alimentary Pharmacology & Therapeutics.* 2004;20(3):295-302.

190. Lauritsen K, Junghard O, Eklund S. Esomeprazole 20 mg compared with lansoprazole 15 mg for maintenance therapy in patients with healed reflux oesophagitis [abstract]. *J Gastroenterol Hepatol.* 2002;17(Suppl):A1007.

191. Bardhan KD, Cherian P, Bishop AE, et al. Pantoprazole therapy in the long-term management of severe acid peptic disease: clinical efficacy, safety, serum gastrin, gastric histology, and endocrine cell studies. *American Journal of Gastroenterology.* 2001;96(6):1767-1776.

192. Freston JW, Rose PA, Heller CA, Haber M, Jennings D. Safety profile of lansoprazole: The US clinical trial experience. *Drug Safety.* 1999;20(2):195-205.

193. Leufkens H, Claessens A, Heerdink E, van Eijk J, Lamers CB. A prospective follow-up study of 5669 users of lansoprazole in daily practice. *Alimentary Pharmacology & Therapeutics.* 1997;11(5):887-897.

194. Klinkenberg-Knol EC, Festen HP, Jansen JB, et al. Long-term treatment with omeprazole for refractory reflux esophagitis: efficacy and safety. *Annals of Internal Medicine.* 1994;121(3):161-167.

195. Lundell L, Miettinen P, Myrvold HE, et al. Lack of effect of acid suppression therapy on gastric atrophy. Nordic Gerd Study Group. *Gastroenterology.* 1999;117(2):319-326.

196. Brunner G, Harke U. Long-term therapy with pantoprazole in patients with peptic ulceration resistant to extended high-dose ranitidine treatment. *Alimentary Pharmacology & Therapeutics.* 1994;8(Suppl 1):59-64.

197. Solcia E, Rindi G, Havu N, Elm G. Qualitative studies of gastric endocrine cells in patients treated long-term with omeprazole. *Scandinavian Journal of Gastroenterology - Supplement.* 1989;166:129-137; discussion 138-129.
198. Solcia E, Fiocca R, Havu N, Dalvag A, Carlsson R. Gastric endocrine cells and gastritis in patients receiving long-term omeprazole treatment. *Digestion.* 1992;51(Suppl 1):82-92.
199. Lundell L, Backman L, Ekstrom P, al. e. Prevention of relapse of reflux esophagitis afetr endoscopic healing: the efficacy and safety of omeprazole compared with ranitidine. *Scandinavian Journal of Gastroenterology.* 1991;26:248-256.
200. Dent J, Yeomans ND, Mackinnon M, al. e. Omeprazole vs ranitidine for prevention of relapse in reflux oesophagitis. A controlled double blind trial of their efficacy and safety. *Gut.* 1994;35:590-598.
201. Lamberts R, Creutzfeldt W, Stockmann F, Jacubaschke U, Maas S, Brunner G. Long-term omeprazole treatment in man: effects on gastric endocrine cell populations. *Digestion.* 1988;39(2):126-135.
202. Hallerback B, Unge P, Carling L, al. e. Omeprazole or ranitidine in long-term treatment of reflux oesophagitis. *Gastroenterology.* 1994;107:1035-10311.
203. Kuipers EJ, Lundell L, Klinkenberg-Knol EC, et al. Atrophic gastritis and Helicobacter pylori infection in patients with reflux esophagitis treated with omeprazole or fundoplication. *New England Journal of Medicine.* 1996;334(16):1018-1022.
204. Claessens A, Heerdink ER, van Eijk J, Lamers C, Leufkens HGM. Characteristics of diarrhoea in 10 008 users of lansoprazole in daily practice: Which co-factors contribute? *Pharmacoepidemiology & Drug Safety.* 2002;11(8):703-708.
205. Klinkenberg-Knol EC, Nelis F, Dent J, et al. Long-term omeprazole treatment in resistant gastroesophageal reflux disease: efficacy, safety, and influence on gastric mucosa.[see comment]. *Gastroenterology.* 2000;118(4):661-669.
206. Caos A, Breiter J, Perdomo C, Barth J. Long-term prevention of erosive or ulcerative gastro-oesophageal reflux disease relapse with rabeprazole 10 or 20 mg vs. placebo: results of a 5-year study in the United States. *Alimentary pharmacology & therapeutics.* Aug 1 2005;22(3):193-202.
207. Stolte M, Meining A, Schmitz JM, Alexandridis T, Seifert E. Changes in Helicobacter pylori-induced gastritis in the antrum and corpus during 12 months of treatment with omeprazole and lansoprazole in patients with gastro-oesophageal reflux disease. *Alimentary Pharmacology & Therapeutics.* 1998;12(3):247-253.
208. Johnson M, Guilford S, Libretto SE. Patients have treatment preferences: A multicentre, double-blind, crossover study comparing rabeprazole and omeprazole. *Current Medical Research & Opinion.* 2002;18(5):303-310.
209. Cataldo MG, Brancato D, Donatelli M, Morici ML, Aspetti S, Spina P. Treatment of patients with duodenal ulcer positive for Helicobacter pylori infection: Ranitidine or omeprazole associated with colloidal bismuth subcitrate plus amoxicillin. *Current Therapeutic Research Clinical and Experimental.* 1996;57(3):168-174.
210. Gunasekaran T, Gupta S, Gremse D, et al. Lansoprazole in adolescents with gastroesophageal reflux disease: Pharmacokinetics, pharmacodynamics, symptom relief efficacy, and tolerability. *Journal of Pediatric Gastroenterology & Nutrition.* 2002;35(SUPPL. 4):S327-S335.

211. Madrazo-de la Garza A, Dibildox M, Vargas A, Delgado J, Gonzalez J, Yanez P. Efficacy and safety of oral pantoprazole 20 mg given once daily for reflux esophagitis in children. *Journal of Pediatric Gastroenterology & Nutrition.* 2003;36(2):261-265.
212. Shashidhar H, Peters J, Lin CH, Rabah R, Thomas R, Tolia V. A prospective trial of lansoprazole triple therapy for pediatric Helicobacter pylori infection. *Journal of Pediatric Gastroenterology & Nutrition.* 2000;30(3):276-282.
213. Gunasekaran TS, Hassall EG. Efficacy and safety of omeprazole for severe gastroesophageal reflux in children. *Journal of Pediatrics.* 1993;123(1):148-154.
214. Cucchiara S, Minella R, Iervolino C, et al. Omeprazole and high dose ranitidine in the treatment of refractory reflux oesophagitis. *Archives of Disease in Childhood.* 1993;69(6):655-659.
215. Pilotto A, Leandro G, Franceschi M, Ageing, Acid-Related Disease Study G. Short- and long-term therapy for reflux oesophagitis in the elderly: a multi-centre, placebo-controlled study with pantoprazole. *Alimentary Pharmacology & Therapeutics.* 2003;17(11):1399-1406.
216. Hui WM, Lam SK, Lau WY. Omeprazole and ranitidine in duodenal ulcer healing and subsequent relapse: a randomised double-blind study with weekly endoscopic assessment. *J Gastroenterol Hepatol.* 1989;4(Suppl 2):35-43.
217. Furuta T, Shirai N, Xiao F, et al. Polymorphism of interleukin-1beta affects the eradication rates of Helicobacter pylori by triple therapy. *Clinical Gastroenterology & Hepatology.* 2004;2(1):22-30.
218. Kawamura M, Ohara S, Koike T, et al. The effects of lansoprazole on erosive reflux oesophagitis are influenced by CYP2C19 polymorphism. *Alimentary Pharmacology & Therapeutics.* 2003;17(7):965-973.
219. Ohkusa T, Maekawa T, Arakawa T, et al. Effect of CYP2C19 polymorphism on the safety and efficacy of omeprazole in Japanese patients with recurrent reflux oesophagitis. *Alimentary pharmacology & therapeutics.* Jun 1 2005;21(11):1331-1339.
220. James OF, Parry-Billings KS. Comparison of omeprazole and histamine H2-receptor antagonists in the treatment of elderly and young patients with reflux oesophagitis. *Age & Ageing.* 1994;23(2):121-126.
221. Diav-Citrin O, Arnon J, Shechtman S, et al. The safety of proton pump inhibitors in pregnancy: a multicentre prospective controlled study. *Alimentary pharmacology & therapeutics.* 2005;21(3):269-275.

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

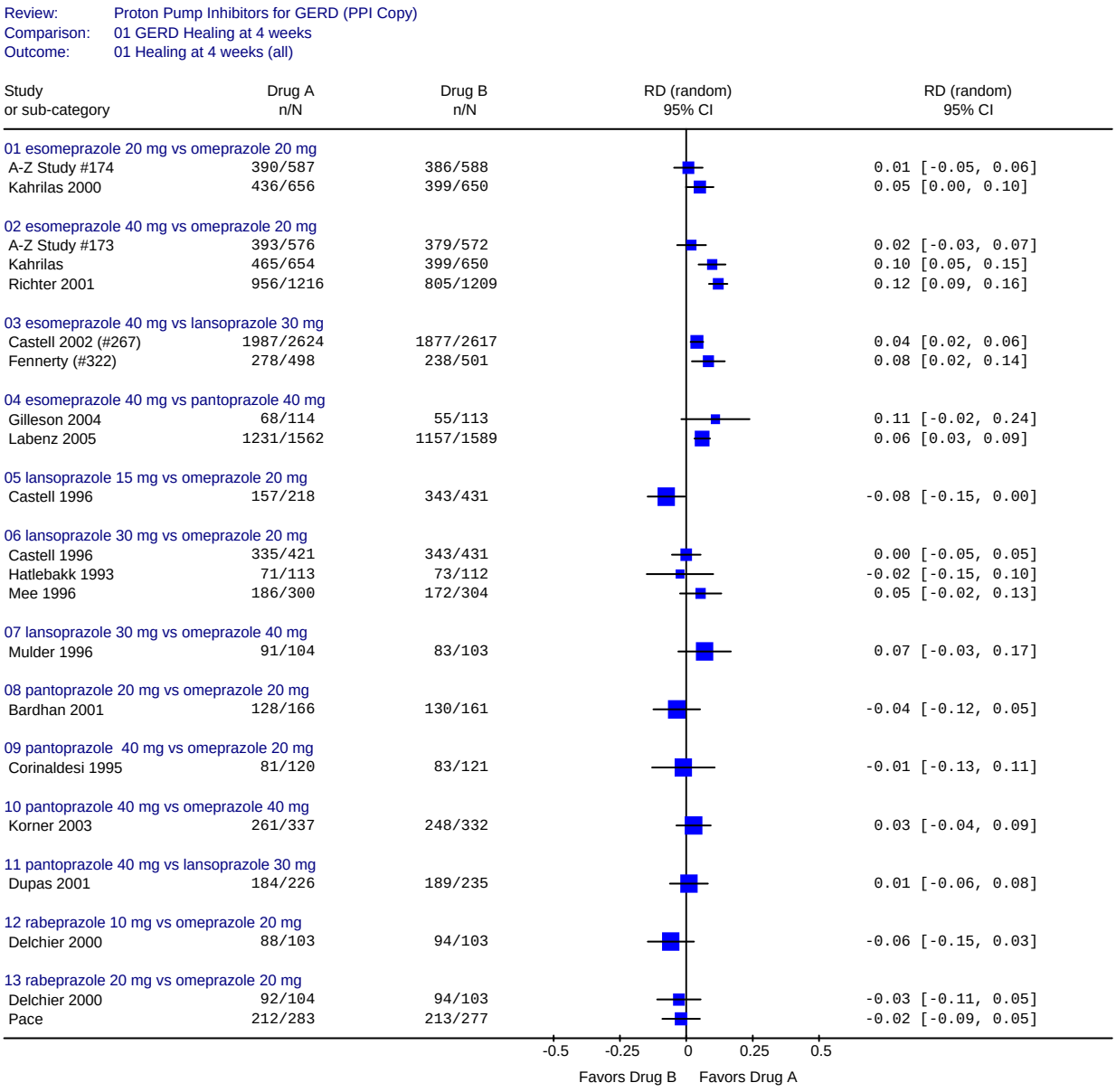


Figure 2. Esophagitis healing rates at 8 weeks in head-to-head trials of PPIs (risk difference, 95% CI)

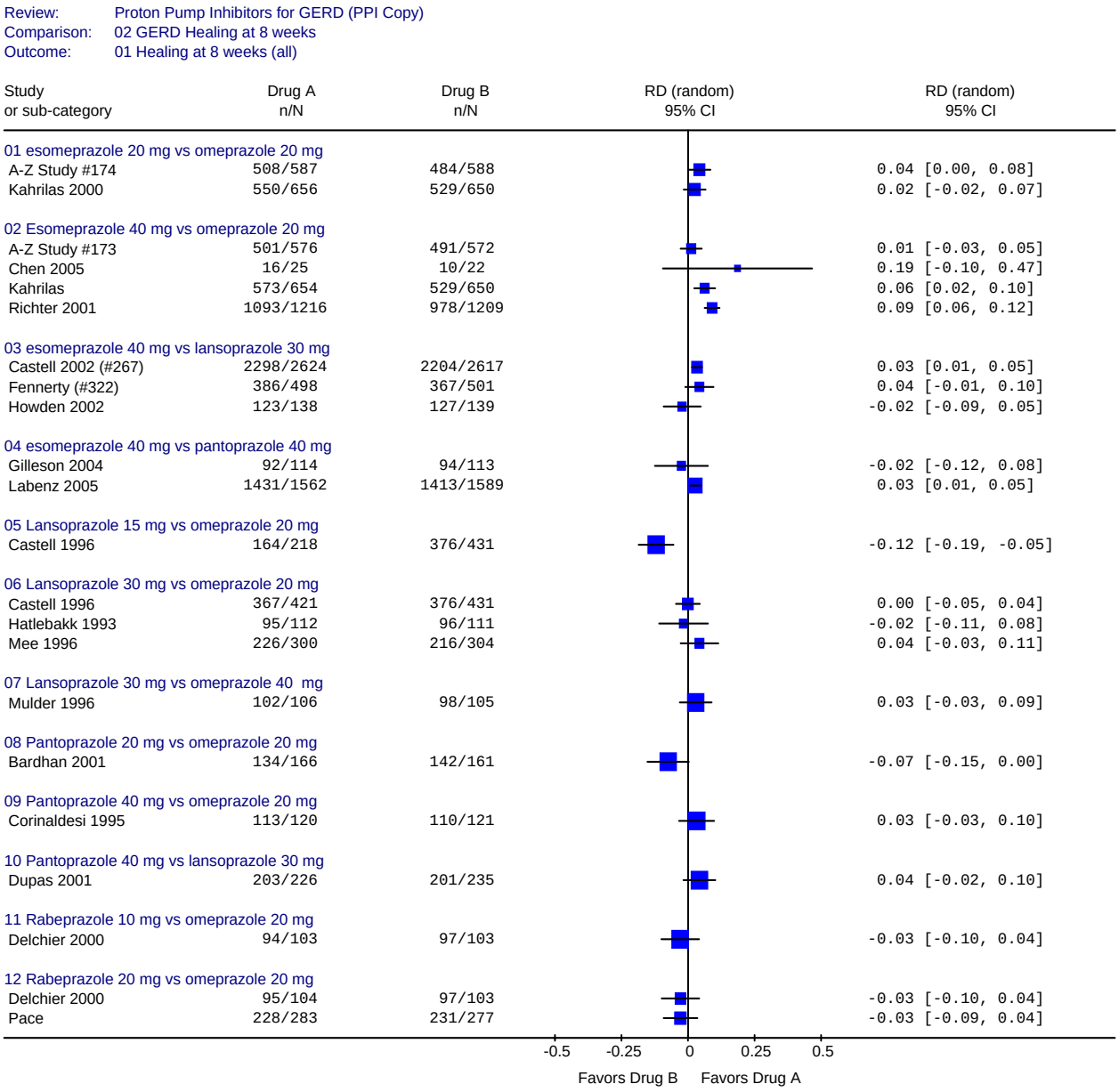


Figure 3. Rates of complete resolution of symptoms at 4 weeks in head-to-head trials of PPIs (risk difference, 95% CI)

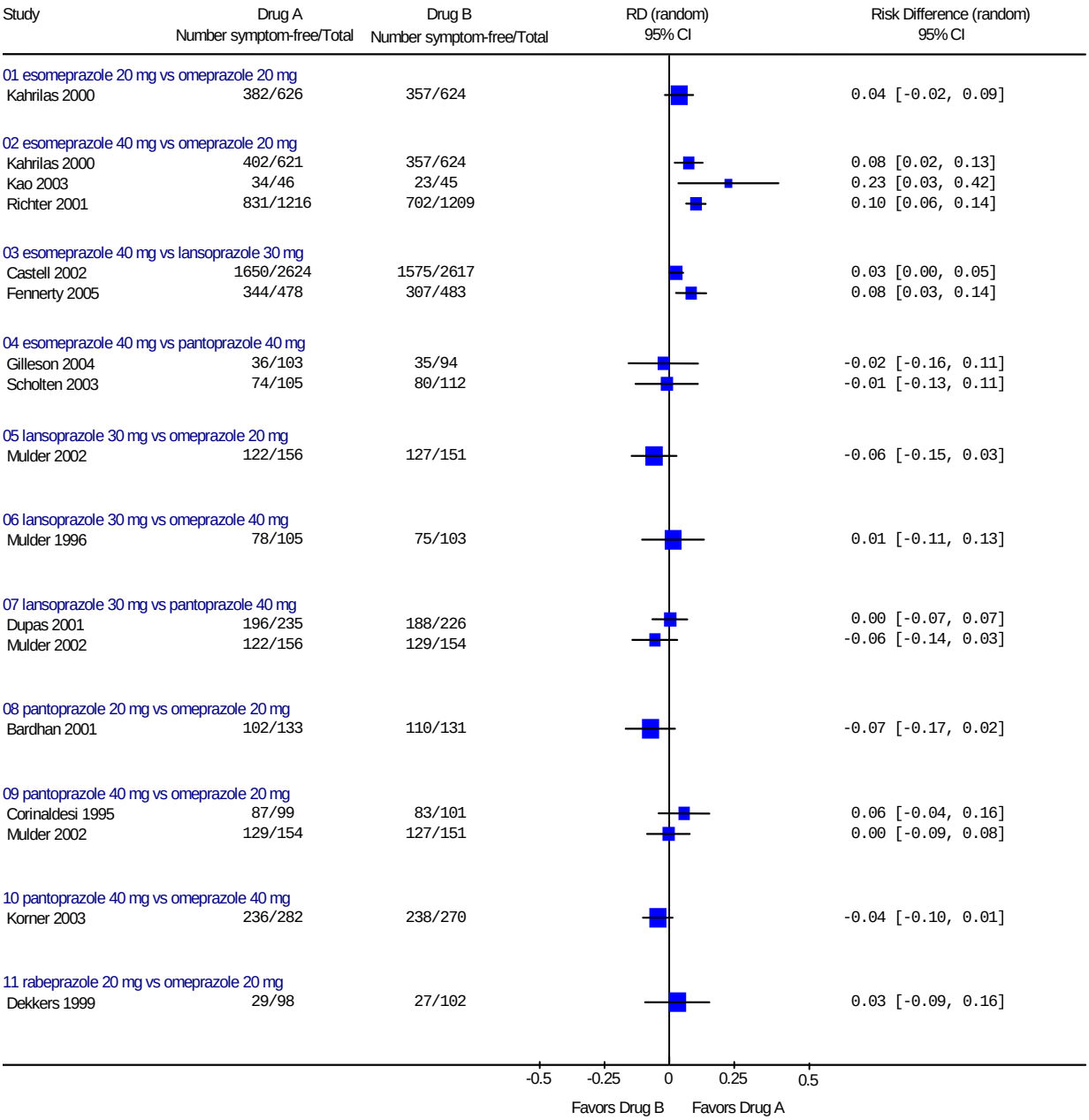


Figure 4. Healing at 4 weeks in patients with moderate to severe esophagitis (risk difference, 95% CI)

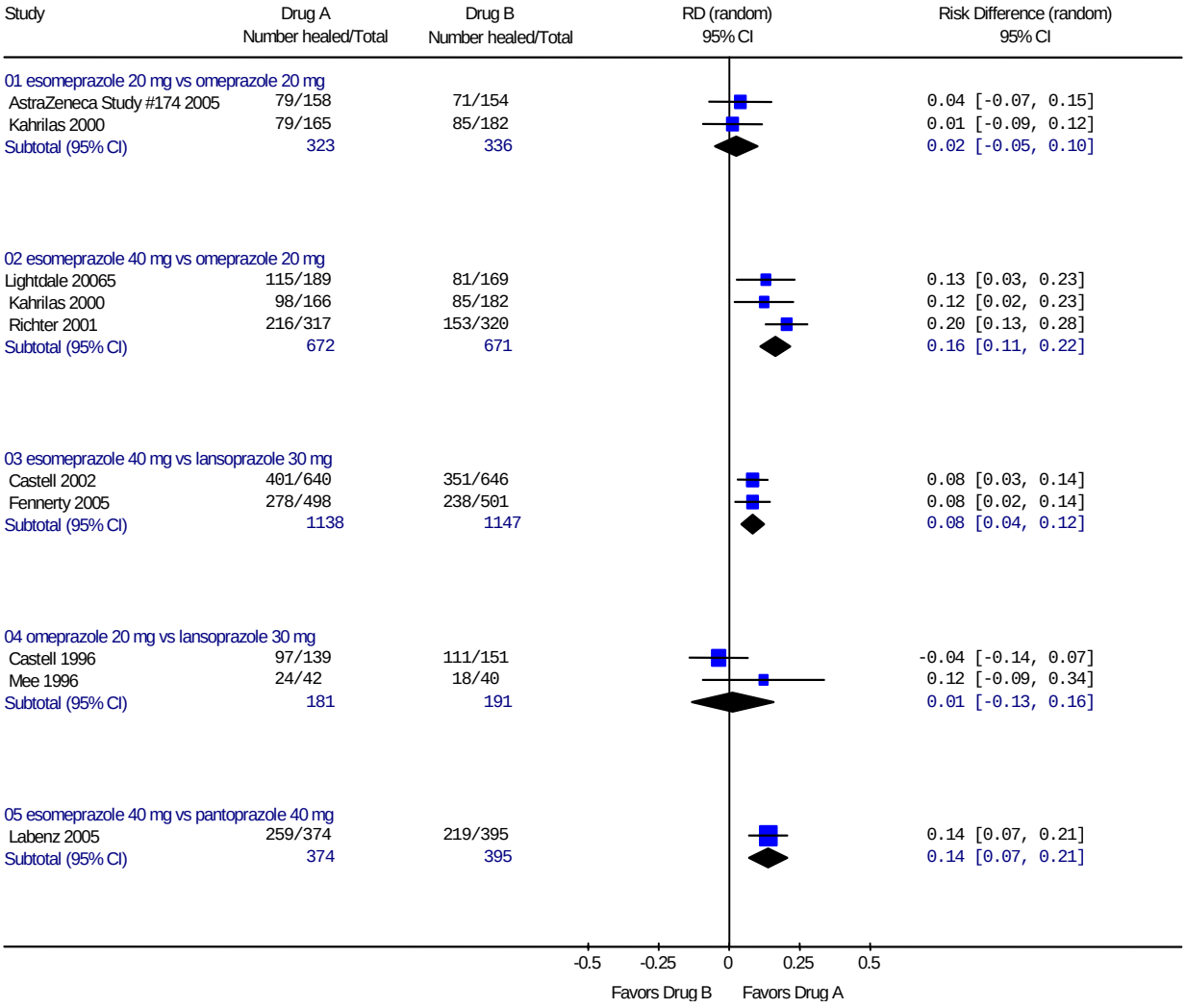


Figure 5. Healing at 8 weeks in patients with moderate to severe esophagitis (risk difference, 95% CI)

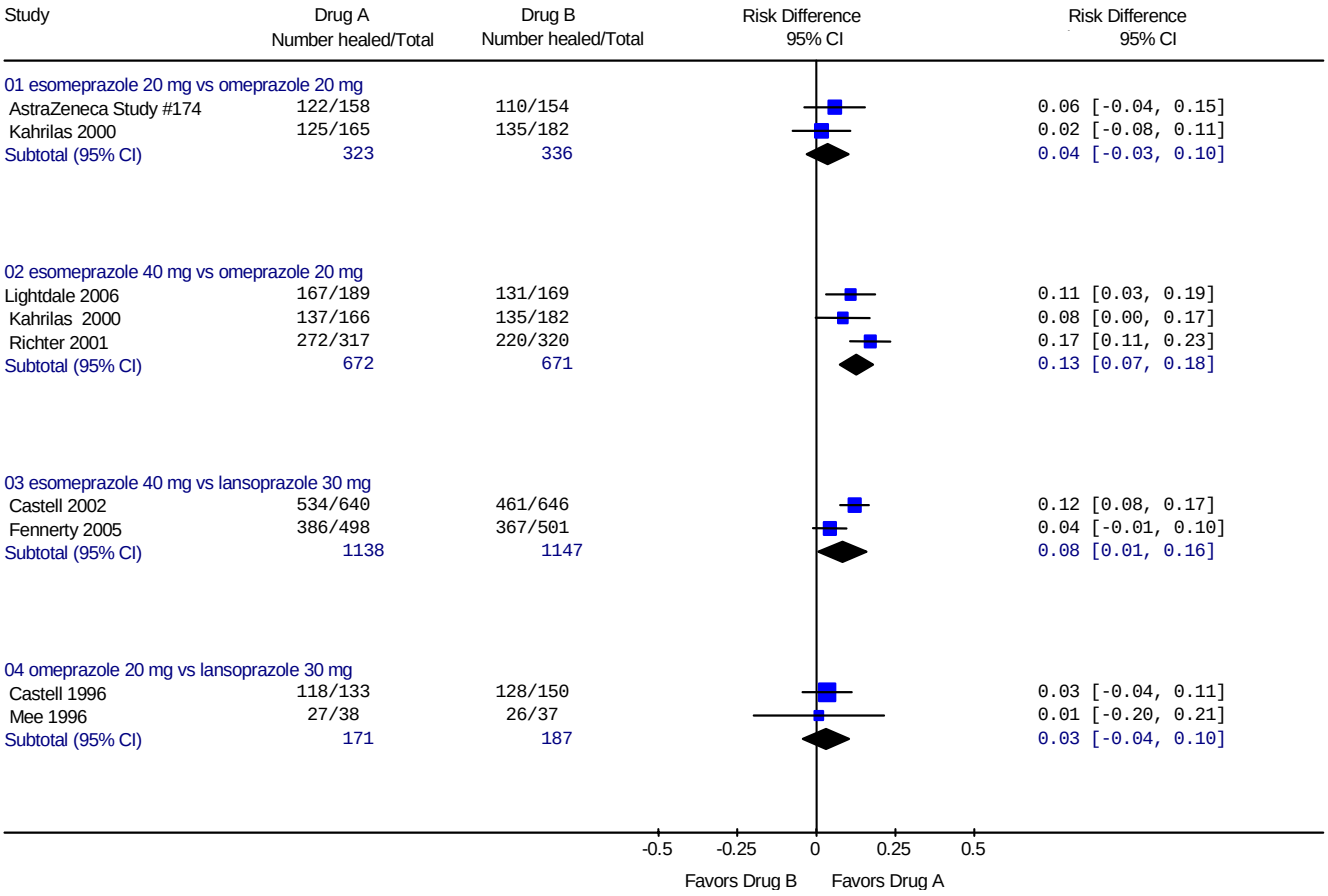
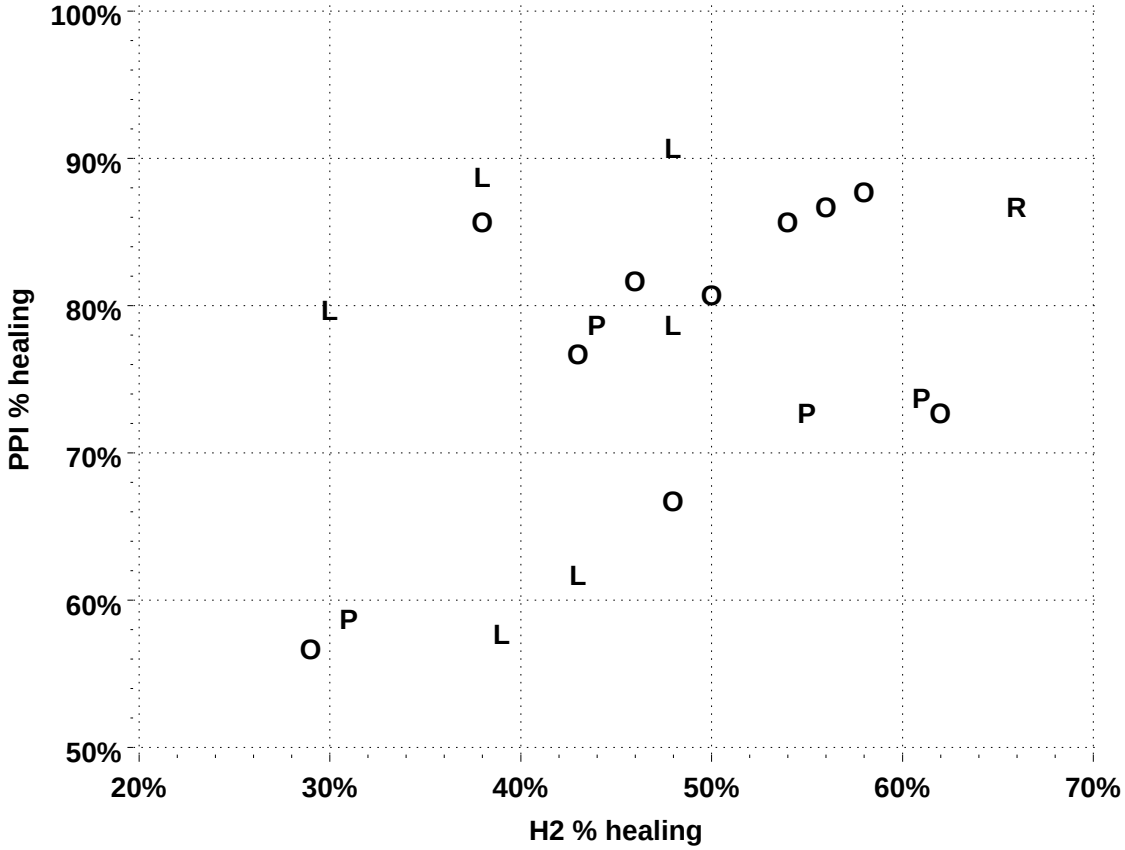


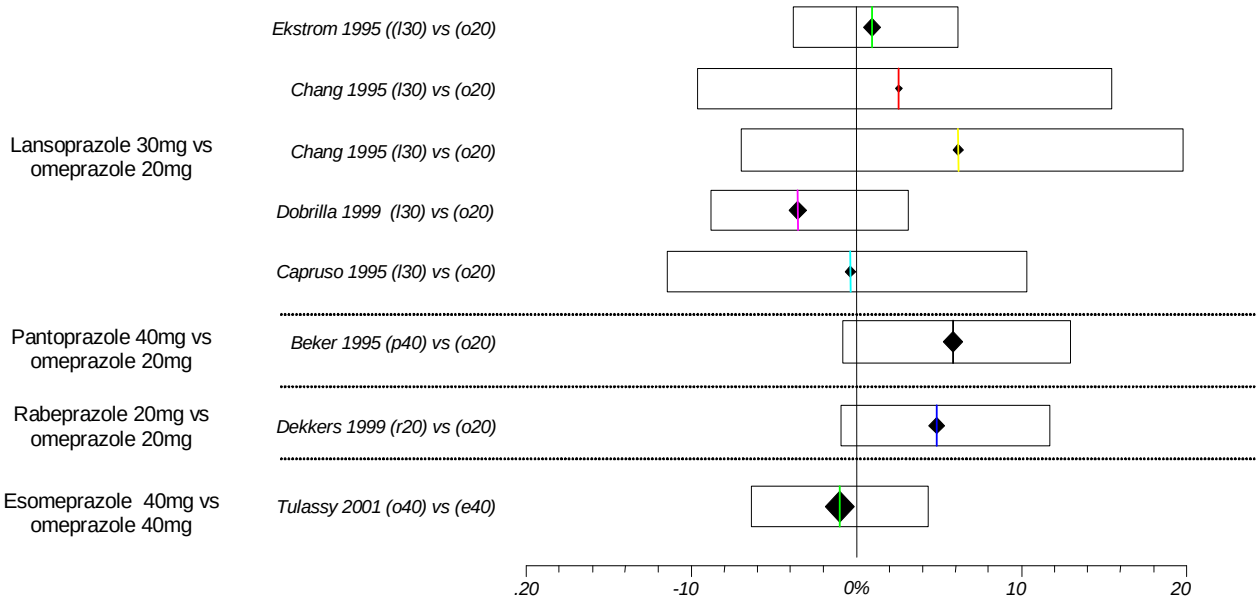
Figure 6. PPI vs. H2 Receptor antagonists for esophagitis healing at 8 weeks: results of 22 randomized controlled trials



Estimated healing rate	Mean	95% CrI	
Lansoprazole	78.8%	69.7%	86.4%
Omeprazole	79.3%	72.2%	85.3%
Pantoprazole	71.2%	59.0%	81.4%
Rabeprozole	85.6%	67.9%	95.4%

Difference between PPIs	Mean difference	95% CrI	
Lansoprazole vs Omeprazole	-0.5%	-11.6%	10.0%
Lansoprazole vs Pantoprazole	7.5%	-5.9%	22.1%
Lansoprazole vs Rabeprazole	-6.9%	-20.5%	12.2%
Omeprazole vs Pantoprazole	8.1%	-4.3%	21.7%
Omeprazole vs Rabeprazole	-6.4%	-18.9%	12.2%
Pantoprazole vs Rabeprazole	-14.4%	-30.4%	5.5%

Figure 7. Duodenal ulcer healing at 4 weeks: PPI vs PPI (% risk difference)



Study	Risk difference (%) (95% CI)
Lansoprazole 30mg vs omeprazole 20mg once daily	
Ekstrom 1995	0.96 (-3.80, 6.15)
Chang 1995	2.55 (-9.62, 15.5)
Chang 1995	6.14 (-7.0, 20)
Dobrilla 1999	-3.57 (-8.84, 3.14)
Capruso 1995	-0.34 (-11.41, 10.32)
	Pooled risk difference = -0.2 (95% CI -3.0, 2.6)
Pantoprazole 40mg vs omeprazole 20mg once daily	
Beker 1995	5.85 (-0.84, 12.95)
Rabeprazole 20mg vs omeprazole 20mg once daily	
Dekkers 1999	4.84 (-0.96, 11.70)
Esomeprazole 40mg vs omeprazole 40mg once daily	
Tullassay 2001	-0.97 (-6.4, 4.35)

Figure 8. PPI vs. H2 Receptor antagonists for duodenal ulcer healing at 4 weeks

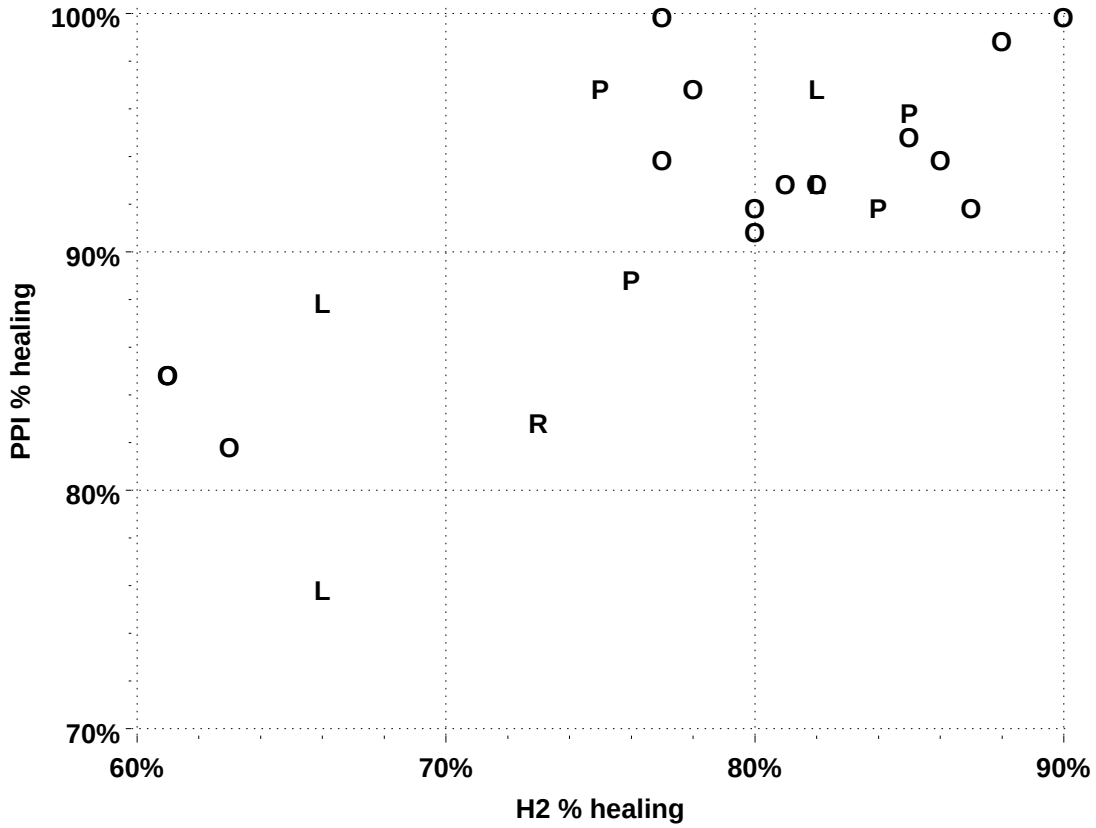


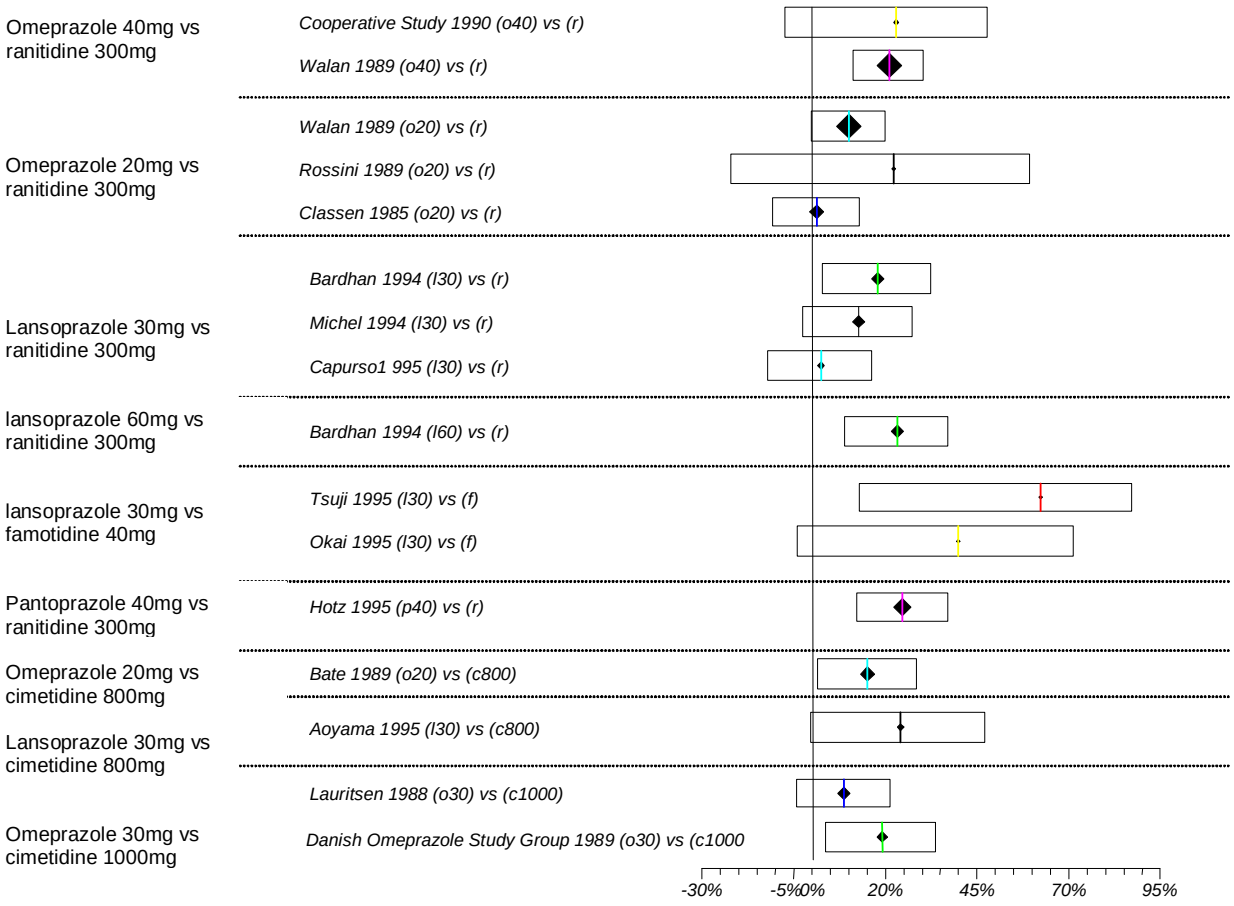
Figure 8. PPI vs. H2 Receptor antagonists for duodenal ulcer healing at 4 weeks (continued)

Duodenal ulcer healing rate at 4 weeks

Estimated healing rate	when H2 healing is…	Mean	95% CrI	
Lansoprazole	60%	73.3%	55.8%	86.9%
	73%	89.6%	85.0%	93.5%
	80%	93.9%	89.5%	97.1%
	90%	97.0%	92.6%	99.3%
Omeprazole	60%	82.6%	75.5%	88.7%
	73%	90.9%	88.7%	93.1%
	80%	93.7%	91.9%	95.4%
	90%	96.3%	94.5%	97.8%
Pantoprazole	—	93.9%	90.9%	96.2%
Rabeprozole	—	82.6%	70.9%	91.1%

Difference between PPIs	when H2 healing is…	Mean difference	95% CrI	
Lansoprazole vs Omeprazole	60%	-9.3%	-28.1%	6.1%
	80%	0.2%	-4.6%	3.8%
	90%	0.8%	-4.0%	3.8%
Lansoprazole vs Pantoprazole	80%	0.0%	-5.0%	4.4%
Lansoprazole vs Rabeprazole	73%	7.0%	-2.5%	19.3%
Omeprazole vs Pantoprazole	80%	-0.2%	-3.1%	3.3%
Omeprazole vs Rabeprazole	73%	8.3%	-0.2%	20.3%
Pantoprazole vs Rabeprazole	—	11.3%	2.4%	23.2%

Figure 9. Gastric ulcer: PPI vs H2-Antagonist healing at 4 weeks (% risk difference)



Study	Risk difference (%) (95% CI)
Cooperative Study 1990 (o40) vs(r)	22.92% (-7.50%, 47.83%)
Walan 1989 (o40) vs (r)	21.02%(11.31%, 30.37%)
Walan 1989 (o20) vs (r)	9.97% (-0.19%, 19.92%)
Rossini 1989 (o20) vs (r)	22.22% (-22.28%, 59.36%)
Classen 1985 (o20) vs (r)	1.09% (-10.66%, 12.83%)
Bardhan 1994 (l30) vs (r)	17.82% (2.82%, 32.26%)
Michel 1994 (l30) vs (r)	12.66% (-2.53%, 27.31%)
Capurso1 995 (l30) vs (r)	2.43% (-12.18%, 16.35%)
Bardhan 1994 (l60) vs (r)	23.22% (8.78%, 37.08%)
Tsuji 1995 (l30) vs (f)	62.50% (12.85%, 87.18%)
Okai 1995 (l30) vs (f)	40.00% (-4.08%, 71.22%)
Hotz 1995 (p40) vs (r)	24.67% (12.15%, 37.01%)
Bate 1989 (o20) vs (c800)	15.08% (1.45%, 28.38%)
Aoyama 1995 (l30) vs (c800)	24.06% (-0.38%, 47.17%)
Lauritsen 1988 (o30) vs (c1000)	8.56% (-4.24%,21.27%)
Danish Omeprazole Study Group 1989 (o30) vs (c1000mg)	19.07% (3.49%, 33.82%)

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 (gastrooesophageal 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" (409)
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)

1. Achem, SR, Kolts, BE, MacMath, T, et al. Effects of omeprazole versus placebo in treatment of noncardiac chest pain and gastroesophageal reflux. *Digestive Diseases & Sciences.* 1997;42:2138-45.

2. Avner, DL, Dorsch, ER, Jennings, DE, et al. A comparison of three doses of lansoprazole (15, 30 and 60 mg) and placebo in the treatment of duodenal ulcer. The Lansoprazole Study Group. *Alimentary Pharmacology & Therapeutics.* 1995;9:521-8.

3. Avner, DL, Movva, R, Nelson, KJ, et al. Comparison of once daily doses of lansoprazole (15, 30, and 60 mg) and placebo in patients with gastric ulcer. *American Journal of Gastroenterology.* 1995;90:1289-94.

4. Bate, CM, Booth, SN, Crowe, JP, et al. Omeprazole 10 mg or 20 mg once daily in the prevention of recurrence of reflux oesophagitis. Solo Investigator Group. *Gut.* 1995;36:492-8.

5. Birbara, C, Breiter, J, al., e. Rabeprazole for the prevention of recurrent erosive or ulcerative gastro-esophageal reflux disease. *European Journal of Gastroenterology & Hepatology.* 2000;12:889-97.

6. Borjesson M, Rolny P, Mannheimer C, Pilhall M. Nutcracker oesophagus: a double-blind, placebo-controlled, cross-over study of the effects of lansoprazole. *Alimentary Pharmacology & Therapeutics.* 2003;18(11-12):1129-1135.

7. Bytzer P, Blum A, De Herdt D, Dubois D. Six-month trial of on-demand rabeprazole 10 mg maintains symptom relief in patients with non-erosive reflux disease. *Aliment Pharmacol Ther.* 2004;20(2):181-188.

8. de Muckadell O, Havelund T, Harling H, et al. The effect of omeprazole on the outcome of endoscopically treated bleeding peptic ulcers: a randomized double-blind placebo-controlled multicentre study. *The Netherlands Journal of Medicine.* Vol. 1996;48:A3-A4.

9. Dean BB, Gano Jr. AD, Knight K, Ofman JJ, Fass R. Effectiveness of proton pump inhibitors in nonerosive reflux disease. *Clinical Gastroenterology and Hepatology.* 2004;2(8):656-664.

10. Dehesa M, Larisch J, Dibildox M, et al. Comparison of 2 schedules based on pantoprazole for eradication of Helicobacter pylori in patients with active duodenal ulcer. *Rev Gastroenterol Mex.* 1998;63(2):66-71.

11. Dent, J, Hetzel, DJ, MacKinnon, MA, et al. Evaluation of omeprazole in reflux oesophagitis. *Scandinavian Journal of Gastroenterology - Supplement* 1989;166:76-82; discussion 94.

12. Dent, J. Australian clinical trials of omeprazole in the management of reflux oesophagitis. *Digestion.* 1990;47:69-71.

13. Deviere J, Costamagna G, Neuhaus H, et al. Nonresorbable copolymer implantation for gastroesophageal reflux disease: a randomized sham-controlled multicenter trial. *Gastroenterology.* 2005;128(3):532-540.

14. Earnest, DL, Dorsch, E, Jones, J, et al. A placebo controlled dose ranging study of lansoprazole in the management of reflux esophagitis. *American Journal of Gastroenterology.* 1998;93:238-43.

15. Feng LY, Yao XX, Jiang SL. Effects of killing Helicobacter pylori quadruple therapy on peptic ulcer: a randomized double-blind clinical trial. *World journal of gastroenterology* : WJG. 2005;11(7):1083-1086.

16. Gardner JD, Rodriguez-Stanley S, Robinson M, Miner Jr PB. Cisapride inhibits meal-stimulated gastric acid secretion and post-prandial gastric acidity in subjects with gastro-oesophageal reflux disease. *Alimentary pharmacology & therapeutics.* 2002;16(10):1819-1829.

17. Graham DY, McCullough A, Sklar M, Sontag SJ, Roufail WM, Stone RC, et al. Omeprazole versus placebo in duodenal ulcer healing. The United States experience. *Digestive Diseases & Sciences.* 1990;35(1):66-72.

18. Graham, D.Y., N.M. Agrawal, D.R. Campbell, M.M. Haber, C. Collis, N.L. Lukasik, B. Huang, and N.S.-A.G.U.P.S. Group, Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs: results of a double-blind, randomized, multicenter, active- and placebo-controlled study of misoprostol vs lansoprazole. *Archives of Internal Medicine.* 2002;162(2): p. 169-75.

19. Havelund, T, Laursen, LS, Lauritsen, K. Efficacy of omeprazole in lower grades of gastro-oesophageal reflux disease. *Scandinavian Journal of Gastroenterology - Supplement* 1994;201:69-73.

20. Hawkey C, Talley NJ, Yeomans ND, et al. Improvements with esomeprazole in patients with upper gastrointestinal symptoms taking non-steroidal antiinflammatory drugs, including selective COX-2 inhibitors. *The American journal of gastroenterology.* 2005;100(5):1028-1036.

21. Henry D, Brent P, Whyte I, Mihaly G, Devenish-Meares S. Propranolol steady-state pharmacokinetics are unaltered by omeprazole. *European journal of clinical pharmacology.* 1987;33(4):369-373.

22. Hetzel, DJ, Dent, J, Reed, WD, et al. Healing and relapse of severe peptic esophagitis after treatment with omeprazole. *Gastroenterology.* 1988;95:903-12.

23. Howden CW, Kenyon CJ, Beastall GH, Reid JL. Inhibition by omeprazole of adrenocortical response to ACTH: clinical studies and experiments on bovine adrenal cortex in vitro. *Clinical science* (London, England :. 1986;1979) 70(1):99-102.

24. Johnson DA, Orr WC, Crawley JA, et al. Effect of esomeprazole on nighttime heartburn and sleep quality in patients with GERD: a randomized, placebo-controlled trial. *American Journal of Gastroenterology.* Sep 2005;100(9):1914-1922.

25. Johnsson, F, Weywadt, L, Solhaug, JH, et al. One-week omeprazole treatment in the diagnosis of gastro-oesophageal reflux disease. *Scandinavian Journal of Gastroenterology.* 1998;33:15-20.

26. Karateev AE, Murav'ev Iu V, Radenska-Lopovok SG, Nasonova VA. Efficacy of antihelicobacter therapy in NSAID-induced gastropathies. *Klin Med.* 2003;81(8):37-41.

27. Kaviani, M.J., M.R. Hashemi, A.R. Kazemifar, S. Roozitalab, A.A. Mostaghni, S. Merat, M. Alizadeh-Naini, and H. Yarmohammadi, Effect of oral omeprazole in reducing re-bleeding in bleeding peptic ulcers: a prospective, double-blind, randomized, clinical trial. *Alimentary Pharmacology & Therapeutics.* 2003;17(2): p. 211-6.

28. Lai, K.C., S.K. Lam, K.M. Chu, W.M. Hui, K.F. Kwok, B.C. Wong, H.C. Hu, W.M. Wong, O.O. Chan, and C.K. Chan, Lansoprazole reduces ulcer relapse after eradication of Helicobacter pylori in nonsteroidal anti-inflammatory drug users--a randomized trial. *Alimentary Pharmacology & Therapeutics.* 2003;18(8): p. 829-36.

29. Laursen, LS, Havelund, T, Bondesen, S, et al. Omeprazole in the long-term treatment of gastro-oesophageal reflux disease. A double-blind randomized dose-finding study. *Scandinavian Journal of Gastroenterology.* 1995;30:839-46.

30. Lepsch M, Strayer S. Omeprazole and placebo have same long-term effect on dyspepsia. *Journal of Family Practice.* 2003;52(9):687-688.

31. Li Ying F, Xin Peng G, Shu Ting H, Xi Xian Y. Randomized double-blind controlled study of killing hp quadruple therapy on peptic ulcer and quality of ulcer healing. *World Chinese Journal of Digestology.* 2000;8(6):678-680.

32. Littner MR, Leung FW, Ballard ED, 2nd, Huang B, Samra NK, Lansoprazole Asthma Study G. Effects of 24 weeks of lansoprazole therapy on asthma symptoms, exacerbations, quality of life, and pulmonary function in adult asthmatic patients with acid reflux symptoms. *Chest.* Sep 2005;128(3):1128-1135.

33. Lundell L. New information relevant to long-term management of endoscopy-negative reflux disease. *Alimentary Pharmacology and Therapeutics, Supplement.* 1997;11(2):93-98.

34. Marzio, L., L. Cellini, and D. Angelucci, Triple therapy for 7 days vs. triple therapy for 7 days plus omeprazole for 21 days in treatment of active duodenal ulcer with Helicobacter pylori infection. *Digestive & Liver Disease.* 2003;35(1): p. 20-3.

35. Orr WC, Goodrich S, Robert J. The effect of acid suppression on sleep patterns and sleep-related gastro-oesophageal reflux. *Alimentary pharmacology & therapeutics.* Jan 15 2005;21(2):103-108.

36. Peura DA, Kovacs TO, Metz DC, Siepman N, Pilmer BL, Talley NJ. Lansoprazole in the treatment of functional dyspepsia: two double-blind, randomized, placebo-controlled trials. *American Journal of Medicine.* 2004;116(11):740-748.

37. Pilotto, A., G. Leandro, M. Franceschi, Ageing, and G. Acid-Related Disease Study, Short- and long-term therapy for reflux oesophagitis in the elderly: a multi-centre, placebo-controlled study with pantoprazole. *Alimentary Pharmacology & Therapeutics.* 2003;17(11): p. 1399-406.

38. Richter, JE, Bochenek, W, Group, PUGS. Oral pantoprazole for erosive esophagitis: a placebo-controlled, randomized clinical trial. *American Journal of Gastroenterology.* 2000;95:3071-80.

39. Robinson, M, Lanza, F, Avner, D, et al. Effective maintenance treatment of reflux esophagitis with low dose lansoprazole. A randomized, double blind, placebo controlled trial. *Annals of Internal Medicine.* 1996;124:859-67.

40. Schenk, BE, Kuipers, EJ, Klinkenberg-Knol, EC, et al. Omeprazole as a diagnostic tool in gastroesophageal reflux disease. *American Journal of Gastroenterology.* 1997;92:1997-2000.

41. Sgouros SN, Vlachogiannakos J, Karamanolis G, et al. Long-term acid suppressive therapy may prevent the relapse of lower esophageal (Schatzki's) rings: a prospective, randomized, placebo-controlled study. *American Journal of Gastroenterology.* Sep 2005;100(9):1929-1934.

42. Sloan S. Rabeprazole-based therapy in the management of symptomatic gastroesophageal reflux disease. *American Journal of Gastroenterology.* 2003;98(3 Suppl).

43. Sontag, SJ, Hirschowitz, BI, Holt, S, et al. Two doses of omeprazole versus placebo in symptomatic erosive esophagitis: The US multicenter study. *Gastroenterology.* 1992;102:109-118.

44. Sontag, SJ, Kogut, DG, Fleischmann, R, et al. Lansoprazole prevents recurrence of erosive reflux esophagitis previously resistant to H2-RA therapy. The Lansoprazole Maintenance Study Group. *American Journal of Gastroenterology.* 1996;91:1758-65.

45. Steward DL, Wilson KM, Kelly DH, et al. Proton pump inhibitor therapy for chronic laryngo-pharyngitis: a randomized placebo-control trial. Otolaryngology--head and neck surgery : *official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2004;131(4):342-350.

46. Stordal K, Johannesdottir GB, Bentsen BS, et al. Acid suppression does not change respiratory symptoms in children with asthma and gastro-oesophageal reflux disease. *Archives of Disease in Childhood.* Sep 2005;90(9):956-960.

47. Sugimoto M, Furuta T, Shirai N, et al. Different dosage regimens of rabeprazole for nocturnal gastric acid inhibition in relation to cytochrome P450 2C19 genotype status. *Clin Pharmacol Ther.* 2004;76(4):290-301.

48. Vakil, NB, Shaker, R, Johnson, DA, et al. The new proton pump inhibitor esomeprazole is effective as a maintenance therapy in GERD patients with healed erosive oesophagitis: A 6-month, randomized, double-blind, placebo-controlled study of efficacy and safety. *Alimentary Pharmacology & Therapeutics.* 2001;15:927-935.

49. Veldhuyzen Van Zanten, S., S. Machado, and J. Lee, One-week triple therapy with esomeprazole, clarithromycin and metronidazole provides effective eradication of Helicobacter pylori infection. *Alimentary Pharmacology & Therapeutics.* 2003;17(11): p. 1381-7.

50. Venables, TL, Newland, RD, Patel, AC, et al. Maintenance treatment for gastro-oesophageal reflux disease. A placebo-controlled evaluation of 10 milligrams omeprazole once daily in general practice. *Scandinavian Journal of Gastroenterology.* 1997;32:627-32.

51. Voderholzer WA, Klauser AG, Muhldorfer BE, Muller-Lissner SA. Effect of gastric secretory inhibitors and cisapride on gastric volume in healthy volunteers. *Eur J Gastroenterol Hepatol.* 1992;4(8):635-638.

52. Wheeldon, T.U., T.T. Hoang, D.C. Phung, A. Bjorkman, M. Granstrom, and M. Sorberg, Helicobacter pylori eradication and peptic ulcer healing: the impact of deleting the proton pump inhibitor and using a once-daily treatment. *Alimentary Pharmacology & Therapeutics.* 2003;18(1): p. 93-100.

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.

2. Andersson, T, Rohss, K, Hassan-Alin, M, et al. Pharmacokinetics (PK) and dose-response relationship of esomeprazole (E) abstract. *Gastroenterology.* 2000;118:A1210.

3. Anonymous. Comparison of two doses of intravenous pantoprazole in peptic ulcer bleeding. *Gut.* 1999;45(Suppl V):A104.

4. Anonymous. Therapeutic efficacy and tolerance of AG17-19 in duodenal ulcer patients: a multicentre, randomized, double blind, dose finding and comparative study versus rantidine. Multicentre study in West Germany. *Gut.* 1989;30:A725.

5. Arkkila, et al., Safety of peptic ulcer treatment with only helicobacter pylori eradication without the following proton pump. *Gut.* 2000. 47(Suppl III).

6. Athmann, C, Mander, I, Brunner, G, et al. Histology and safety parameters during long-term maintenance with pantoprazole in sever acid-peptic disease. *Gastroenterology.* 1998;114:A60.

7. Baisley, K., et al., Rabeprazole 20mg compared with esomeprazole 40mg in the control of intragastric pH in healthy volunteers. *Gut.* 2002. 50(Suppl 2): p. A63 Abs 229.

8. Baldi, F, Bardhan, KD, Borman, BC, et al. Lansoprazole maintains healing in patients with reflux esophagitis. *Gastroenterology.* 1996;110:A55.

9. Barbara L, Saggioro A, Olsson J, Cisternino M, Franceschi M. Omeprazole 20 mg om and ranitidine 150 mg bd in the healing of benign gastric ulcers - an Italian multicentre study. *Gut.* Vol. 1341;28.

10. Bardhan KD, Naesdal J, Bianchi-Porro G, et al. Treatment of refractory peptic ulcer with omeprazole. *Gut.* 1988;29(Suppl 5):A724.

11. Bardhan, KD, Crowe, J, Thompson, RPH, et al. Lansoprazole vs ranitidine maintenance treatment for prevention of duodenal ulcer relapse. *Gastroenterology.* 1996;110:A135.

12. Bardhan, KD, Long, R, Hawkey, CJ, et al. Lansoprazole, a new proton pump blocker, vs. ranitidine in the treatment of reflux erosive esophagitis. *Gastroenterology.* 1991;100:A30.

13. Bate CM, Bradby GVH, Wilkinson SP, et al. Omeprazole provides faster ulcer healing and symptom relief than cimetidine in the treatment of gastric ulcer. *Gut.* 1988;29(Suppl 10):A1440.

14. Bate CM, Green JRB, Axon ATR, et al. Omeprazole Is More Effective than Cimetidine in the Prevention of Recurrence of GORD-Associated Heartburn and the Occurrence of Underlying Oesophagitis. *Gut.* Vol. 1996;39(3).

15. Baxter, G., K. Eriksson, and L.-G. Nilsson, Lansoprazole 15 mg provided as effective acid control as esomeprazole 20mg. *Gut.* 2001. 49(Suppl III): p. abstract 2430.

16. Bayerdorffer, E., et al., Effective one-week triple therapy with esomeprazole, clarithromycin and metronidazole for eradication of Helicobacter pylori in the absence of antimicrobial resistance: a prospective randomized trial. *Gut.* 2002. 51(Suppl III): p. A96, Abs 15.44.

17. Bayerdorffer E, Meining A, Hochter W, et al. Double-blind trial of 80 mg omeprazole and 2250 mg amoxicillin for cure of Helicobacter pylori infection in gastric ulcer patients. *Gut.* Vol. 1995;37(1).

18. Beker, JA, Dekkers, CPM, Thjodleifsson, B, et al. Rabeprazole sodium 20 mg once daily is similar to omeprazole 20 mg once daily in the healing of active duodenal ulcer. *Gastroenterology.* 1997;112:A70.

19. Benhaim, MC, Evreux, M, Salducci, J, et al. Lansoprazole and ranitidine in treatment of reflux oesphagitis: double blind comparative trial. *Gastroenterology.* 1990;98:A20.

20. Bishop, AE, Romanska, H, Polak, JM, et al. Effect of long-term maintenance with pantoprazole on serum gastrin and histology parameters in sever acid-peptic disease. *Gastroenterology.* 1998;114:A75.

21. Breiter, J, Birbara, C, Niecestro, R, et al. Rabeprazole prevents recurrence of pathology and symptoms in patients with healed erosive or ulcerative gastroesophageal reflux disease. *Gastroenterology.* 1999;116:A128.

22. Brunner, G, Creutzfeldt, W, Harke, U, et al. Efficacy and safety of long-term treatment with omeprazole in patients with acid related diseases resistant to ranitidine. *Canadian Journal of Gastroenterology.* 1989;3:72A-76A.

23. Buchner, M, Carro, GP, Dietrich, K, et al. Comparison of 20mg pantoprazole s.i.d. and 200 ug misoprostol b.i.d. in the prevention of the development of gastrointestinal lesions in rheumatic patients with continuous NSAID intake. *Digestive Diseases.* 2001;1658:A609.

24. Caos, A, Lanza, F, Humphries, TJ. Rabeprazole heals gastric ulcers, relieves pain and decreases indirect health care costs. *Gut.* 1999;44:A125.

25. Carling, L, Axelsson, CK, Forsell, H, et al. Lansoprazole versus omeprazole in long term maintenance treatment of reflux oesophagitis: a Scandinavia multicenter trial. Abstract 1036. *Gut.* 1996;39:A182.

26. Castell, D.O., et al., Sustained heartburn resolution is a good predictor of subsequent symptom status in GERD patients with erosive esophagitis. *Gastroenterology.* 2002. 122(4 Suppl 1): p. A467, Abs T1495.

27. Castell, DO, Kahrilas, PJ, Johnson, DA, et al. Esomeprazole provides more effective healing than lansoprazole in GERD patients with erosive esophagitis (EE). *American Journal of Gastroenterology.* 2001;96:S6.

28. Castell, DO, Kahrilas, PJ, Richter, JE, et al. Esomeprazole is more effective than lasnoprazole for treating daily and nocturnal heartburn in GERD patients with erosive esophagitis (EE). *American Journal of Gastroenterology.* 2001;96:S6.

29. Chand, N., D.A. Johnson, and M. Tabangin, Sleep disturbance in patients with erosive esophagitis: effects of treatment with esomeprazole. *American Journal of Gastroenterology.* 2002. 97(9 Suppl S): p. S32, Abs 95.

30. Classen M, Dammann HG, Domscke W, et al. Omeprazole heals duodenal, but not gastric, ulcers more rapidly than ranitidine. *Gut.* Vol. 1985;26.

31. Cloud, ML, Olovich, K, Enas, N, et al. Ly307640 versus placebo in healing duodenal ulcers. *Gastroenterology.* 1995;108:A73.

32. Cloud, ML, Olovich, K, Enas, N. Ly307640 versus placebo in healing erosive, ulcerative reflux esophagitis. *Gastroenterology*. 1995;108:A73.

33. Cremer M, the International Multicenter G. A controlled, double-blind comparison between omeprazole and ranitidine in the treatment of benign gastric ulcer. *Acta Gastroenterologica Belgica.* 1988;51(2):A2.

34. Dekkers, CPM, Beker, JA, Thjodleifson, B, et al. Rabeprazole sodium 20 mg once daily is similar to omeprazole 20 mg once daily in the healing of active gastric ulcer. *Gastroenterology.* 1997;112:A99.

35. Delchier JC, Cohen G, Humphries TJ. Rabeprazole is comparable in efficacy to omeprazole in erosive GERD and provides more rapid heartburn. *Gut.* 1999;45(Suppl V):A41.

36. Delchier, JC, G, C, Humphries, T. Rabeprazole is comparable in efficacy to omeprazole in erosive GORD and provides more rapid heartburn relief. *Gut.*
37. Dent, J, Klinkenberg-Knol, EC, Elm, G, et al. Omeprazole in the long term management of patients with reflux oesophagitis refractory to histamine H2 receptor antagonists. *Gastroenterology International.* 1998;1:A30.

38. de Muckadell O, Havelund T, Harling H, et al. The effect of omeprazole on the outcome of endoscopically treated bleeding peptic ulcers: a randomized double-blind placebo-controlled multicentre study. *The Netherlands Journal of Medicine.* Vol. 1996;48:A3-A4.

39. DeVault, K.R., S. Zuckerman, and J.G. Levine, Influence of symptom duration on baseline severity of erosive esophagitis and response to treatment with esomeprazole or omeprazole. *American Journal of Gastroenterology.* 2002. 97(9 Suppl S): p. S19-S20, Abs 58.

40. DeVault, KR, Fennerty, MB, Hwang, C, et al. Esomeprazole vs omeprazole in GERD patients with erosive esophagitis (EE): influence of baseline heartburn severity. *American Journal of Gastroenterology.* 2001;96:S10.

41. DeVault, KR, Kovacs, TOG, Metz, DC, et al. Pantoprazole relieves nighttime heartburn more effectively than ranitidine in gastroesophageal reflux disease patients with healed erosive esophagitis. *American Journal of Gastroenterology.* 1999;94:2582.

42. Di Mario F, Dal Bo N, Battaglia G, et al. Pantoprazole in eradication of peptic ulcer H Pylori (H Pylori) positive patients: A multicentre randomised prospective study by GISU interdisciplinary. *Gut.* 1999;45(Suppl III):A113.

43. Dohmen, W., W.A.M. Fuchs, and R.E.A. Seelis, Gastro-esophageal reflux disease (GERD): an investigation of efficacy and patients' satisfaction of an "on-demand" therapy- lansoprazole vs. esomeprazole. *Gut.* 2002. 51(Suppl III): p. A224.

44. Eissele, R, Brunner, G, Fisher, B, et al. Evaluation of enterochromaffin-like (ECL) cell hyperplasia during long-term treatment with the proton pump inhibitor lansoprazole. *Gastroenterology.* 1993;104:A74.

45. Eissele, R., G. Gatz, and U. Hole, Pantaprazole 40 mg and esomeprazole 40 mg show equivalent healing rates in patients with GERD. *Gut.* 2002. 51(Suppl III): p. A165.

46. Eriksson, K., G. Baxter, and L.-G. Nilsson, Speed of onset of intragastric acid control. Lansoprazole and esomeprazole compared. *Gut.* 2001. 49(Suppl III): p. Abs 2392.

47. Fennerty, M.B., S. Zuckerman, and J.G. Levine, The impact of duration of GERD symptoms on severity of esophagitis and response to treatment with esomeprazole or lansoprazole. *American Journal of Gastroenterology.* 2002. 97(9 Suppl S): p. S19 Abs 57.

48. Fennerty, MB, Laine, L, Sugg, J, et al. Esomeprazole based triple therapy is more effective than dual therapy for eradication of H pylori. *Gastroenterology.* 2000;118:A495.

49. Florent, C, Forestier, M, Joubert-Collin, M. Lansoprazole versus omeprazole: efficacy and safety in acute gastric ulcer. *Gastroenterology.* 1993;104:A80.

50. Furuta, T, Ohashi, K, Takashima, M, et al. The effect of genetic differences in CYP2C19 on cure rates for Helicobacter pylori by dual therapy with rabeprazole and amoxicillin. *Gastroenterology.* 1999;116:725.

51. Gardner, JD, Rindi, G, Dayal, Y, et al. Evolution of Helicobacter pylori infection, gastritis, and enterochromaffin-like cell hyperplasia in 443 patients with gastroesophageal reflux disease treated for 1 year with rabeprazole or omeprazole. *Gastroenterology.* 1999;116:731.

52. Gardner, JD, Rindi, G, Fiocca, R, et al. Changes in H. pylori infection and accompanying pathology during 4 years of rabeprazole treatment. *Gut.* 1999;45:A116.

53. Gardner, JD, Sloan, S, Barth, JA. Onset, duration, and magnitude of gastric antisecretory effects of rabeprazole and omeprazole. *American Journal of Gastroenterology.* 1999;94.

54. Genta, RM, Magner, DJ, D'Amico, D, et al. Safety of long-term treatment with a new PPI, esomeprazole in GERD patients. *Gastroenterology*. 2000;118:A16.

55. Gunasekaran, R., Fitzgerald J. Pharmacokinetics of lansoprazole in adolescents with GERD. *Journal of Pediatric Gastroenterology & Nutrition.* 2000;31(Suppl 2):S97.

56. Gupta SK, Tolia V, Heyman MB, et al. Adolescent patients with gastroesophageal reflux disease: results from a randomized trial of lansoprazole. *Journal of Pediatric Gastroenterology & Nutrition.* 2000;31(Suppl 2):S97-S98.

57. Hahn, EG, Bossekckert, E, Dammann, HG. Tolerability and safety profile of pantoprazole based on 100,134 patients, results of German Post Marketing Surveillance (PMS) Program. *Gastroenterology.* 1997;112:A138.

58. Harding S, Kiljander SK, Field SK, et al. Efficacy of esomeprazole 40 mg twice daily for 16 weeks in adults with asthma: a randomized placebo-controlled trial. *Gastroenterology.* 2005;128(4 Suppl 2):Abstract 414.

59. Harding S, Kiljander SK, Field SK, et al. Effects of esomeprazole 40 mg twice daily in adults with moderate to severe asthma who had previously been treated with inhaled steroids and long-acting B2 agonists. *Gastroenterology.* 2005;128(4 Suppl 2):Abstract 415.

60. Hassan-Alin, M, Niazi, M, Rohss, K, et al. Esomeprazole, the S-isomer of omeprazole, is optically stable in humans. *Gastroenterology.* 2000;118:A1244-45.

61. Hassan-Alin, M., et al., Bioavailability of omeprazole and its two optical isomers, esomeprazole/S-omeprazole and R-omeprazole in healthy subjects. *Journal of Clinical Pharmacology.* 2002. 42(9): p. 1066, Abs 69.

62. Hawkey, CJ, Atherton, JC, Treichel, HC, et al. Rabeprazole vs omeprazole in 7-day, triple therapy H. pylori eradication regimens for peptic ulcer. *Gut.* 2001;48:A34-A34.

63. Humphries, T, Spera, AC, Breiter, JR, et al. Rabeprazole sodium once daily is superior to ranitidine 150 mg bid in the healing of active duodenal ulcer. *Gastroenterology.* 1997;112:A154.

64. Humphries, TJ, Dekkers, CPM, Beker, JA, et al. Rabeprazole vs omeprazole for maintenance therapy of healed erosive GERD: results of a 1-year multicenter trial. *American Journal of Gastroenterology.* 1998;93:1616.

65. Humphries, TJ, Nardi, RV, Lazar, JD. Drug-drug interaction evaluation of rabeprazole sodium: a clean/expected state? *Gut.* 1996;39:A47.

66. Humphries, TJ, Nardi, RV, Spera, AC, et al. Co-administration of rabeprazole sodium (E3810) does not effect the pharmokinetics of anhydrous theophylline or warfarin. *Gastroenterology.* 1996;110:A138.

67. Humphries, TJ, Spera, AC, Breiter, JR, et al. Rabeprazole sodium (E3810) once-daily is superior to ranitidine 150 mg qid in the healing of erosive or ulcerative gastroesophageal reflux disease. *Gastroenterology.* 1996;110:A139.

68. Humphries, TJ, Thjodleifson, B, C, P. Rabeprazole and omeprazole in long-term maintenance of erosive or ulcerative GERD. *American Journal of Gastroenterology.* 1999;94:A41.

69. Humphries, TJ. A review of the drug-drug interaction potential orabeprazole sodium based on CYP-450 interference or absorption effects. Digestion. 1998;59:776.

70. Jansen, JB, Hazenberg, BP, Tan, TG, et al. Lansoprazole (30 mg) is more effective than high-dose ranitidine (2 x 300 mg) in moderate to severe reflux esophagitis. A Dutch multicenter trial. Gastroenterology. 1996;110:A143.

71. Johnson, D.A. and A. Roach, Esomeprazole pellets are stable following in vitro suspension in common beverages. *American Journal of Gastroenterology.* 2002. 97(9 Suppl): p. S20, Abs 59.

72. Johnson, D.A., et al., Esomeprazole once daily for 6 months is effective therapy for maintaining healed erosive esophagitis and for controlling gastroesophageal reflux disease symptoms: A randomized, double-blind, placebo-controlled study of efficacy and safety. *American Journal of Gastroenterology.* 2001. 96(1).

73. Johnson, D.A., et al., Sustained heartburn resolution during the first four weeks of PPI therapy predicts subsequent healing in GERD patients with erosive esophagitis. *Gastroenterology.* 2002. 122(4 Suppl 2): p. A467, Abs T1494.

74. Johnson, D.A., S. Zuckerman, and J.G. Levine, Impact of age on baseline severity of esophagitis and heartburn, and subsequent healing following treatment with esomeprazole or lansoprazole. *American Journal of Gastroenterology.* 2002. 97(9 Suppl S): p. S14 Abs 47.

75. Johnson, DA, Benjamin, SB, Whipple, J, et al. Efficacy and safety of esomeprazole as maintenance therapy in GERD patients with healed erosive esophagitis (EE). *Gastroenterology.* 2000;118:A17.

76. Johnson, DA, Vakil, NB, Hwang, C, et al. Evidence-based analysis of the benefit of esomeprazole for preventing relapse of erosive esophagitis (EE). *American Journal of Gastroenterology.* 2001;96:S270.

77. Johnsson, F, Hatlebakk, JG, Klintenberg, AC. The symptom relieving effect of esomeprazole 40 mg daily in patients with heartburn. *Gastroenterology.* 2001;120:A437.

78. Jokubaitis, L, Murthy, A, Hegedus, R, et al. The future of acid suppression therapy trial with rabeprazole: preliminary analysis of acute symptom relief. *American Journal of Gastroenterology.* 2000;95:2423-2424.

79. Junghard, O, Hassan-Alin, M, Hasselgren, G. The effect of AUC and CMAX of esomeprazole on acid secretion and intragastric pH. *Gastroenterology.* 2000;118:A17.

80. Kaspari S, Biedermann A, Mey J. Pantoprazole 20 mg is superior to ranitidine 150 mg BID in healing mild gastroesophageal reflux. *Gut.* 1999;45(Suppl V):A178.

81. Katz, PO, DeVault, KR, Hwang, C, et al. Baseline severity of heartburn does not influence resolution of heartburn in patients with endoscopy-negative GERD. *American Journal of Gastroenterology.* 2001;96:S20.

82. Katz PO, Ballard D, Koch F, et al. Nocturnal gastric acididty after bedtime dosing of proton pump inhibitors in patients with nighttime GERD symptoms. *Gastroenterology.* 2006;130(2):A175.

83. Kawamura, N, Sugiyama, T, Saito, M, et al. Eradication efficacy of rabeprazole, a new proton pump inhibitor, in triple therapy for Helicobacter pylori does not depend on P450 genotype of the patients. *Gut.* 2000;47:A105.

84. Koizumi W, Tanabe S, Hibi K, et al. Omeprazole, amoxicillin with or without metronidazole in the eradication of Helicobacter pylori: prospective randomized study. *J Gastroenterol Hepatol.* 1995;10(4 suppl):A131.

85. Kujundzic M, Ljubicic N, Banic M, et al. The frequency of relapse and bleeding previous gastroduodenal lesions in NSAID-users on maintenance therapy. *Gut.* 2000;47(Suppl 3):A84.

86. Kulig, M., et al., Quality of life in patients with gastroesophageal reflux disease. *Gastroenterology.* 2002;122(4 Suppl 1): p. S20.

87. Lanza, F, Goff, J, Silvers, D, et al. Lansoprazole for one year prevents recurrence of duodenal ulcer. *Gastroenterology.* 1994;106:A122.

88. Lauritsen, K., et al., The effect of esomeprazole 40mg on healing, reflux symptoms and quality of life in patients with reflux esophagitis. *Gastroenterology.* 2002;122(4 Suppl 1): p. A200.

89. Lauritsen K, on behalf of a danish multicentre study. Gastric ulcer recurrence after six weeks` treatment with omeprazole and cimetidine - six months double blind comparative follow-up study. *Gut.* 1988;29(Suppl 10):A1441.

90. Lauritsen, K., O. Junghard, and S. Eklund, Esomeprazole 20 mg compared with lansoprazole 15 mg for maintenance therapy in patients with healed reflux oesophagitis. *Journal of Gastroenterology and Hepatology.* 2002;17(Suppl): p. A1007.

91. Levine, JG, Hwang, C, Roach, A, et al. Evidence-based analysis of the benefit of esomeprazole in the treatment of erosive esophagitis (EE). *American Journal of Gastroenterology.* 2001;96:S273.

92. Lind, T., O. Junghard, and K. Lauritsen, Esomeprazole and lansoprazole in the management of patients with reflux oesophagitis (RO): combining results from two clinical studies. *Journal of Gastroenterology and Hepatology.* 2002;17(Suppl): p. A1024.

93. Louw, JA, C., vR, Simjee, AE, et al. Lansoprazole vs omeprazole in duodenal ulcer healing. *South African Medical Journal.* 1993;83:777.

94. Lundell, L, Dalenback, J, Hattlebakk, J, et al. Omeprazole or antireflux surgery in the long-term management of gastroesophageal reflux disease: results of a multicentre, randomized clinical trial. *Gastroenterology.* 1998;114:A207.

95. Malfertheiner, P., et al., Which factors have an impact on healing and symptom relief in patients with erosive and non-erosive GERD treated with esomeprazole? An analysis based on the ProGERD Study initiative. *Gastroenterology.* 2002;122(4 Suppl 1): p. S1283.

96. Malfertheiner P, Kirchner T, Kist M. Effect of pantoprazole based triple therapy on H pylori eradication and gastric ulcer healing and relevance. Gut. 2000;47(Suppl III):A127.

97. Mentis, A, Rokkas, T. MIC's of Rabeprazole, a recently developed proton pump inhibitor, and omeprazole, against Helicobacter pylori. *Gut.* 2000;47:PA130.

98. Merrit, GJ, Humphries, TJ, Spera, AC, et al. Effect of rabeprazole sodium on the pharmacokinetics of diazepam in healthy male volunteers. *Pharmacol Res.* 1997;14:S556.

99. Mattson C, Lundell L, Miettinen P, et al. Quality of life in the long term management of gastroesophageal reflux disease treated with omeprazole or antireflux surgery. *Quality of Life Research.* 1999;8(7):662.

100. Miehlke, S., et al., Treatment of Helicobacter pylori resistant to both metronidazole and clarithromycin - prospective, randomized trial comparing 7-day rifabutin-based triple therapy with high-dose omeprazole/amoxicillin dual therapy. *Gut.* 2002. 51(Suppl III): p. A212.

101. Miner, P, Sloan, S, Filippone, J, et al. Significant heartburn relief after the first dose of rabeprazole sodium in non-erosive reflux disease (NERD) patients. *Gastroenterology.* 2000;118:A338.

102. Moum D, Meineche-Schmidt V, Junghard O et al. Esomeprazole 40 mg once daily provides high symptom relief in uninvestigated GERD patients after 4 weeks' treatment. Scan J Gastroenterol 2003;38 (Suppl 238) A-P1.

101. Pantoflickova, D, Dorta, G, Jornod, P, et al. Identification of the characteristics influencing the degree of antisecretory activity of PPIs. *Gastroenterology.* 2000;118:A1290.

102. Phua SY, Thompson GA, Ngu MC, Ing AJ. The effect of pantoprazole on laryngopharyngeal sensitivity in patients with GORD: a randomised double blind placebo controlled trial. *Respirology*. 2005;10(Suppl):A56.

103. Pilotto, A, Dal Bo, N, Francheschi, M, et al. Comparison of three proton pump inhibitors (PPI) in combination with amoxycillin and metronidazole for one week to cure helicobacter pylori infarction in the elderly. *Gut.* 1998;43:A91.

104. Pilotto, A, Francheschi, M, Leandro, G, et al. Comparison of omeprazole, lansoprazole and pantoprazole in the treatment of elderly patients with esophagitis. *Gastroenterology.* 1999;116:A283.

105. Plein, K, Stolte, M, Fuchs, W, et al. Lansoprazole vs. ranitidine efficacy in healing acute reflux esophagitis and influence on hyperregenerative esophagopathy. *Gut.* 1995;37:A38.

106. Ramirez-Barba, EJ, Di Silvio, M, Dibildox, M, et al. Superiority of 20 mg patoprazole (PANTO) vs 150 mg x 2 ranitidine (RANI) in healing and symptom relief of patients with mild reflux esophagitis. *Gastroenterology*. 1998;114:A264.

107. Rampal, P, Courrier, A, Lemerez, M, et al. Efficacy and safety of lansoprazole 30 mg versus omeprazole for 21 days treatment of acute esophagitis. *Gastroenterology.* 1995;108:A200.

108. Richter, JE, Johnson, DA, Magner, DJ, et al. Six month safety and tolerability of esomeprazole as maintenance therapy in GERD patients with healed erosive esophagitis (EE). *Gastroenterology.* 2000;118:A1299.

109. Robinson, M, Kogut, D, Jennings, D, et al. Lansoprazole heals erosive reflux esophagitis better than ranitidine. In: *American Gerontological Association; 1992; San Francisco, CA; 1992.*

110. Robinson M, Sloan S, Gardner JD, Hahne WF, Humphries TJ. Gastric acid suppression with rabeprazole: How much is needed to normalise oesophageal acid exposure in GERD. *Gut.* 1999;44(Suppl 1):A112.

111. Rohss, K, Lundin, C, Rydholm, H, et al. Esomeprazole 40 mg provides more effective acid control than omeprazole 40 mg. *In: American College of Gastroenterology 65th Annual Scientific Meeting; 2000 3/25/02; New York, NY; 2000.*

112. Rohss, K, Wilder-Smith, C, Claar-Nilsson, C, et al. Esomeprazole provides more effective acid control than standard doses of all other proton pump inhibitors. *Gastroenterology.* 2001;120:A419.

113. Rohss, K., C. Claar-Nilsson, and L. Jansson, Esomeprazole 20 mg provides more effective acid control than rabeprazole 10 mg following repeated drug administration. *Scandinavian Journal of Gastroenterology.* 2002. 37(6 Suppl 235): p. 34 Abs 61.

114. Rohss, K., et al., Esomeprazole 40 mg provides more effective acid control than lansoprazole 30 mg. *Gastroenterology.* 2000;118(No. 4): p. 344.

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.

116. Rohss, K., et al., Esomeprazole 40mg provides more effective acid control than standard doses of all other proton pump inhibitors. *Gastroenterology.* 2001;120(5): p. A419.

117. Sachs, G. and J.M. Shin, Pharmacological basis for different rates of recovery of acid secretion after PPI treatment. *Gastroenterology.* 2002;122(4 Suppl 1): p. A47 Abs 389.

118. Saitoh, T, Otuka, H, Hirakawa, J, et al. Effect of rabeprazole, lansoprazole and omeprazole on gastric pH during the early post-administration phase. *Gastroenterology.* 2000;118:A476.

119. Scholten, T., U. Hole, and G. Gatz, Pantoprazole 40 mg showed a significantly faster relief of GERD-associated symptoms than esomeprazole 40 mg. *Gut.* 2002;51(Suppl III): p. A169.

120. Simon, B, Mueller, P, Gatz, G, et al. Equivalent effect of patoprazole 40 mg o.d. and esomeprazole 40 mg o.d. on intra-esophageal pH in patients with symptomatic GERD. *American Journal of Gastroenterology.* 2001;96:S35.

121. Sontag, S, Robinson, M, Roufail, W, et al. Daily omeprazole is needed to maintain healing in erosive esophagitis Abstract 65. *American Journal of Gastroenterology.* 1992;87:1258.

122. Sostek, M.B., et al., An in vitro study of the administration of esomeprazole eneric-coated pellets through naso-gastric and gastrostomy tubes. *American Journal of Gastroenterology.* 2002;97(9 Suppl): p. S3-4, Abs 9.

123. Sostek, M.B., et al., Esomeprazole: nasogastric tube administration of the contents of an opened capsule suspended in water compared with oral administration in healthy volunteers. *American Journal of Gastroenterology*. 2002;97(9 Suppl): p. S23, Abs 69.

124. Spera, AC, Humphries, TJ, Merritt, J, et al. No dosage adjustment is required when rabeprazole sodium 20 mg is administered once daily to elderly patients. *Gastroenterology.* 1997;112:A908.

125. Talley, N.J., et al., Predictors of treatment response in patients with endoscopy-negative reflux disease (ENRD). *American Journal of Gastroenterology.* 2002;97(9 Suppl): p. S12, Abs 36.

126. Talley, N.J., O. Junghard, and I. Wiklund. Why do patients with gastroesophageal reflux disease have poor health-related quality of life. in *DDW. 2001. Atlanta, GA.*

127. Talley, NJ, Venables, TL, Green, JR, et al. Esomeprazole 40 mg and 20 mg is efficacious in the long-term management of patients with endoscopy-negative GERD: a placebo-controlled trial of on on-demand therapy for 6 months. *Gastroenterology.* 2000;118:A658.

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.

129. Thomson, ABR, Claar-Nilsson, C, Hasselgren, G, et al. Esomeprazole 40 mg provides more effective acid control than lansoprazole 30 mg during single and repeated administration. *Gut.* 2000;47:A63.

130. Troiano, F.P. and J.D. Rogge, Successful treatment of Zollinger-Ellison Syndrome with esomeprazole. *American Journal of Gastroenterology.* 2002;97(9 Suppl): p. S179, Abs 545.

131. Tulassay, Z, Kryszewski, A, Dite, P, et al. 7-day treatment with esomeprazole-based triple therapy eradicates H. pylori (HP) and heals patients with duodenal ulcer (DU) disease. *Gastroenterology.* 2000;118.

132. Vakil, N.B., D.A. Johnson, and C. Hwang, Effect of baseline grade of esophagitis on maintenance of healing rates. *American Journal of Gastroenterology.* 2000;95(9): p. 2439, Abs 98.

133. Vakil, N.B., et al., Esomeprazole is effective as maintenance therapy in GERD patients with healed erosive esophagitis (EE). *Gastroenterology*. 2000;118(4): p. A22, Abs 350.

134. Vakil, N.B., P.J. Kahrilas, and D. Magner, Does baseline Hp status impact erosive esophagitis (EE) healing rates? *American Journal of Gastroenterology.* 2000;95(9): p. 2438, Abs 96.

135. Vakil, N.B., S. Zuckerman, and J.G. Levine, Dysphagia in uncomplicated reflux disease. *Gastroenterology.* 2002;122(4 Suppl 1): p. A583, Abs W1189.

136. Vakil, N.B., S. Zuckerman, and J.G. Levine, H pylori infection and the severity of esophagitis and healing with lansoprazole and esomeprazole. *Gastroenterology.* 2002; 122(4 Suppl 1): p. A199-A200 Abs 1290.

137. Vakil, N.B., S. Zuckerman, and J.G. Levine, Nocturnal heartburn in patients with erosive esophagitis and its resolution with proton pump inhibitors. *Gastroenterology.* 2002;112(4 Suppl 1): p. A200, Abs S1291.

138. van Rensburg, CJ, Honiball, PJ, Grundling, HD, et al. Prophylactic efficacy and safety of 40 mg pantoprazole against relapse in patients with healed reflux oesophagitis - a two year study. *Gastroenterology.* 1997;112:A321.

139. van Rensburg CJ, Louw JA, Girdwood AH, Simjee AE, Marks IN. A Multicentre Trial of Two-stage Lansoprazole (Lz) Therapy in Aggressive Gastric Ulcer (GU). *Gut.* Vol. 1995;37(2).

140. Venables T, Newland R, Patel AC, et al. A comparison of omeprazole 10mg and 20mg OM with ranitidine 150mg BD for the treatment of GERD in primary care. *Gut.* Vol. 1995;37(2).

141. Wahlqvist, P., In Finland, Sweden and the UK, esomeprazole is cost-effective compared with omeprazole for the acute treatment of patients with reflux oesophagitis. *Value in Health.* 2000;3(5): p. 358.

142. Walan A, Bader JP, Classen M, Lamers C, Piper DW, Rutgersson R. Omeprazole and ranitidine in the treatment of benign gastric ulcer - an international multicentre study. *Gut.* Vol. 1340;28.

143. Warrington, S., et al., Rabeprazole is more potent than esomeprazole in control of gastric pH in healthy volunteers. *Gut.* 2001;49(Suppl III): p. Abs 2800.

144. Welage, L.S., et al., Pharmacokinetic comparison of five proton pump inhibitors. *American Journal of Gastroenterology.* 2002;97(9 Suppl): p. S18-S19 Abs 1303.

145. White, C.M., et al., Esomeprazole capsule contents suspended in water can be efficiently delivered through nasogastric and gastronomy tubes. *American Journal of Gastroenterology.* 2002;97(9 Suppl): p. S18-S19, Abs 55.

146. Wilder-Smith, C, Claar-Nilsson, C, Hasselgren, G, et al. Esomeprazole 40 mg provides faster and more effective acid control than rabeprazole 20 mg in patients with symptoms of GERD. *American Journal of Gastroenterology.* 2001;96:S45.

147. Wilder-Smith, C, Rohss, K, Claar-Nilsson, C. Esomeprazole 20 mg provides more effective acid control than lansoprazole 15 mg. *American Journal of Gastroenterology.* 2001;96:S44.

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.*

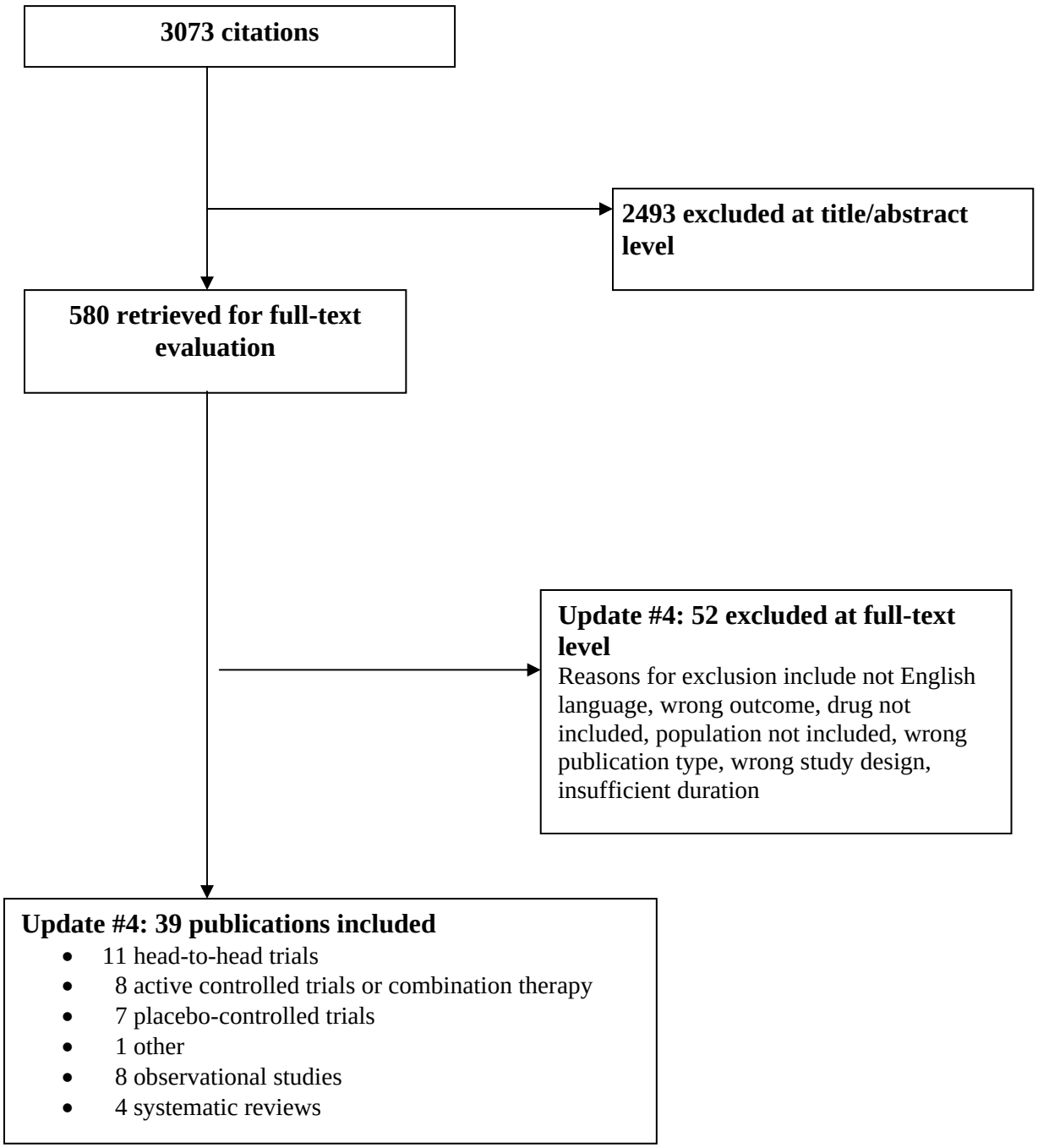
149. Wilder-Smith, C, Rohss, K, Lundin, C, et al. Esomeprazole (E) 40 mg provides more effective acid control than pantoprazole (P) 40 mg. *Gastroenterology.* 2000;118:A22.

150. Wilder-Smith, C., et al., Esomeprazole 40mg provides faster and more effective acid control than lansoprazole 30mg in patients with symptoms of gastroesophageal reflux disease. *Gastroenterology.* 2002;122(4 Suppl 1): p. A200, Abs S1293.

151. Wilder-Smith, C., et al., Esomeprazole 40mg provides more effective acid control than rabeprazole 20mg. *Gut.* 2000;47(Suppl III): p. A63.

152. Wormsley, KG, Bardhan, KD, Morgan, AG, et al. Lansoprazole is more effective than ranitidine in gastric ulcer. *Gut.* 1992;33:T190.

Appendix E. Results of search and selection of included articles



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 ulceraton 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 thatn 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 tow or more mucosal folds, but which involve less that 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 squamocolmnar juntion 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

Hansen AN, Bergheim R, Fagertun H, Lund H, Wiklund I, Moum B. Long-term management of patients with symptoms of gastro-oesophageal reflux disease -- a Norwegian randomised prospective study comparing the effects of esomeprazole and ranitidine treatment strategies on health-related quality of life in a general practitioners setting. *International Journal of Clinical Practice.* 2006;60(1):15-22.

GERD

Fass R, Sontag S, Traxler B, Sostek M. Treatment of patients with persistent heartburn symptoms: a double-blind, randomized trial. *Clinical Gastroenterology & Hepatology.* 2006;4:50-56.

Lightdale C, Schmitt C, Hwang C, Hamelin B. A Multicenter, Randomized, Double-Blind, 8-Week Comparative Trial of Low-Dose Esomeprazole (20 mg) and Standard-Dose Omeprazole (20 mg) in Patients with Erosive Esophagitis. *Dig Dis Sci.* 2006:1-6.