Drug Class Review on Proton Pump Inhibitors

FINAL REPORT

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INTRODUCTION

Proton pump inhibitors (PPIs) reduce stomach acid. 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 1988. 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).

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

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different PPIs. The Oregon Evidence-based Practice Center developed the scope of the review by writing preliminary key questions, identifying the populations, interventions, and outcomes of interest and based on these, the eligibility criteria for studies. These were reviewed by the Oregon Health Resources Commission subcommittee for anti-ulcer therapies, comprised of local experts (pharmacists, primary care clinicians, and gastroenterologists), in public meetings and refined based on their input. In consultation with the subcommittee, we selected the following key questions to guide this review:

1. What is the comparative efficacy of different PPIs in adult 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, the subcommittee specified endoscopic healing (or endoscopic recurrence) of esophagitis as an 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. While there is a general relationship between the degree of esophagitis and the severity of symptoms, 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. Over many years, esophagitis can lead 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.

2. What is the comparative efficacy of different proton pump inhibitors in adult 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 symptomatic 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 most 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 symptomatic 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 adult 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 (2003, Issue 3), Medline (1966-November Week 1, 2003), Embase (1980-4th quarter, 2003), Premedline (through November 13, 2003), 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 strategy). Subcommittee members were invited to provide additional citations. Pharmaceutical manufacturers were invited to submit dossiers, including citations. All citations were imported into an electronic database (EndNote 6.0).

Study Selection

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.[1-3] 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. 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.

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

One reviewer abstracted the following data 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.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix B, which were submitted to the Health Resources Commission in December 2001. 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).[1, 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). In one systematic review,[4] results are reported as relative risks. A relative risk of 2.0 for esophagitis healing with Drug A versus Drug B means that patients taking Drug A are twice as likely to heal as those taking Drug B. As a measure of the variance around these estimates, the 95% confidence interval (CI) is also reported. If the 95% CI includes 0 (or 1 in the case of relative risks), then the difference is not statistically significant. Meta-analysis was done using StatsDirect (CamCode, UK) 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. 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.[5]

RESULTS

Overview

Searches and review of reference lists identified 2308 citations: 222 from the Cochrane Central Register of Controlled Trials, 938 from MEDLINE, 75 from PreMedline, 664 from Embase, 231 from reference lists, and 178 from pharmaceutical company submissions. We included 115 randomized controlled trials and 11 systematic reviews. 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. An additional 29 citations provided information for background, methodology, drug interactions, and adverse effects. We did not examine in detail placebo-controlled trials if studies using an active control were available for a key question (see Appendix C). We excluded reports that were published in abstract form only (see Appendix D).

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, all were funded by the pharmaceutical industry, and industry employees often served as co-authors.

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

1a. 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?

We identified 16 randomized controlled trials comparing two PPIs for healing of esophagitis and gastroesophageal reflux symptom relief (Evidence Table 1).[6-21] Omeprazole was the comparator in all but four studies.[10, 16, 18, 21] The scales used to grade esophagitis in these studies are described in Appendix E. They made the following comparisons:

- lansoprazole versus omeprazole(five studies)[6, 11, 13, 14, 20]
- rabeprazole versus omeprazole (two studies)[8, 9]
- pantoprazole versus omeprazole (two studies)[7, 19]
- esomeprazole versus omeprazole (two studies)[12, 15]

- esomeprazole versus lansoprazole (two studies),[16, 18]
- esomeprazole versus pantoprazole (one study)[21]
- omeprazole versus both lansoprazole and pantoprazole (one study)[17]
- lansoprazole versus pantoprazole (one study).[10]

Two studies[15, 16]met all criteria for internal validity, one was rated poor,[11] and the rest were fair. (Details of quality ratings are listed in the evidence table, last column.) 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.

Esophagitis Healing

All of the PPIs were effective at healing esophagitis. Healing rates at 4 weeks ranged from 61.2% to 91.2%, and at 8 weeks ranged from 71.1% to 94.2%. Figure 1 shows differences in healing rates at 4 and/or 8 weeks for the ten trials that provided this information. Three studies[8, 12, 16] did not provide number healed/total, and three trials[17, 20, 21] reported only symptom relief, not esophagitis healing. There was no difference between lansoprazole 30mg, omeprazole 20mg or 40 mg, pantoprazole 40mg, and rabeprazole 20mg in healing rates at 4 or 8 weeks. The pooled risk difference for 3 studies that compared lansoprazole 30 mg to omeprazole 20 mg was 1.17 (95% CI –3.02, 5.36) at 4 weeks and 0.76 (95% CI –0.02, 4.29) at 8 weeks.[6, 11, 13] One study[6] found omeprazole 20mg had a higher healing rate than lansoprazole 15mg; however, in the same study, lansoprazole at a higher dose (30mg) was as effective as omeprazole 20mg in healing at 4 and 8 weeks.

Two trials compared esomeprazole 40mg to omeprazole 20mg, and both found a greater healing rate in the esomeprazole group.[12, 15] In the earlier study,[12] raw data are not reported, and results are given as cumulative life table rates only. No other study used this method of analysis, so it is difficult to compare these results with those of studies that reported an intention to treat analysis of simple proportions healed. Using life table analysis may overestimate results by excluding patients who are lost to followup or are withdrawn from the study. A more recent and larger (n= 2425) good quality trial (Richter) from the same group of authors also found esomeprazole 40mg had a significantly higher healing rate at both 4 and 8 weeks than omeprazole 20mg.[15] In the esomeprazole group the healing rate at 4 weeks was 78.6% and at 8 weeks it was 89.9%. This study also reports cumulative life table analysis for healing rates at 4 and 8 weeks. Crude rates and cumulative life table rates in each group were very different. For example, in the esomeprazole group, the cumulative life table rate of healing at 4 weeks was 93.7%, whereas the crude rate was 78.6%.

Although it was well conducted, the applicability of the study is poor for two reasons. First, it compared esomeprazole 40mg to a lower dose (20mg) of omeprazole (the standard dose of esomeprazole is 20 mg or 40 mg). One study that used omeprazole 40mg found a healing rate of 79.9% at 4 weeks and 90.5% at 8 weeks,[14] comparable to the rates found at esomeprazole 40mg in the Richter study.

Second, the subjects of the study are not described adequately, leaving open the possibility that there was selection bias. The baseline characteristics reported in the article are sex, age, race, H. pylori status, esophagitis grade, duration of GERD, and "heartburn" (none, mild, moderate, severe). It is not clear whether the severity of heartburn was measured before or

after the patients had been taken off non-study PPIs and H2-RAs. Selection bias is possible because patients who were not doing well with omeprazole 20mg to begin with might have been preferentially referred to the study.

Another large, good quality trial compared esomeprazole 40mg to lansoprazole 30mg for acute treatment of erosive esophagitis in 5241 patients at multiple centers in the US.[16] Healing rates were significantly higher in the esomeprazole group at 4 weeks (79.4% vs 75.1%, $p<0.01$) and at 8 weeks (92.6% vs 88.8%, $p=0.0001$) using life-table analyses. As in the Kahrilas study discussed above, crude healing rates are also reported after adjustment for baseline severity, and are lower than the rates using life table analysis at 4 weeks (75.7% vs 71.7%, $p \leq 0.01$) and 8 weeks (87.6% vs 84.2%, $p \leq 0.01$). The unadjusted rates or numbers of patients healed and total included in analysis are not given in the report.

Studies presenting only life-table analyses and adjusted rates of healed patients are not included in figure 1 because the numbers of patients healed and unhealed are not reported and cannot be directly compared to the other studies presenting these data.

A second, smaller, fair-quality trial of lansoprazole 30mg versus esomeprazole 40 mg[18] found the two to be equivalent at healing esophagitis at 4 and 8 weeks.

In summary, our review found no differences among omeprazole, lansoprazole, rabeprazole, and pantoprazole in healing rates at 4 and 8 weeks. In two trials esomeprazole 40mg had higher 4-week and 8-week healing rates than omeprazole 20mg, but there are no head-to-head comparisons of omeprazole 40mg versus esomeprazole 40mg. One trial of esomeprazole 40 mg versus lansoprazole 30 mg found better healing rates in the esomeprazole group. At 8 weeks the difference in adjusted crude healing rate was 3.4% corresponding to a number needed to treat of 29 (for every 29 patients treated with esomeprazole one additional patient was healed compared to lansoprazole). However, a second trial of esomeprazole 40 mg versus lansoprazole 30 mg found equivalent healing rates at 4 and 8 weeks.

Three of four trials that compare esomeprazole to another PPI concluded that esomeprazole was more effective, but because of concerns over lack of equivalence in doses used (omeprazole) and method of reporting and analyzing results, these trials do not provide sufficient evidence that esomeprazole is more efficacious than any other PPI. Clear reporting of numbers of patients healed and unhealed at 4 and 8 weeks in these trials would help to clarify this. A request to the authors for this information and an explanation of the unusual method of analysis has been submitted and is still pending.

Four controlled clinical trials of esomeprazole compared to omeprazole for the healing of esophagitis were submitted to the FDA for approval of esomeprazole.[22] Two of these studies were subsequently published and are discussed above.[12, 15] The other two studies were never published. We did not include them in this report because inadequate information was available to fully assess their quality or determine characteristics of the study population and setting. Briefly, these studies compared esomeprazole 40mg versus omeprazole 20mg and esomeprazole 20mg versus omeprazole 20mg. Neither study found a statistically significant difference at 4 or 8 weeks.

There have been four recent systematic reviews comparing PPIs for esophagitis healing and symptom relief.[23-26] 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.[24-26] 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.[24] 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.[26] Both of these were funded by the manufacturer of esomeprazole.

A third systematic review,[25] 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[23] found that lansoprazole, rabeprazole, and pantoprazole had similar efficacy to omeprazole for healing. No study of esomeprazole had been done at the time.

Relief of Symptoms

Three head-to-head comparisons of PPIs measured symptom relief as a primary outcome,[17, 20, 21] and twelve reported symptoms as a secondary outcome.[6-16, 19] Symptoms in these studies were assessed through patient diaries, investigator-elicited reports, or both. The definition of "relief of symptoms" varied.

In a head-to-head study that measured symptoms and quality of life as primary outcomes,[17] 461 patients were randomized to either omeprazole Multiple Unit Pellet System (MUPS) 20mg, lansoprazole 30 mg, or pantoprazole 40 mg. Symptom relief was equivalent with omeprazole and pantoprazole at 4 (84% and 84%), and 8 weeks (87 and 89%, respectively). Lansoprazole had lower rates (78% at 4 weeks, 81% at 8 weeks). These are cumulative rates, patients who resumed having symptoms were continued to be counted as resolved. Patient satisfaction at 4 and 8 weeks was equivalent for all 3 PPIs at 4 and 8 weeks, however. Data at 12 weeks were recorded but not reported.

In another trial comparing lansoprazole 30 mg with omeprazole 20 mg, more patients taking omeprazole experienced at least one episode of heartburn over 8 weeks (approximately 10% to 15% per group, $p < 0.05$; data are presented graphically only).[20] The proportion of patients who reached "the start of sustained resolution of heartburn" (defined as 7 consecutive days with no heartburn) was higher for lansoprazole at day 1, day 3, day 7, and day 14, but equivalent at 4 and 8 weeks.

Four studies compared symptom relief for lansoprazole versus omeprazole in secondary analyses.[6, 11, 13, 14] Although lansoprazole was seen to improve some symptoms at some time points, there was no strong or consistent pattern to suggest that lansoprazole is more effective or provides faster symptom relief than omeprazole. In one study, lansoprazole was more effective for daytime heartburn only, in another it was more effective for nighttime heartburn only, and in two others there was no difference. In one fair quality study,[6] symptoms were elicited by the investigator at each visit, and patients also kept diaries that included episodes of day and night heartburn. There was no difference in symptom relief between lansoprazole 30mg and omeprazole 20mg. Patient diaries showed the lansoprazole group had a lower mean percentage of nights with heartburn over 8 weeks of treatment, but no difference in days with heartburn or days of antacid use. It is difficult to interpret these data because sometimes the data are given as mean percentages and at other times median percentages are given. For example, at week 1, data are given as means, and at week 8 are given as medians. The investigators report that lansoprazole was superior in symptom relief because after the first day and first week of therapy, patients in the lansoprazole group reported significantly fewer days and nights with heartburn.

Results are given as mean percentages. There were no differences in symptoms, as assessed by investigator questioning during visits, which were assessed at 2, 4, and 6 weeks of treatment. Reporting of diary data seems inconsistent and incomplete.

In another fair quality study,[13] day and nighttime heartburn and epigastric pain according to patients' diaries was improved during the first week of treatment in both groups. After 3 days of treatment, there was a significantly greater improvement in daytime heartburn symptoms in the lansoprazole group (p=0.05) as assessed by a change from baseline according to a visual analogue scale ranging from 0 to 100 mm ("no pain" to "worst pain ever"). There was no difference between treatment groups for epigastric pain or nighttime heartburn, and at 7 days the difference in daytime heartburn was no longer significant (p = 0.18). According to clinical assessment, there was more improvement in daytime epigastric pain after 1 and 8 weeks, but no difference at week 4 and no difference between the groups in any other measure of symptoms (day and nighttime heartburn, dysphagia, odynophagia, acid regurgitation). In a good- to fair quality study of lansoprazole 30mg versus omeprazole 40mg,[14] there was no difference between groups in the number of patients reporting no symptoms at 4 weeks. Symptoms at 8 weeks were not measured. A poor quality study[11] also compared symptom relief for lansoprazole 30mg versus omeprazole 20mg. Patients receiving lansoprazole experienced "greater improvement in heartburn" after 4 weeks than patients in the omeprazole group (p=0.03), but details are not given, and no other significant differences in symptoms are reported. After 8 weeks, the difference in heartburn was no longer statistically significant.

One trial compared pantoprazole 40 mg to esomeprazole 40 mg for symptom relief as the primary outcome.[21] According to patient diaries, the two drugs were equivalent in the proportion of patients reporting no or only mild symptoms after 4 weeks (99% vs 98%). The time to reach adequate relief of GERD-related symptoms according to patient diaries, and investigator assessment of relief of gastrointestinal symptoms were also equivalent in the two groups.

Two other trials that compared esomeprazole to another PPI for esophagitis healing reported symptom relief as a secondary outcome.[12, 16] One[12] reported a higher rate of resolution of symptoms at 4 weeks (64.7%) with esomeprazole 40mg than omeprazole 20mg (57.2%) or esomeprazole 20mg (61.0%). In addition, esomeprazole 40mg had a shorter time to relief of heartburn symptoms. The number of days until the first heartburn-free day, number of days until sustained resolution of heartburn (7 consecutive days without heartburn), and number of heartburn-free days and nights were all improved with esomeprazole 40mg compared with the other preparations. This study reports that by day 1, 29.9% of patients in the esomeprazole group already had sustained resolution of symptoms, so the validity of this measure is not clear. The differences between esomeprazole 20mg and omeprazole 20mg were not statistically significant. In the second, larger trial, resolution of heartburn by 4 weeks was 68.3% for esomeprazole 40mg versus 58.1% for omeprazole 20mg ($p < 0.001$).[15] Neither study reported symptom outcomes at 8 weeks.

A good-quality trial[16] of esomeprazole 40 mg versus lansoprazole 30 mg reports more patients with sustained resolution of heartburn in the esomeprazole group, as judged by investigator assessment of patient diaries, at 4 weeks (62.9% vs 60.2%, $p \leq 0.05$). This difference in risk is 2.7%, corresponding to a number needed to treat of 37. Complete resolution of heartburn was defined as 7 consecutive days without heartburn. Sustained resolution of heartburn occurred faster with esomeprazole (7 days vs 8 days, $p \leq 0.01$). There was also faster resolution of nocturnal heartburn and a greater percentage of heartburn-free nights in the

esomeprazole group, but no difference in percentage of heartburn-free days, or in the time to first resolution of heartburn and nocturnal heartburn. Symptoms at 8 weeks were not reported.

Two fair quality studies found no difference in symptom relief (heartburn, acid regurgitation, or pain on swallowing) between pantoprazole and lansoprazole,[10] or pantoprazole and omeprazole,[7] at 4 weeks. Symptoms at 8 weeks are not reported. One study measured symptoms at 4 and 8 weeks in a comparison of rabeprazole 20mg versus omeprazole 20mg.[8] On 12 measures of symptom relief and overall well-being, no differences were found between the two groups.

Prevention of Relapse

Three randomized controlled trials compared one PPI to another for long-term (6 months or more) maintenance therapy for esophagitis relapse prevention (Evidence Table 2).[4, 27-29] Two of these found no differences in endoscopic or symptomatic relapse rates for lansoprazole versus omeprazole after 48 weeks of treatment,[4] or rabeprazole versus omeprazole after 13 weeks, 26 weeks, one year, and five years.[27, 29]

A recent head-to-head trial[28]compared relapse rates at 6 months in patients randomized to esomeprazole 20 mg or lansoprazole 15 mg. Only those patients who were healed and symptom-free after using esomeprazole 40 mg for 4 to 8 weeks were enrolled in the maintenance phase of the study. According to life-table analysis, a higher proportion of patients in the esomeprazole group remained healed (83% vs 74%) over 6 months. The authors also present data by baseline severity. More patients in the esomeprazole group remained healed across all grades of disease severity, whereas the efficacy of lansoprazole decreased with increasing severity of disease. 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 had responded to esomeprazole for initial healing of esophagitis, the study may be biased towards esomeprazole.

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.[30] Before randomization, all of the patients were treated with omeprazole. Six patients did not heal after 6 to 8 weeks of omeprazole; the remainder (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.

1b. 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,[23] four PPIs were better than ranitidine at healing esophagitis, but there were no differences among them. No study of esomeprazole was included.[23]

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[31-41] lansoprazole (five studies),[42-46] pantoprazole (five studies),[47-51] and rabeprazole (1 study).[52]

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,[23] 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 recent study compared pantoprazole 10mg, 20 mg, or 40 mg to ranitidine 150 mg for prevention of relapse of healed esophagitis in 371 patients.[53] 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 2001 systematic review identified 15 studies of relapse prevention.[23] 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.

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

2a. 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?

Nine randomized controlled trials compared one PPI to another.[8, 54-61] The details of these studies are summarized in Evidence Table 3. Six of these trials compared lansoprazole

30mg to omeprazole 20mg.[54-58, 61] One study each compared pantoprazole 40mg and rabeprazole 20mg to omeprazole 20mg[8, 59] and one study comparing esomeprazole 40mg to omeprazole 40mg.[60] 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.[62]

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 40mg versus omeprazole 40mg also showed no difference in healing rates.[60] 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.[8] 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 4).[57] 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 4 compared lansoprazole to placebo[63, 64] or ranitidine.[65] 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.

2b. 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?

Twenty-five randomized controlled trials compared a PPI with an H2-RA. Of these, 22 papers were reviewed.[66-87] 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[88] 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[87, 89-91] These studies were consistent with the studies reported above and are not added to figure 4. One of these studies reported symptom relief only.[87]

2c. 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?

Only one study compared one PPI to another in the treatment of gastric ulcer.[92] This fair quality study of 227 patients compared rabeprazole 20mg to omeprazole 20mg and is summarized in Evidence Table 5, with the other gastric ulcer studies. 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 were found.

2d. 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?

Fourteen studies compared a PPI to an H2-RA for treatment of gastric ulcer (Evidence Table 5).[58, 66, 93-104] There were two studies of maintenance therapy and one followup study of relapse rates in patients healed in one of the above studies.[64, 105, 106] One of the maintenance studies included patients with either gastric or duodenal ulcer, all of which were resistant to H2-

RA therapy.[105] No study compared esomeprazole or 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.[95] 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[107] 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.[105] 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[106] of patients who had healed after 6 weeks of treatment with omeprazole or cimetidine[94] found no significant difference in relapse rates. All of these studies had high or differential dropout rates.

2e. 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?

No study compared one PPI to another.

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 adult patients with NSAID-induced ulcer?

Three studies assessed PPIs compared to another drug in healing ulcers induced by NSAIDs.[108-110] The details of these studies are summarized in Evidence Table 6.

Figure 6 shows the risk differences for healing of NSAID-induced gastric ulcers at 8 weeks. All confidence intervals overlap, regardless of comparison.

Symptoms (GI pain, dyspepsia, heartburn, reflux, and antacid use) were assessed at visits (none, mild, moderate, severe) and by patient diary in all studies. Results for symptoms did not include all those measured. In those symptom categories reported, improvement was not different between omeprazole 20mg and 40mg or between lansoprazole 15mg and 30mg, but was superior to the comparator drug.

One study[109] 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.

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.

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.[111] 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.

Four trials published more recently[112-115]are presented in Evidence Table 7, along with two of the treatment studies that included a prevention phase.[109, 110] 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. One study[112] 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[113] randomized patients to pantoprazole 40mg or placebo for 3 months. The third study[114]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,[115] 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,[112] 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%.

In the study of pantoprazole versus placebo,[113] 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,[114] 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."[113] 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.[112]

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

A recent, good-quality meta-analysis reviewed 14 head-to-head trials of PPIs combined with antibiotics in triple-therapy regimens for h. pylori eradication.[116] 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.[117] 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.[118] This review found no difference between lansoprazole and omeprazole in eradication rate.

Since these reviews, 17 studies were published that directly compared one PPI to another in combination with the same antibiotic(s).[60-62, 119-132] They made the following comparisons:

- rabeprazole 20mg versus omeprazole 40mg, plus amoxicillin (one study)[119]
- lansoprazole 60mg versus omeprazole 40mg, plus amoxicillin and metronidazole (one study)[121]
- omeprazole 40mg versus pantoprazole 40mg, plus clarithromycin and metronidazole (one study)[128]
- omeprazole 20mg versus lansoprazole 30mg, plus clarithromycin and tinidazole (one study) [61]

- various doses of lansoprazole, rabeprazole, pantoprazole and esomeprazole versus omeprazole, plus clarithromycin and amoxicillin (eight studies)[60, 62, 120, 122, 124-127, 133]
- omeprazole 20 mg, lansoprazole 30 mg, or rabeprazole 10mg (all twice daily) each combined with amoxicillin and clarithromycin (one study),[129]
- rabeprazole 10 mg or 20mg or lansoprazole 30mg twice daily, each combined with amoxicillin and clarithromycin (three studies),[123, 130, 132]
- 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).[131]

None of these studies was conducted in the US. Nine were conducted in Japan, two in Italy, one in England, one in Germany, one in Sweden, two in multiple European countries, one in Canada, and one in Colombia.

These studies were fair quality, with the exception of one fair to poor quality study that was not blinded.[119] 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).[127] In addition, the doses of clarithromycin, amoxicillin and metronidazole also vary. 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.

Ten studies included patients with documented ulcer.[60-62, 119, 121, 122, 126, 129, 130, 132] Five studies included patients with ulcers or non-ulcer dyspepsia[120, 123-125, 128] The proportion of non-ulcer patients ranged from 12%[123] to 71%.[125] One study conducted in a low-income population in Colombia included patients with "gastritis" and did not check for ulcer,[127] and one included both patients with previous or present recurrent ulcer.[131]

As would be expected based on these differences, eradication rates varied in these studies, from a low of 62.5% (rabeprazole 20mg)[119] to a high of 100% (pantoprazole 40mg).[128] One study found a significantly lower eradication rate for pantoprazole (40mg) than for omeprazole 40mg or high-dose pantoprazole (80mg), and another found a lower rate for rabeprazole (20 mg or 40 mg) than lansoprazole 30 mg.[130] No other study found a significant difference regardless of dose or specific PPI.

2j. 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?

Four fair quality systematic reviews assessed PPIs compared to H2-RA-based eradication regimens.[117, 134-136] All found similar eradication rates for the PPIs compared to H2-RAs.

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 adult patients being treated for symptoms of gastroesophageal reflux, peptic ulcer, and NSAID-induced ulcer?

Adverse Events

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,[4, 29, 137] 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,[4] 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,[27] and 26 of 243 (11%) withdrew at 5 years;[29] the numbers in each group did not differ significantly. In the third long-term maintenance study,[137] 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.[64]

Several reports of long-term (ranging from 1 year up to 11 years) followup of individual PPIs (omeprazole, lansoprazole, and pantoprazole) have been published.[138-152] 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 8. 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.[153]

Also in Evidence Table 8 is a head-to-head study designed to determine patient preferences about switching from one PPI to another.[154]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.

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 1, 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 CYP2A4 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 1. Clinically Significant Drug Interactions

	Omeprazole	Esomeprazole	Rabeprazole	Lansoprazole	Pantoprazole
Drugs with pH dependent absorption (e.g. ketoconazole, iron, digoxin, 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)
Glyburide					No significant interaction (3)
Antipyrene					No significant interaction (3)
Metronidazole					No significant interaction (3)
Prednisone				No significant interaction (4)	

(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.

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?

In head-to-head comparisons, no sub-groups based on demographics, other medications, or co-morbidities were studied. In included head-to-head studies, the populations included were middle aged, with mean ages ranging from a low of 43,[63] to a high of 70.[114] From 38% to 89% of the patients enrolled were male. The ethnicity of participants was only stated in four trials,[6, 16, 28, 63]. In these studies (3 conducted in the US, one[28] 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.[155] 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.[12, 92] There were no differences between PPIs (omeprazole, rabeprazole, esomeprazole) based on these characteristics.

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.

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,[124, 156] and that rapid metabolizers may have a higher failure rate in eradicating H. pylori.[119, 120] Results of subgroup analysis found no effect by race in one study of esomeprazole and lansoprazole in healing erosive esophagitis[16].

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.[157] 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.

SUMMARY AND DISCUSSION

Results for the key questions are summarized in Table 2. 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.

GERD

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. Twelve 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. The evidence that esomeprazole is more effective than the other PPIs for healing and symptoms is mixed. Two trials reported esomeprazole 40mg to be more effective than omeprazole 20mg for esophagitis healing at 4 and 8 weeks. The justification for using esomeprazole 40mg rather than 20mg in these studies is that these are the FDA approved doses, not necessarily equivalent doses. One of these also found esomeprazole 20 mg better than omeprazole 20 mg at healing at 8 weeks (absolute risk difference 3%), but no difference at 4 weeks in healing or resolution of heartburn. There are no head-to-head comparisons of omeprazole 40mg versus esomeprazole 40mg. One study found esomeprazole 40mg had higher healing rates than lansoprazole 30mg when results were presented by life-table analysis or adjusted for severity at baseline. The absolute risk difference in healing at 8 weeks was 3.8% by life-table analysis and 3.2% by adjusted crude rate analysis (NNT 26 and 29). The absolute risk difference in resolution of heartburn symptoms at 4 weeks was 2.7% (NNT 37). A second study of lansoprazole 30 mg versus esomeprazole 40 mg found them to be equivalent in healing and symptom relief. Because the esomeprazole studies use different methods of reporting and analyzing data, it is difficult to compare the results to results from other studies of PPIs for 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 and rabeprazole. A 6-month study found higher remission rates for esomeprazole 20 mg compared with lansoprazole 15 mg. Pantoprazole was more effective than ranitidine in one 12-month study.

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 only one study 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, so the strength of the evidence for comparing PPIs is poor. Only three trials compared a PPI to another drug, two with omeprazole and one with 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 six 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.

Helicobacter Pylori Eradication

The evidence regarding comparative effectiveness of various PPIs for eradicating H. pylori is fair, with five systematic reviews, and 17 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, and rabeprazole when compared to lansoprazole in one study. Symptom resolution was not assessed in these studies.

Complications

The comparative evidence on long-term adverse effects is limited. 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. There are no long-term head-to-head comparative studies (clinical or observational) specifically designed to monitor adverse effects. In long term followup studies of individual drugs, no important differences in long-term findings were apparent, but comparisons across these studies is 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 CYP2A4 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.

Subgroups

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.

Table 2. Summary of Evidence

Key Question 1: GERD	Quality of Evidence	Conclusion
Esophagitis healing	Good for (o), (l), (r), (p), Good for (e 40mg) vs (o 20mg) Poor for equivalent doses of e vs o. Fair for (e 40 mg) vs (l 30 mg)	12 head-to-head trials and three good quality systematic reviews found no differences among omeprazole, lansoprazole, rabeprazole, and pantoprazole in healing rates at 4 and 8 weeks. In two trials esomeprazole 40mg had higher 4-week and 8-week healing rates than omeprazole 20mg, but there are no head-to-head comparisons of omeprazole 40mg versus esomeprazole 40mg. One trial of esomeprazole 40 mg versus lansoprazole 30 mg found better healing rates in the esomeprazole group when results were adjusted for severity of illness, while another trial found them to be equivalent
GERD symptoms	Good for (o), (l), (r), (p), Good for (e 40mg) vs (o 20mg), Poor for equivalent doses of e vs o Good for (e 40 mg vs (l 30 mg) Fair for (o 40 mg) vs (l 30 mg), and (p 40 mg vs e 40 mg)	8 head-to-head trials and a previous systematic review of other study designs found no difference in relief of symptoms between omeprazole, lansoprazole, rabeprazole, or pantoprazole. A fair quality trial found patients taking lansoprazole had faster relief than those taking omeprazole. In two trials, more patients taking esomeprazole 40 mg had resolution of symptoms at 4 weeks than omeprazole 20 mg. In one of these, esomeprazole 40mg resulted in faster relief of symptoms.
GERD relapse	Good for (o), (l), (r) Fair for (e), (p)	One head-to-head trial[28] 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.
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 one head-to-head study was 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.

Key Question 2: Ulcer, H. pylori eradication	**Quality of Evidence**	**Conclusion**
Eradication of H. pylori	Fair	Two fair quality systematic reviews and 17 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.
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. No long-term studies of esomeprazole were found.
Short-term studies	Fair	Evidence from short-term head-to-head comparison trials do not indicate a difference in the rate of overall adverse events, serious adverse events or the rate of drop outs 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.

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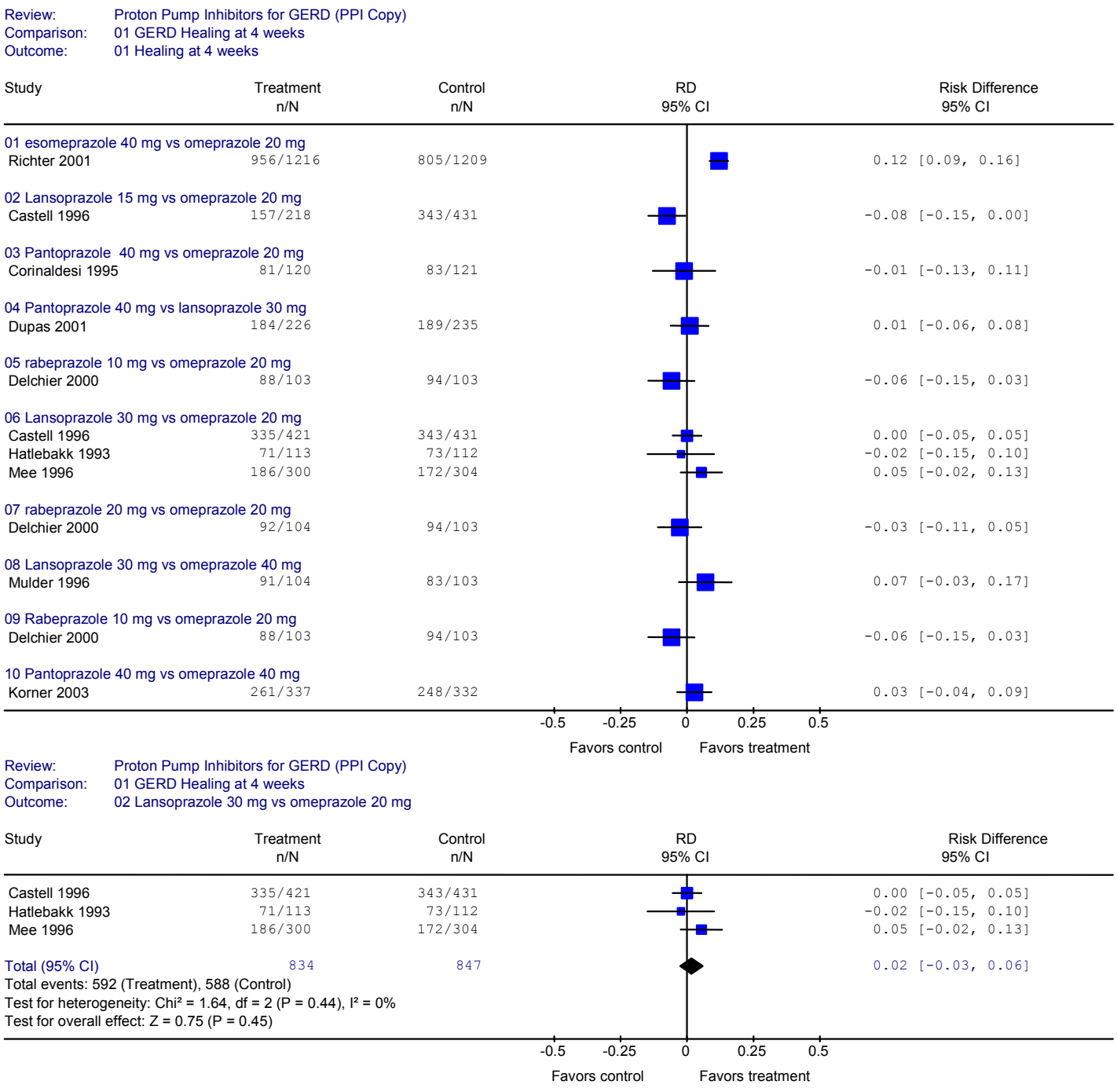
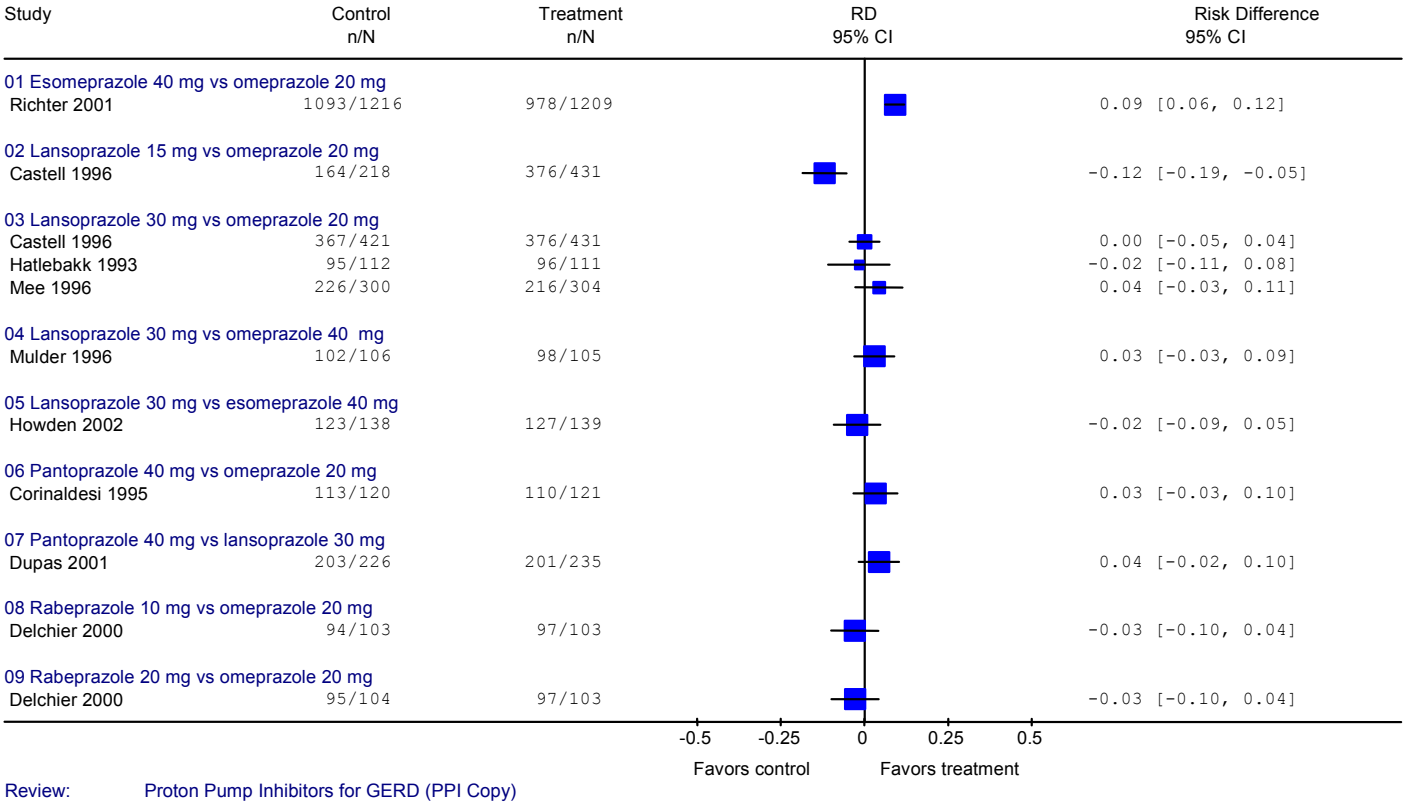
Figure 1. Head-to-head trials of esophagitis healing at 4 weeks and 8 weeks.



Review: Proton Pump Inhibitors for GERD (PPI Copy)
Comparison: 02 GERD Healing at 8 weeks
Outcome: 01 Healing at 8 weeks



Review: Proton Pump Inhibitors for GERD (PPI Copy)
Comparison: 02 GERD Healing at 8 weeks
Outcome: 02 Lansoprazole 30 mg vs omeprazole 20 mg

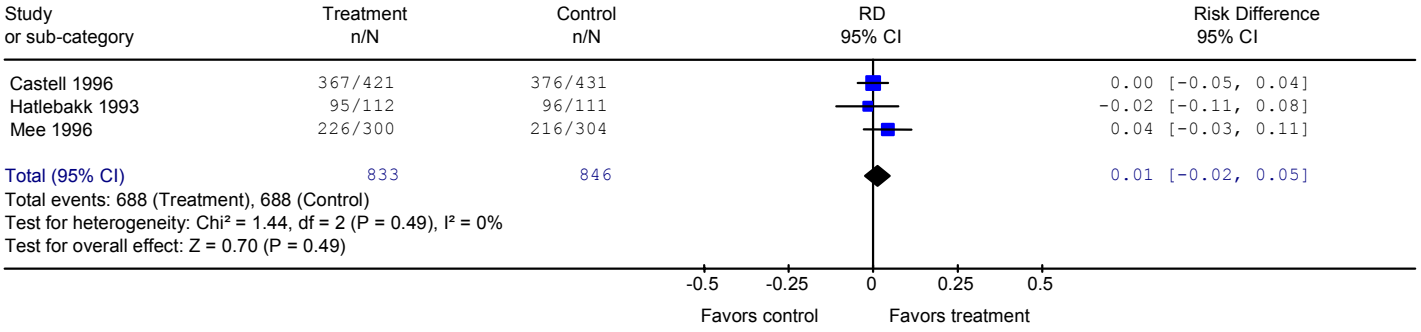
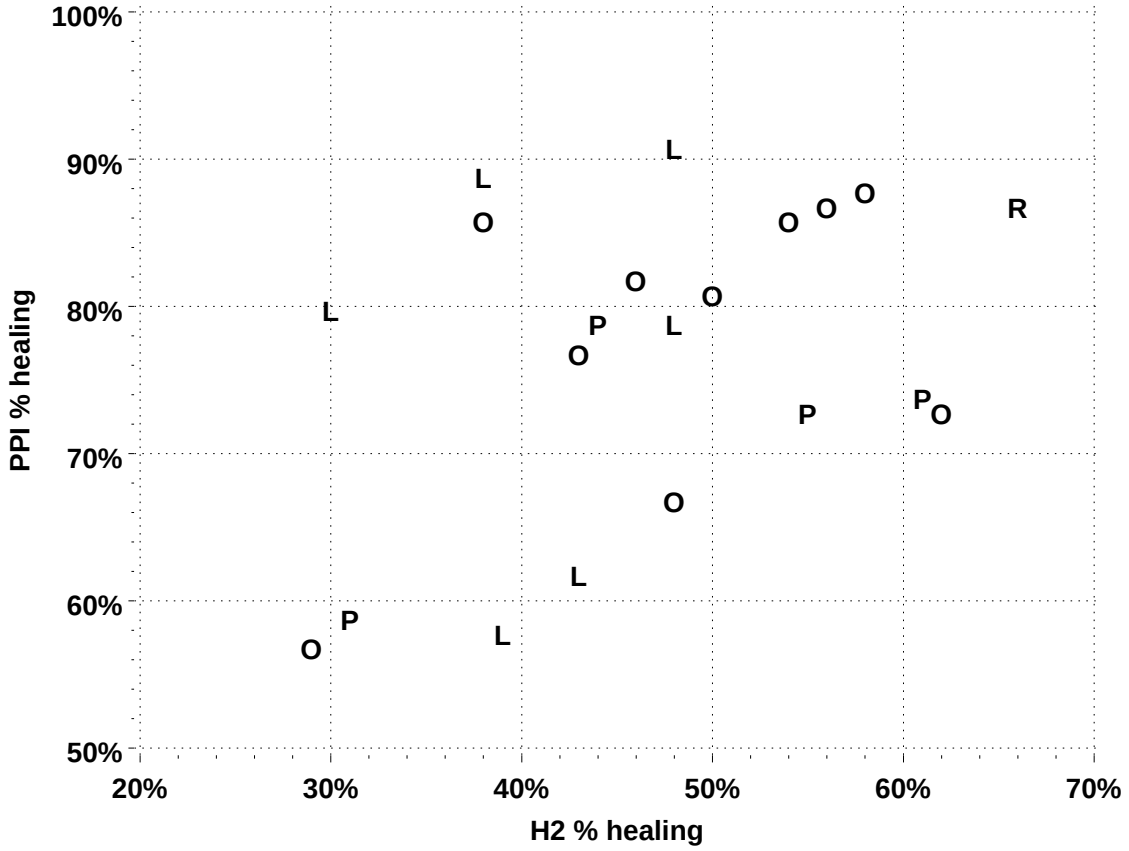


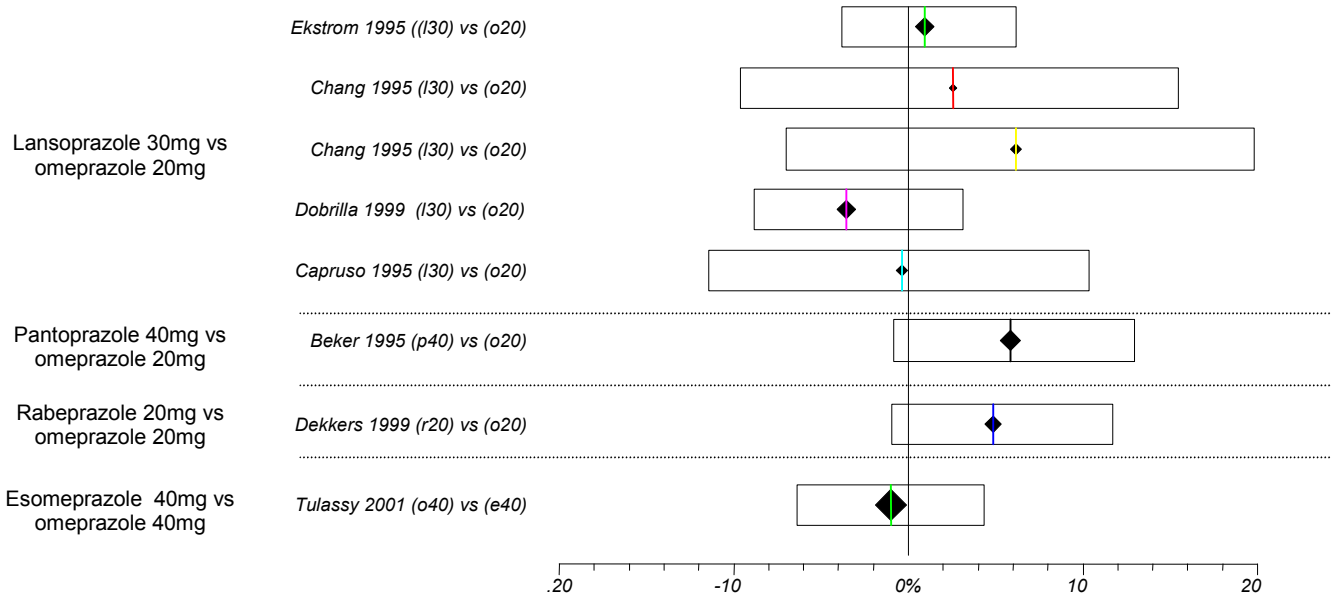
Figure 2. PPI vs. H2 Receptor antagonists for esophagitis healing at 8 weeks.



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

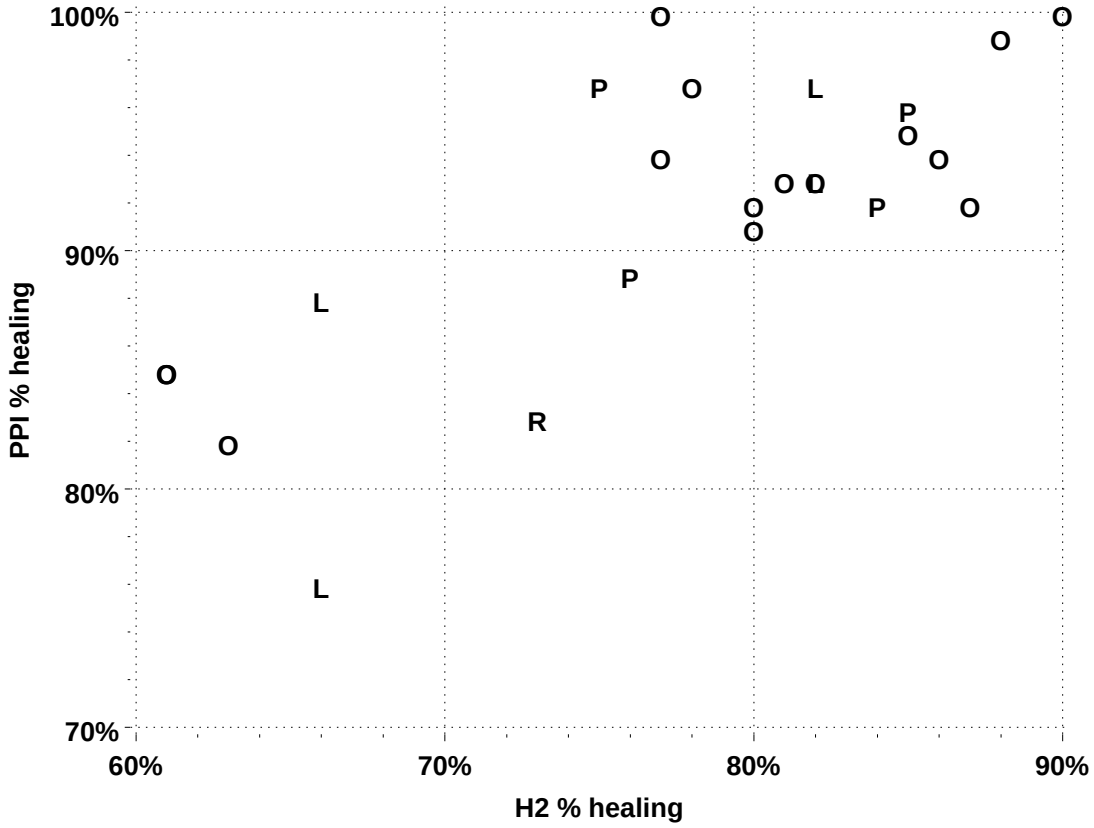


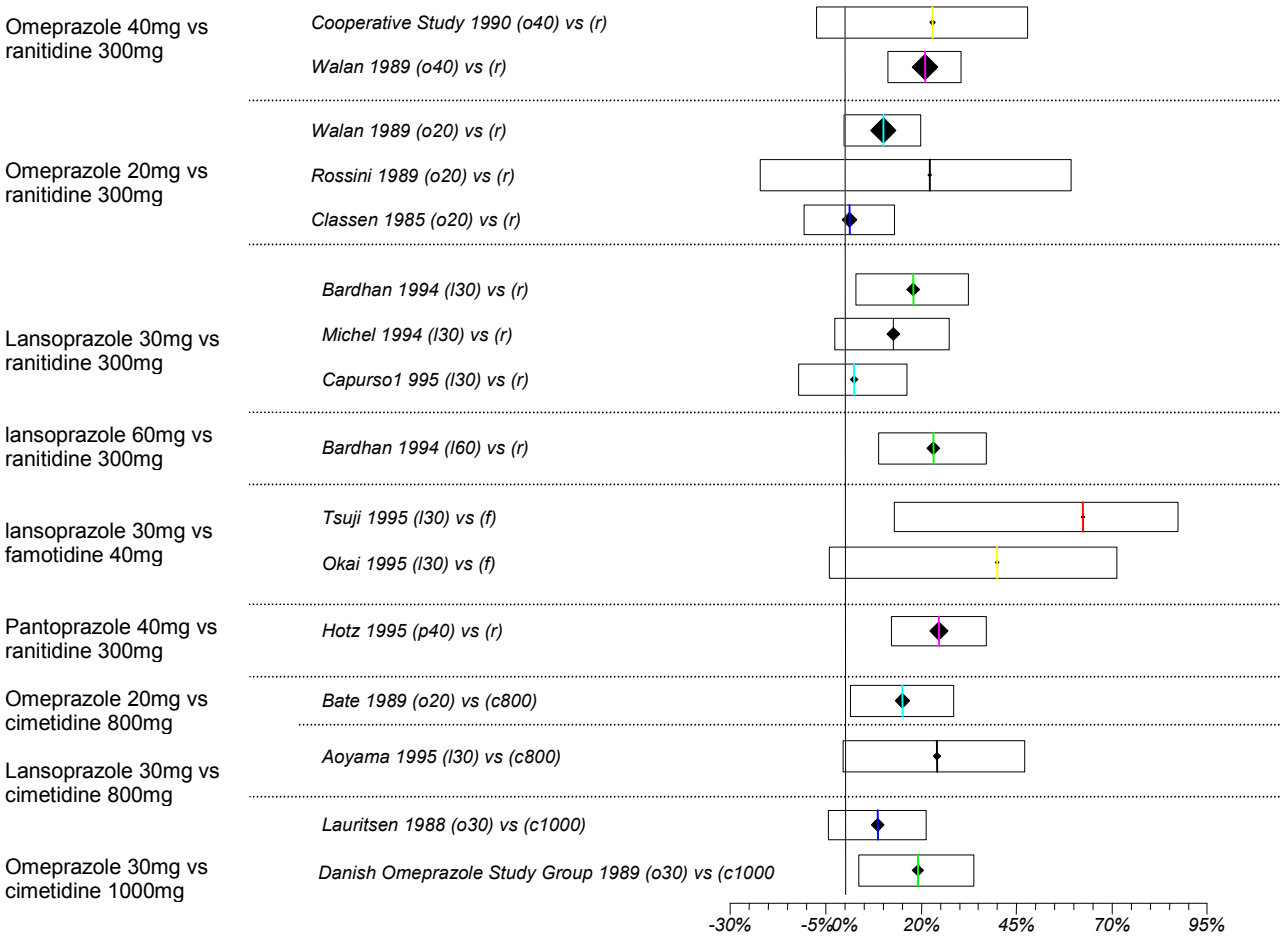
Figure 4 (continued)

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%

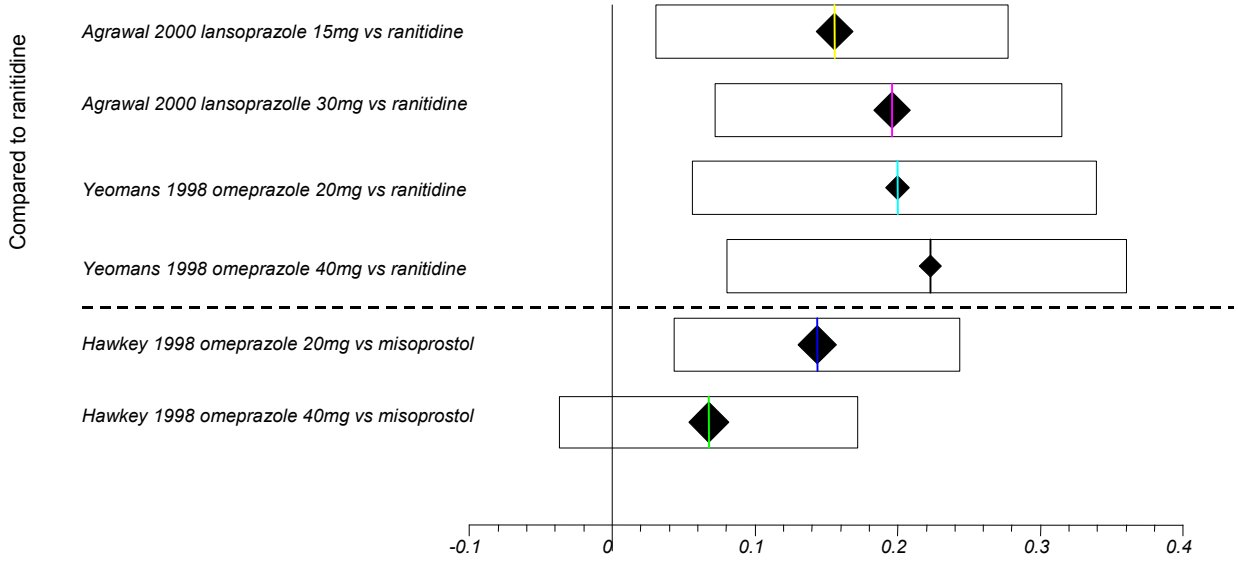
Difference between PPIs	when H2 healing is…	Mean difference	95% CrI	
Lansoprazole vs Omeprazole	60%	-9.3%	-28.1%	6.1%
	80%	0.2%	-4.6%	3.8%
	90%	0.8%	-4.0%	3.8%
Lansoprazole vs Pantoprazole	80%	0.0%	-5.0%	4.4%
Lansoprazole vs Rabeprazole	73%	7.0%	-2.5%	19.3%
Omeprazole vs Pantoprazole	80%	-0.2%	-3.1%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

Figure 5. 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%)

Figure 6. NSAID-induced gastric ulcer healing rates at 8 weeks (% risk difference)



Evidence Table 1. Randomized controlled trials of GERD treatment: PPI vs PPI

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Castell 1996	1070 US patients at multiple centers (number excludes placebo), mean age 47, (range 18-84); 60-68.4% male; 85% white, 9% black, 5% Hispanic.	Grade 2: 61%-71% Grade 3: 24%-30% Grade 4: 6%-9% (See Appendix E for scale) 6.5%-8.7% Barrett's esophagus	1284 enrolled, 1226 analyzed (total with placebo)	(l)15: 72.0% (l)30: 79.6% (o)20: 87.0% (l)30 vs (l)15 p<.05 (o)20 vs (l)15 p<.05 Other comparisons NS	(l)15: 75.2% (l)30: 87.1% (o)20: 87.0% (l)30 vs (l)15 p<.05 (o)20 vs (l)15 p<.05 Other comparisons NS
Castell et al. 2002	5241 patients, multiple centers, mean age 47 (range 18-75), 57% male, 91% white, 6% black, 3% other.	Grade A: 36% Grade B: 40% Grade C: 18% Grade D: 6% (LA Grade) Heartburn Severity None: 1% Mild: 10% Moderate: 47% Severe: 42%	5241 enrolled, ITT Number screened NR (l) 30 mg (n=2617) (e) 40 mg (n=2624)	(e) 79.4% (l) 75.1% (p≤.001) (life-table analysis) (e) 75.7% (l) 71.7% (p≤0.01, stratified by baseline severity)	EE (e) 92.6% (l) 88.8% (p=.0001) (life-table analysis) (e) 87.6% (l) 84.2% (p<0.01, stratified by baseline severity)
Corinaldesi 1995	241 patients at 30 centers, Belgium, France, Italy, the Netherlands, median age 50-52, (range 18-88); 63% male; ethnicity not given.	Grade 2: 82% Grade 3: 18% (Savary-Miller)	Number screened not given, 241 randomized, 208 evaluable; 3 withdrew, 23 did not attend f/u.	(p)40: 67.5% (o)20: 68.6% p=NS	(p)40: 80.8% (o)20: 79.3% p=NS

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Evidence Table 1. Randomized controlled trials of GERD treatment: PPI vs PPI

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Withdrawals Due to Adverse Events	Quality rating	Funding source and role of funder
Castell 1996	Not given	*Median percentage of days with heartburn:* (l)15: 12.3% (l)30: 8.6% (o)20: 11.8% *Median percentage with heartburn:* (l)15: 9.3 (l)30: 6.5 *(not ITT)* (l)15 vs (o)20 p<0.05 nights (l)15 vs (l)30 p< days and nights All other comparisons NS	(o)20: 2% (l)30: 1.7% (l)15: 0.9%	Fair: randomization and allocation method not reported, attrition not reported	Supported by TAP Pharmaceuticals, Inc.
Castell et al. 2002	*Complete resolution of heartburn:* (l) 60.2% (e) 62.9% (p≤.05) *Heartburn-free nights:* (l) 85.8% (e) 87.1% (p≤.05) *Heartburn-free days:* NS	Not reported	No difference in treatment-related adverse effects. Withdrawal due to adverse event 1.8% vs. 1.9%.	Good	Supported by AstraZeneca, also listed in author credits
Corinaldesi 1995	*Heartburn free:* (o)20: 82.2% (p)40: 87.9% p=NS	Not reported	(p)40: 0.8% (o)20: 1.7%	Poor: randomization and allocation method not reported, no intention-to-treat analysis, baseline characteristics not analyzed.	Last author from Byk Gulden Pharma-ceuticals, study supported by same.

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Evidence Table 1. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Dekkers 1999	202 patients of 27 investigators in 10 European countries, mean age 53 + 15.63, (range 20-86); 62% male; ethnicity not given.	Grade 2: 43% Grade 3: 52% Grade 4: 4% (modified Hetzel-Dent)	Number screened not given, 202 enrolled, 192 completed.	(r)20: 81% (o)20: 81% (Not ITT) p=NS	(r)20: 92% (o)20: 94% (Not ITT) p=NS
Delchier 2000	300 patients of 61 investigators at 50 European centers, mean age 53 (+15), (range 18-80); 62% male; ethnicity not given.	Mean grade 2.6-2.7, median 3.9, (modified Hetzel-Dent) 7% had Barrett's esophagus, 41% positive for H. pylori	358 screened, 310 randomized, 298 completed.	(r)20: 88.5% (r)10: 85.4% (o)20: 91.2% p=NS	(r)20: 91.3% (r)10: 91.3% (o)20: 94.2% p=NS
Dupas 2001	461 patients at 29 hospital centers and 45 private practices in France; mean age 54 (±14.6); 74% male; ethnicity not given	83% Grade 2 17% Grade 3 (Savary-Miller)	Number screened not given; 461 randomized, 385 completed	(p)40 ITT: 80.90% (l)30 ITT: 80% p=NS	(p)40 ITT: 89.80% (l)30 ITT: 90% p=NS

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Evidence Table 1. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Withdrawals Due to Adverse Events	Quality rating	Funding source and role of funder
Dekkers 1999	*Heartburn frequency (resolution):* (r)20: 29.6% (o)20: 26.5% *Daytime severity (resolution):* (r)20: 61.9% (o)20: 60.8% *Nighttime severity resolution:* (r)20: 61.6% (o)20: 57.3% p=NS for all	*Heartburn frequency resolution:* (r)20: 37.8% (o)20: 31.4% *Daytime severity resolution:* (r)68.0% (o)20: 66.0% *Nighttime severity resolution:* (r)20: 64.4% (o)20: 66.7% p= NS for all	(r)20: 1% (o)20: 0	Fair: randomization and allocation method not reported intention-to-treat for symptoms only, not for healing.	Last author (corresponding author) and 5th authors with Eisai Ltd, funding info not given.
Delchier 2000	*Severity of daytime and nighttime heartburn:* p=NS (numbers not given)	*Severity of daytime and nighttime heartburn:* p=NS (numbers not given)	(r)10: 5% (r)20: 5% (o)20: 2%	Fair: randomization and allocation method not reported, followup somewhat high (76%-83%).	Funded by Eisai Ltd, London, last author (corresponding author) from Eisai
Dupas 2001	*Symptom free (all symptoms - heartburn, acid regurgitation, pain or swallowing):* ITT: (p)40: 83% (l)30: 92% p=NS	Not reported	(p)40: 13% (l)30: 2.5%	Fair: randomized method not clear, allocation method not reported	Funded by BYK France, last author from BYK

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Evidence Table 1. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Hatlebakk 1993	229 patients at 9 hospitals in Norway and Sweden; mean age 55; 66% male; ethnicity not given	(l)30 group: Grade 0: 2.6% Grade 1: 34.5% Grade 2: 50.9% Grade 3: 12.1% (o)20 group: Grade 0: 2.7% Grade 1: 38.9% Grade 2: 55.8% Grade 3: 2.7% (See Appendix E for scale)	Number screened not given, 229 enrolled.	(l)30: 61.2% (o)20: 64.6% p=NS	(l)30: 81.9% (o)20: 85.0% p=NS
Howden et al, 2002	284 patients at multiple centers, mean age 46.5 (range 19-78), 39% male, 80% white, 5% black, 15% other.	Grade 2: 61% Grade 3:30% Grade 4: 8% (see Appendix E for scale)	284 enrolled; # screened, eligible not reported, 277 evaluated lansoprazole 30mg (n=139) esomeprazole 40mg (n=138)	lansoprazole 30 mg vs esomeprazole 40mg 77.0% vs 78.3% (p=NS)	lansoprazole 30 mg vs esomeprazole 40mg 91.4% vs 89.1% (95% CI of difference -4.7, 9.2)

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Evidence Table 1. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Withdrawals Due to Adverse Events	Quality rating	Funding source and role of funder
Hatlebakk 1993	Data not given: states (l)30 had greater improvement in heartburn (p=0.03)	Data not given, but states no significant differences in any symptoms.	(o)20: 0.9% (l)30: 0	Poor: randomization and allocation method not reported, no intention-to-treat analysis, eigibility criteria not specified, some differences at baseline.	Not reported
Howden et al, 2002	Not reported	Not reported	2/143 (1.4%) lansoprazole vs 5/141 (3.5%) esomeprazole	Fair: randomization and allocation concealment methods not reported.	Supported by TAP Pharmaceuticals.

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Evidence Table 1. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Kahrilas 2000	1960 US patients at 140 centers; mean age 46; 60% male; ethnicity not given.	Grade A: 33% Grade B: 40% Grade C: 19% Grade D: 5% (Los Angeles classification) 9.6% H. pylori	3354 screened, 1960 randomized. 44 did not complete study due to an adverse event and 115 for other reasons including loss to f/u and withdrawal of consent.	(e)40: 75.9% (e)20: 70.5% (o)20: 64.7% (cumulative life table rate) (e)20 vs (o)20 p=0.09 (e)40 vs (o)20 "significantly" higher (p not given)	(e)40: 92.2% (e)20: 89.9% (o)20: 86.9% (cumulative life table rate) (e)40 vs (o)20 p<0.001 (e)20 vs (o)20 p<0.05
Korner et al, 2003	669 patients at multiple centers, mean age 53.8 (sd 14), 60% male, ethnicity not reported.	84% Grade II 16% Grade III (Savary-Miller)	669 included; number screened, eligible not reported. pantoprazole 40 mg (n=337) omeprazole MUPS 40 mg (n=332)	ITT results reported as odds ratios only. PP results, pantoprazole 40 mg (n=282) vs omeprazole MUPS 40 mg (n=270) 70.9% vs 72.6%	ITT results reported as odds ratios only. "Healing rates after 8 weeks of treatment were also similar in both groups."

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Evidence Table 1. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Withdrawals Due to Adverse Events	Quality rating	Funding source and role of funder
Kahrilas 2000	*Resolution of heartburn* (e)40: 64.7% (e)20: 61.0% (o)20: 57.2% (e)40 vs (o)20 p=0.005 other comparisons NS	"Cumulative analysis at week 8 not done because pts could complete the study at week 4 with healed reflux esophagitis, even if symptoms were present"	(e)40: 2% (e)20: 2.6% (o)20: 2%	Fair: Randomization method not reported, intention-to-treat for symptoms only, not healing, baseline characteristics not analyzed, more dropped for "other" reasons in (o) groups, more for adverse events in (e)20 group (18 vs 13).	4 of 9 authors from Astra Zeneca, study supported by grant from Astra Zeneca.
Korner et al, 2003	ITT results not reported PP, pantoprazole 40mg vs omeprazole MUPS 40mg: *Heartburn relief:* 83.7% vs 88.1% *Relief of pain on swallowing:* 83.1% vs 91.9% (p-values not reported)	ITT results not reported PP, pantoprazole 40mg vs omeprazole MUPS 40mg: *Heartburn relief:* 91.1% vs 92.6% *Relief of pain on swallowing:* 94.1% vs 96.3% (p-values not reported)	4/337 (1%) pantoprazole, 7/332 (2%) omeprazole MUPS	Fair: ITT results not reported, randomization and allocation concelatment methods not reported.	Supported by a grant from ALTANA Pharma AG, Germany.

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Evidence Table 1. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Mee 1996	604 patients at multiple centers, UK and Ireland, mean age 53; 67% male; ethnicity not given.	Grade 1: 39% Grade 2: 44% Grade 3: 15% Grade 4: 2% (Savary-Miller)	604 enrolled, 565 eligible, 537 evaluable	(l)30: 62% (o)20: 56.6% p=NS	(l)30: 75.3% (o)20: 71.1% p=NS
Mulder 1996	211 patients at multiple centers in The Netherlands; mean age 55; 70% male; ethnicity not given.	Grade 1: 0.47% (1 patient) Grade 2: 68% Grade 3: 24% Grade 4A: 8% (Savary-Miller)	Number screened not given, 211 enrolled, 3 lost to followup, 3 withdrew for lack of efficacy, 1 withdrawn for receiving double dose.	(l)30 ITT 85.50% PP 86.20% (o)40 ITT 79% PP 79.6% p=NS	(l)30 ITT: 93.40% PP 95.70% (o)40 ITT: 90.50% PP 93.4% p=NS

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Evidence Table 1. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Withdrawals Due to Adverse Events	Quality rating	Funding source and role of funder
Mee 1996	Not given	*Improvement in daytime epigastric pain* (l)30: 85.9% (o)20: 72.5% *Improvement in nighttime epigastric pain* (l)30: 85.9% (o)20: 67.3% p=NS (includes only pts who attended 8-week visit who reported baseline pain)	Not reported	Good/Fair: Allocation concealment method not given.	1 of 2 authors from Lederle Laboratories, funding info not given.
Mulder 1996	(l)30 No symptoms: ITT: 73.60% (o)40 No symptoms: ITT 71.40%	"Because of the low number of patients not healed at 4 weeks, analysis of symptoms was not performed at 8 weeks."	None	Fair: randomization and allocation concealment not reported,	Supported by Hoechst Marion Roussel BV and Janssen-Cilag BV, Netherlands

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Evidence Table 1. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Mulder et al. 2002	461 patients, multiple centers Mean age 51.2 (range 18-80) 59% male Ethnicity NR	Savary-Miller class: I: 59% II: 29% III: 8% IVa: 4% Heartburn Severity None: 4% Mild: 22% Moderate: 45% Severe: 29%	461 enrolled Number screened NR ome 20 mg (n=151) lan 30 mg (n=156) pan 40 mg (n=154)	NR	NR
Richter et al, 2001a	2425 patients at 163 US centers; mean age 47 (sd 12); 61% male; ethnicity not given.	Grade A: (e)40 35%; (o)20 32% Grade B: (e)40 39%; (o)20 42% Grade C: (e)40 21%; (o)20 20% Grade D: (e)40 5%; (o)20 7% (LA classification)	4798 screened, 2425 randomized; 109 did not complete: 24 for adverse events, 25 investigator-initiated decision, 25 lost to followup, 31 consent withdrawn, 4 lack of therapeutic response.	(e)40 ITT 78.60% cumulative life table rate 93.70% (o)20 ITT 66.60% cumulative life table rate 83.20%	ITT 89.90% cumulative life table rate 93.70% ITT 80.90% cumulative life table rate 84.20%

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Evidence Table 1. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Withdrawals Due to Adverse Events	Quality rating	Funding source and role of funder
Mulder et al. 2002	(ome vs lan vs pan) Heartburn relief : 84% vs. 78% vs. 84% ome vs lan 90% CI -1.44 to 13.24 pan vs lan 90% CI -1.07 to 13.49 Satisfied: 79% vs. 76% vs. 79%. ome vs lan 90% CI -4.04 to 11.68 pan vs lan 90% CI -4.94 to 10.80 pan vs ome 90% cI -4.12 to 7.13	(ome vs lan vs pan) Heartburn relief : 87% vs. 81% vs. 89% pan vs ome 90% CI -4.55 to 7.64 ome vs lan 90% CI -0.79 to 12.81 pan vs lan 90% CI 0.94 to 14.17 Satisfied: 89% vs. 86% vs. 91% ome vs lan 90% CI -2.68 to 9.69 pan vs lan 90% CI -0.97 to 10.99 pan vs ome 90% CI -4.12 to 7.13	No difference in AEs between groups. None considered treatment related. Total withdrawals due to AE: 6/461 (1.3%) Total AEs: 73/461 (15.8%)	Fair: randomization and allocation methods not reported. More withdrawals in L group.	Supported by AstraZeneca
Richter et al, 2001a	(e)40 resolution of heartburn: 68.30% (o)20 resolution of heartburn: 58.10%	"Cumulative analysis at week 8 not done because pts could complete the study at week 4 with healed reflux esophagitis, even if symptoms were present"	1% in each group	Good	Supported by Astra Zeneca, one or more authors from Astra Zeneca.

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Evidence Table 1. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Richter et al., 2001b	3510 patients, multiple centers, mean age 47 (range 18-89); 57% male, 88% white, 5% black, 7% other.	Grade 0: <1% Grade 1: 0% Grade 2: 68% Grade 3: 25% Grade 4: 7% (See Appendix E for scale)	3410 enrolled; number screened, eligible not reported.	Not evaluated	Not evaluated
Scholten et al., 2003	217 patients at multiple centers, mean age 53 (sd ~14); 99% white	Grade B: 73% Grade C: 27% (LA Classification)	217 enrolled; number screened, eligible not reported.	Not evaluated	Not evaluated

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Evidence Table 1. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Withdrawals Due to Adverse Events	Quality rating	Funding source and role of funder
Richter et al., 2001b	lansoprazole 30mg vs omeprazole 20mg *Sustained resolution of heartburn:* 77.2% vs 76.2% (p=NS)	lansoprazole 30mg vs omeprazole 20mg *Sustained resolution of heartburn:* 84.3% vs 83.0% (p=NS) More patients talking lansoprazole did not have a single episode of day or night heartburn (between 10% and 15%, p<0.05, data are presented graphically only)	40/1754 (2%) lansoprazole 33/1756 (2%) omeprazole.	Fair: ITT results not reported, randomization and allocation concelatment methods not reported.	Supported by a grant from TAP Pharmaceuticals
Scholten et al., 2003	pantoprazole 40 mg vs esomeprazole 40 mg *No or only mild heartburn:* 99% vs 98%	Not evaluated	3 patients discontinued due to adverse events not related to study drug (myocardial infarction, headache, allergic reaction). Groups not reported.	Fair: ITT results not reported, randomization and allocation concelatment methods not reported.	Supported by a grant from ALTANA Pharma AG, Germany.

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Evidence Table 2. Randomized controlled trials of GERD relapse prevention: PPI vs PPI

Author Year	Population, setting	Esophagitis Grade (grading criteria), other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Carling 1998	248 patients at 23 centers in Denmark, Finland, and Sweden; mean age 56 (+/- 12); 62% male; ethnicity not given	Grade 2: 72% Grade 3: 22% Grade 4: 6% (Savary-Miller)	289 treated , 262 healed, 248 continued to maintenance phase, 226 included in per protocol analysis.
Jasperson 1998	30 patients in Germany whose esophagitis healed after 6-8 weeks of omeprazole; mean age 57; 60% male; ethnicity not given.	All Grade 4 (Savary-Miller)	36 treated, 6 did not heal, 30 included.
Lauritsen et al. 2003	1224 patients in Europe and South Africa with history of heartburn and endo-verified GERD. Mean age: 49 Male: 61% White: 98%	LA grade A: 38% B: 45% C: 14% D: 3% H. pylori positive: 31%	1391 enrolled in healing phase, 1236 (89%) randomized for maintenance treatment. ITT = 1224 (615(e), 609(l)). Healing phase: 31/1391 (2.2%) withdrawn for AE; 63 (4.5%) lack of therapeutic response; 61 (4.4%) lost, excluded, other. Randomized pop. exclusion: 12/1236 (0.1%) excluded from ITT for noncompliance or persistent esophagitis at entry. Maintenance phase: 51/1236 (4.1%) withdrawn for AE; 124 (10.0%) lack of therapeutic response; 50 (4.0%) lost, other. Similar AE profiles between groups.

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, NS = non-significant

Evidence Table 2. Randomized controlled trials of GERD relapse prevention: PPI vs PPI (continued)

Author Year	Results	Quality rating	Funding source and role of funder
Carling 1998	*Endoscopic relapse by 48 weeks:* (l)30: 8.7% (o)20: 8.2% *Symptomatic relapse by 48 weeks:* (l)30: 0.8%	Fair: allocation concealment not reported, more excluded from lansoprazole group at entry, more Grade 2 in lansoprazole group at baseline.	Supported by Wyeth Ayerst and Wyeth Lederle
Jasperson 1998	*Endoscopic remission at 4 weeks:* (o)20: 90% (l)30: 20% (p)40: 30%	Fair: allocation concealment not reported, blinding of patients not reported, very small sample size. There was selection bias.	Not reported.
Lauritsen et al. 2003	*Endoscopic remission at 6 months.* (e) 84% vs. (l) 76% (p<.0002)	Fair: small differences at baseline (slightly > males on Eso, slightly more H. pylori positive on Lan); not ITT: 12 randomized but not included in ITT analysis for not taking any study drug OR persistant esophagitis at baseline (combined); 4 in Eso group, 8 in Lan group	Sponsored by AstraZeneca

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, NS = non-significant

Evidence Table 2. Randomized controlled trials of GERD relapse prevention: PPI vs PPI

Author Year	Population, setting	Esophagitis Grade (grading criteria), other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Thjodleifsson et al. 2000 Thjodleifsson et al. 2003	243 patients at 21 centers in Europe with a previous diagnosis of erosive GERD healed within 90 days of enrollment; mean age 52.7 (+/- 14.3); 67% male; ethnicity not given.	Grade 0: 77% Grade 1: 22% 1 missing (modified Hetzel-Dent)	210/243 completed one year; 13 withdrew due to adverse events. 123 completed 5 years; 26 withdrew due to adverse events. No differences between groups.

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, NS = non-significant

Evidence Table 2. Randomized controlled trials of GERD relapse prevention: PPI vs PPI (continued)

Author Year	Results	Quality rating	Funding source and role of funder
Thjodleifsson et al. 2000 Thjodleifsson et al. 2003	*Endoscopic relapse at 13 weeks:* rabeprazole 10mg: 1.2% rabeprazole 20mg: 2.6% omeprazole 20mg: 1.2% *Endoscopic relapse at 26 weeks:* rabeprazole 10mg: 1.2% rabeprazole 20mg: 3.8% omeprazole 20mg: 1.2% *Endoscopic relapse at 52 weeks:* rabeprazole 10mg: 4.9% rabeprazole 20mg: 3.8% omeprazole 20mg: 4.8% Endoscopic relapse at 5 years: rabeprazole 10mg: 9.8% rabeprazole 20mg: 11.5% omeprazole 20mg: 13.3% p=NS for all comparisons	Fair: allocation concealment not reported, not clear if maintenance of comparable groups.	Funded by Eisai, Ltd, UK

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, NS = non-significant

Evidence Table 3. Randomized controlled trials of duodenal ulcer treatment: PPI vs PPI

Author Year Setting	Age, Gender, Race Other Population Characteristics	Intervention	Control	Number
Dobrilla 1999 Italy Multicenter	Mean age 45 (range 18 - 69) 66% male 52% smokers 34% alcohol use 90% Helicobacter pylori positive	Lansoprazole 30mg once a day x 4 weeks, then those with healed ulcer randomized to 15 or 30mg lansoprazole daily x 12 months	Omeprazole 40mg once a day, then those with healed ulcer switched to omeprazole 20mg daily x 12 months	251 eligible (167 (l), 84 (o)), unclear number found H. pylori positive who decided not to participate. Maintenance phase: 243 enrolled (164 (l), 79(o))
Chang 1995 Taiwan single center (from abstract only – full text not available for this draft)	Not available	Lansoprazole 30mg once daily x 4 weeks	Omeprazole 20mg once daily x 4 weeks	111 enrolled (57 (l), 54 (o))

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 3. Randomized controlled trials of duodenal ulcer treatment: PPI vs PPI (continued)

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Dobrilla 1999 Italy Multicenter	***Healing:*** *4 weeks:* (unclear analysis, only 243 of 251 included) 93.9% (l), 97.5% (o) ***PP analysis (# not reported):*** *4 weeks:* 99% (l), 100% (o) ***Symptoms:*** *No pain at 4 weeks:* 87.9% (l), 87.4% (o) ***Maintenance:*** (unclear analysis) *6 months:* 4.5% (l15), 0% (l30), 6.3% (o) relapse *12 months:* 3.3% (l15), 0% (l30), 3.5% (o) ***PP analysis:*** *6 months:* 0% relapse in all groups *12 months:* 1.9% (l15), 0% (l30), 3.6% (o) relapse *Followup (at 18 months):* 27.3% (l15), 20%(l30), 26.7% (o) relapse	16 during phase I (4 weeks), 10 (6%, l), 6 (7.1%, o) Phase 2 (maintenance): 9 (12.2%, l15), 4 (5.6%, l30), and 8 (11%, o). The most common adverse event was diarrhea. 8 patients withdrew due to adverse events (3 l15, 2 l30, 3 o) including diarrhea, rash, gynecomastia, asthenia, precordial pain, fever, and weight gain. No significant changes in laboratory tests were found. Serum gastrin levels were elevated in both groups at 4 weeks (increase of 23.8pg/ml (l30), 35.8pg/ml (o) NS), and continued to be elevated at 6 and 12 months of maintenance therapy. The (l15) group had the least and the (l30) group had the highest elevation at 6 and 12 months. At 6 months followup all values were returning to baseline.	Fair-poor
Chang 1995 Taiwan single center (from abstract only – full text not available for this draft)	***Healing:*** *4 weeks:* (ITT) 89.5% (l), 83% (o) (PP) 96% (l), 94% (o)	Hypergastrinemia in both groups (approximately 1.6 fold increase) Skin rash and constipation occurred in a few cases (groups not specified)	Not assessed

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 3. Randomized controlled trials of duodenal ulcer treatment: PPI vs PPI (continued)

Author Year Setting	Age, Gender, Race Other Population Characteristics	Intervention	Control	Number
Capurso 1995 Italy multicenter	Reported as 'balanced' for age, sex, weight, smokers, alcohol use, ulcer history, symptoms, ulcer size, and prior complications	Lansoprazole 30mg a day (morning) x 2 to 6 weeks	Omeprazole 20mg once daily x 2 to 6 weeks	107 enrolled, (52 (l), 55(o))
Ekstrom 1995 Sweden Multicenter	Mean age 55 47% smokers 43% alcohol users 10% NSAID users	Lansoprazole 30mg once a day x 4 weeks	Omeprazole 20mg a day x 4 weeks	279 enrolled (143 (l), 136 (o))
Fanti 2001 Italy Single center	Median age 47 (l) and 48 (o) 68% male 56% smokers 54% alcohol users	Lansoprazole 30mg once a day x 4 weeks Plus clarithromycin 500 and tinidazole 1gm x 7 days	Omeprazole 20mg a day x 4 weeks Plus clarithromycin 500 and tinidazole 1gm x 7 days	43 enrolled (22 (l) and 21 (o))
Chang 1995 Taiwan Single center	Mean age 57 and 61 89% male 47% smokers 93% H. pylori positive	Lansoprazole 30mg once daily x 4 weeks	Omeprazole 20mg once daily x 4 weeks	83 enrolled (42 (l), 41 (o))

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 3. Randomized controlled trials of duodenal ulcer treatment: PPI vs PPI (continued)

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Capurso 1995 Italy multicenter	***Healing rates:*** *2 weeks:* 58% (l), 57% (o) *4 weeks:* 94% (l), 94% (o) ***Nighttime pain free:*** *2 weeks:* 94% l), 87% (o) (NS) ***Daytime Pain free*** *2 weeks:* 92% (l), 81% (o) (NS)	8 adverse effects reported: 3 (r), 3 (l), and 2 (o). No biochemistry abnormalities, no significant difference between therapies for changes in gastrin levels or changes in endocrine cells from biopsies	Fair
Ekstrom 1995 Sweden Multicenter	***Healing rates:*** *2 weeks:* Endo: 86.2% (l), 82.1% (o) PPI: 87.9%(l), 82.3 (o) *4 weeks:* Endo: 97.1% (l), 96.2% (o) PPI: 97.7% (l), 96/7% (o) ***Symptoms:*** Most patient's symptoms improved to 'occasional' or 'none' by two weeks, nearly all by 4 weeks in both groups. At 4 weeks the reduction in symptoms favored lansoprazole, p = 0.041 (98% vs 96% with more than occasional symptoms). *Antacids:* no difference found	68 adverse events occurred in 57 patients (23 patients taking (l), 34 taking (o)). No statistically significant difference in the severity was found between the two groups. A statistically significant difference was found in the mean change in ALAT concentration, but the change was minor (0.05 unit increase (l), 0.03 unit decrease (o)).	Fair
Fanti 2001 Italy Single center	***Healing rates:*** *8 weeks:* 100% both groups ***Symptoms:*** " rapid clinical response with disappearance of symptoms in both groups"	"Mild and self-limiting" Total number not reported 1 (l) stomatitis and 1 (o) mild diarrhea	Fair
Chang 1995 Taiwan Single center	***Healing:*** *4 weeks:* 95.2% (l), 92.7% (o) ***H. Pylori eradication:*** *4 weeks:* 78.9% (l), 82.1% (o)	Serum PGA was elevated in both groups (NS), and had returned to baseline at 8 weeks. In both groups, the elevation in PGA was significantly higher in those found to have H. pylori eradication (of those H. pylori positive)	Fair

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 3. Randomized controlled trials of duodenal ulcer treatment: PPI vs PPI (continued)

Author Year Setting	Age, Gender, Race Other Population Characteristics	Intervention	Control	Number
Dekkers 1999 Belgium, England, Germany Multicenter	Mean age 48 (range 20-77) 65% male 51% smokers 54% alcohol users 83% H. pylori positive	Rabeprazole 20mg once daily. Duration not clearly stated, but assumed to be 4 weeks based on outcome measure timing.	Omeprazole 20mg a day x 4 weeks (Duration not clearly stated, but assumed to be 4 weeks based on outcome measure timing.)	205 enrolled (102 (r), 103 (o))
Beker 1995 Multicenter	Median age 44 (range 20 - 86) 70% male 50% smokers 20% alcohol users 58% 2 or more previous ulcers	Pantoprazole 40mg once daily x 2 to 4 weeks	Omeprazole 20mg once daily x 2 to 4 weeks	270 enrolled (135 each group)
Tulassay 2001 Hungary, Poland, Czech Republic Multicenter	Mean age 49 (SD 13) 62% male 100% white 57% smokers all were H. pylori positive	Esomeprazole 40mg plus clarithromycin 500mg and amoxicillin 1gm x 1 week, placebo x 3 weeks	Omeprazole 40mg x 4 weeks plus clarithromycin 500mg and amoxicillin 1gm x 1 week	446 randomized (222 (e) 224 (o))

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 3. Randomized controlled trials of duodenal ulcer treatment: PPI vs PPI (continued)

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Dekkers 1999 Belgium, England, Germany Multicenter	***Healing rates*** (ITT): *2 weeks:* 69% (r), 61% (o) *4 weeks:* 98% (r), 93% (o) ***Healing rates*** (Endo): *2 weeks:* 69% (r), 63% (o) *4 weeks:* 99% (r), 96% (o) ***Pain frequency:*** all patients showed improvement (no statistical difference found) ***Pain severity:*** All patients reported improvement in both daytime and nighttime pain. The only statistically significant difference was found in daytime pain at 4 weeks (92% vs 83% improved, (r) vs (o), p = 0.038). No difference found in the number pain free.	43 patients reported at least on adverse event. (21 (r), 22 (o)). The most common was headache. The mean elevations in serum gastrin levels at 4 weeks were 39.8 pg/ml (r) and 18.9 pg/ml (o).	Fair
Beker 1995 Multicenter	**Healing:** (PP analysis) *2 weeks:* 71% (p), 65% (o) (p=0.31) *4 weeks:* 95% (p), 89% (o) (p= 0.09) ITT analysis results reported as 'similar' ***Symptoms:*** Pain free (of those with pain at baseline) *2 weeks:* 81% (p), 82% (o) (p = 0.87) *Patient diary:* no significant differences in time course of becoming pain free.	21 patients reported adverse events (10 (p), 11 (o)), with a total of 23 events reported. Diarrhea was the most common adverse event reported. 5 were considered serious (1 (p), 4 (o)). 3 in the (o) group were considered possibly related to study treatment (1 angina pectoris, 1 hypertension, 1 vertigo) and patients were withdrawn from study. The other 2 were GI hemorrhage (p), and abdominal pain (o) and considered not related to study drugs. No clinically significant changes in lab values from baseline values. Serum gastrin levels rose in both groups at both 2 and 4 weeks, the change was statistically significant within but not between groups.	Fair
Tulassay 2001 Hungary, Poland, Czech Republic Multicenter	***Healing rates:*** *4-6 weeks:* (ITT) 91% (e), 92% (o) (PP) 94% (e), 96% (o) H. pylori eradication: (ITT) 86% (e), 88% (o) (PP) 89% (e), 90% (o) (NS)	33% of (e) and 29.5% of (o) reported at least one adverse event. Most frequent taste perversion, diarrhea, loose stools. 4 discontinued for adverse events (e: 1 for taste perversion/vomiting, o: 1 for rash, 1 allergic reaction, 1 dysmenorrhea). No clinically relevant trends for changes in laboratory safety variables.	Fair

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 4. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Dobrilla 1999 Italy Multicenter	Mean age 45 (range 18 - 69) 66% male 52% smokers 34% alcohol use 90% Helicobacter pylori positive 21% NSAID users80% treated with (l) x 8-16 weeks for acute ulcer 95% H-2 antagonist resistant acute ulcer	Lansoprazole 15 or 30mg daily x 12 months	Omeprazole 20mg daily x 12 months	Maintenance phase: 243 enrolled (164 (l), 79(o))
Lanza 1997 USA Multicenter	Mean age 43 63% male 76% Caucasian 48% smokers 56% alcohol users	Lansoprazole 15mg once daily x 12 months or until ulcer recurrence	Placebo once daily x 12 months or until ulcer recurrence	186 enrolled (88 (pl), 92 (l))

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 4. Duodenal ulcer recurrence rates on maintenance therapy (continued)

Author, Year Setting	Outcomes Reported	Number of Adverse Effects	Quality Rating	Comments
Dobrilla 1999 Italy Multicenter	***Maintenance:*** (unclear analysis) *6 months:* 4.5% (l15), 0% (l30), 6.3% (o) relapse *12 months:* 3.3% (l15), 0% (l30), 3.5% (o) ***PP analysis:*** *6 months:* 0% relapse in all groups *12 months:* 1.9% (l15), 0% (l30), 3.6% (o) relapse *Followup (at 18 months):* 27.3% (l15), 20%(l30), 26.7% (o) relapse	Serum gastrin levels were elevated in both groups at 4 weeks (increase of 23.8pg/ml (l30), 35.8pg/ml (o) NS), and continued to be elevated at 6 and 12 months of maintenance therapy. The (l15) group had the least and the (l30) group had the highest elevation at 6 and 12 months. At 6 months follow up all values were returning to baseline.	Fair/poor	If assigned to (l) during treatment study, randomized to (l); if assigned to (o) for treatment, (o) for maintenance
Lanza 1997 USA Multicenter	***Recurrence:*** *12 months:* (ITT) 62% (pl) 27%(l) (Endo) 61% (pl), 26% (l) ***Symptoms:*** Median time to becoming symptomatic >12 months both groups *Asymptomatic during 9-12 months:* 75% (l), 58% (pl) *Antacid use (tabs/day):* median 0.08 (l), 0.23 (pl) (P<0.05)	9 adverse events possibly or probably related to study drug. The most common was diarrhea. No significant differences between groups. Serum gastrin levels were significantly higher in (l) group than (pl), median 92pg.ml vs 52 pg/ml (P0.001). Values reached a plateau after one month of treatment and returned to baseline one month after treatment stopped. Gastric biopsies: significant increase in Gastrin cell density in (l) group compared to (pl) group (707cells/mm2 vs 556 cells.mm2), no other differences found.	Fair	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 4. Duodenal ulcer recurrence rates on maintenance therapy (continued)

Author, Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Kovacs 1999 USA Multicenter	Mean age 57 (pl), 54 (l15), 47 (l30) 88% male 57% smokers 39% alcohol users	Lansoprazole 15 or 30mg once daily for up to 12 months	Placebo once daily for up to 12 months	19 (pl), 18 (l15), 19 (l30), other 3 not reported)
Russo 1997 Italy Multicenter	Mean age 44 68% male 55% smokers (43% >15/day) 32% alcohol users H. pylori positive: 91%	If (l30) during healing trial: lansoprazole 15 mg or placebo once daily x 12 months or until recurrence	If (r) during healing trial: ranitidine or placebo 150mg once daily x 12 months or recurrence	Healing: 132 enrolled ((68 (l), 64 (ran) Maintenance: 108 enrolled (30 (l30/l15), 28 (l30/pl), 24 (ran/ran), 26 (ran/pl)
Graham 1992 USA Multicenter	Mean age 48 (o), 50 (ran), 47 (pl) % male: 75% (o), 67% (ran), 69% (pl) Mean index ulcer size (cm): 0.9 (o), 0.8 (ran) (P<0.01); (pl) not reported other variables reported as NS	None	None	240 enrolled (80% of (o), 63% of (ran) and 27% of (pl) patients eligible enrolled)

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 4. Duodenal ulcer recurrence rates on maintenance therapy (continued)

Author, Year Setting	Outcomes Reported	Number of Adverse Effects	Quality Rating	Comments
Kovacs 1999 USA Multicenter	***Recurrence:*** *1 month:* 27% (pl), 13% (l15), 6% (l30) *12 months:* 30% (l15), 15% (l30) All patients on (pl) experienced recurrence or withdrew from study by 6 months. ***Symptoms:*** *Symptom free at* *12 months:* 82% (l15), 76% (l30) All patients on (pl) experienced symptoms, recurrence or withdrew from study by 6 months *Antacid use:* median use (tabs/day): 0.21 (pl), 0 (l15), 0.01 (l30) NS	40 patients reported adverse events (11 (pl), 15 (l15), 14 (l30)). Adverse events possibly or probably related to study drug: 2 (pl), 2 (l15), 6 (l30). None were severe. Withdrawals due to adverse events: 2 (pl), 3 (l15), 1 (l30).No significant changes from baseline on labs, physical exam, or ECG. Serum gastrin levels increased significantly in both (l) groups compared to (pl) (P<0.001). Elevations occurred within 1 month of starting study. 8 patients (3(l15), 5 (l30)) had levels >200pg/ml during study. All returned to baseline within 1 month of stopping study drug. Changes in Grimelius-positive	Fair	Prior to enrollment, healing was achieved in all patients with (l30).
Russo 1997 Italy Multicenter	***Recurrence:*** (ITT) *3 months:* 7% (l/l), 14% (l/pl), 8% (ran/ran), 27% (ran/pl) *6 months:* 17% (l/l), 32% (l/pl), 33% (ran/ran), 46% (ran/pl) *9 months:* 23% (l/l), 36% (l/pl), 38% (ran/ran), 50% (ran/pl) *12 months:* 23% (l/l), 39% (l/pl), 46% (ran/ran), 50% (r/P) (P=0.081 (l/l) vs (ran/ran) ***Symptoms:*** results not reported	***Maintenance***: Reported as 3% (l/l), 18% (l/pl), 0% (ran/ran) (ran/pl) not reported	*Healing:* Good/Fair *Maintenance:* Fair/Poor	Healing: (l30) or (ran). baseline information on maintenance phase participants not reported. Attrition/compliance for maintenance not reported. Results for symptoms during healing phase not reported.
Graham 1992 USA Multicenter	Life table analysis relapse rates: 78% (o), 60% (ran), 50% (pl) (NS)	None reported	Fair	Followup study of (o20) vs (ran) or (o20) vs (pl)

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 5. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Dekkers 1998 Belgium, England, Germany, Iceland, Ireland, Netherlands, Poland, Spain, Sweden Multicenter	Mean age 55 57% male 52% smokers 57% H. Pylori positive 24% antacid use 96% had >/= 0.5cm ulcer	Rabeprazole 20mg once daily. Duration not clearly stated, but assumed to be 6 weeks based on outcome measure timing.	20 mg of omeprazole	227 enrolled	***Healing rates by ITT:*** *3 weeks:* 58% (r), 61% (o) *6 weeks:* 91% (r and o) *3 weeks:* 58% (r), 63% (o) *6 weeks:* 93% (r and o) *3 weeks:* 60% (r), 59% (o) *6 weeks:* 52% (r), 44% (o) ***Pain severity:*** no pain *3 weeks:* 68% (r), 61% (o) *6 weeks:* 84% (r), 68% (o) Overall well-being at 3 and 6 weeks comparable for both groups
DiMario 1994 Italy Multicenter Maintenance study	Mean age 47.9 (23-75) 71% male 13% gastric ulcers, 79% duodenal ulcers, 8% both gastric and duodenal ulcer All ulcers resistant to H2 blocker therapy (unhealed after 8 weeks of therapy)	Omeprazole 20 or 40 mg daily for 4 weeks, extended to 8 weeks if necessary. After healing: omeprazole 20 mg daily (30 patients) omeprazole 20 mg every other day (29 patients) omeprazole 20 mg twice weekly (29 patients)	Ranitidine 150 mg (12 patients only)	# screened, eligible not reported, 102 enrolled	***Recurrence (6 months) by ITT:*** 23.3% Omeprazole 20 mg daily (p <0.02 vs ranitidine) 19.4% Omeprazole 20 mg every other day (p<0.005 vs ranitidine) 58.6% Omeprazole 20 mg twice weekly 66.7% Ranitidine 150 mg

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 5. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Number of Adverse Effects	Quality Rating	Comments
Dekkers 1998 Belgium, England, Germany, Iceland, Ireland, Netherlands, Poland, Spain, Sweden Multicenter	60 patients reported at least one adverse event. (25 (r), 35 (o)). The most common was headache. Slightly elevated creatine phosphokinase at 6 weeks was found in 6 (o) patients. The mean elevations in serum gastrin levels at 6 weeks were 12.7 pg/ml (r)and 10.0 pg/ml (o).	Fair	
DiMario 1994 Italy Multicenter Maintenance study	No side effects were reported during the maintenance treatment period; 1 patient reported headache in healing period (at oemp 40 mg daily; resolved). 11 patients dropped out (27% in omep 20 mg every day group, 0 in omep every other day, 73% in omep 20 mg twice weekly)	Poor- open, differential loss to followup.	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 5. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Kovacs 1999 USA Multicenter Maintenance Study	Mean age 58 (pl), 57 (l15), 58 (l30) 85% male 67% smokers 47% alcohol users 96% acute disease H-2 RA resistant	Lansoprazole 15 or 30mg once daily for up to 12 months (if recurrence occurred, treated with open-label lansoprazole 30mg daily x 8 weeks, then resumed originally assigned maintenance treatment).	Placebo once daily for up to 12 months (if recurrence occurred, treated with open-label lansoprazole 30mg daily x 8 weeks, then resumed originally assigned maintenance treatment).	52 patients eligible, 49 enrolled	***Recurrence:*** median < 2 months (pl), > 12 months (l groups) *At 1 month:* 40% (pl), 0% (l15), 7% (l30) *12 months:* 0% (pl), 17% (l15), 7% (l30) (P<0.001 (l groups vs (pl)) ***Symptoms:*** Of those asymptomatic at baseline 0%? (pl), 100% (l15), 59% (l30) no symptoms at 12 months *Antacid use:* (tabs/day) Median 0.38 (pl), 0.02 (l15), 0.01 (l30)
Cooperative Study 1990 UK Multicenter	Mean age: 57 (o), 61 (ran) 54% male 65% smokers 74% alcohol users	Omeprazole 40mg once daily x 2 to 8 weeks	Ranitidine 150mg twice daily x 2 to 8 weeks	46 enrolled (21 (o), 25 (ran)) 27 enrolled in followup study (12 (o), 15 (ran))	***Healing (PP):*** *4 weeks:* 81% (o), 58% (ran)(NS) *8 weeks:* 93% (o), 87% (ran)(NS) ***Pain free (baseline not reported)*** *2 weeks:* 53% (o), 42% (ran)(NS) *4 weeks:* 73% (o), 38% (ran)(NS) *8 weeks:* 50% (o), 44% (ran) (NS) Nighttime pain at 2 weeks (o) < (r), data not reported, (P<0.03) Daytime pain (o) < (ran)in weeks 3 and 4 by diary card, data not reported, (P<0.03) ***Recurrence:*** *6 months:* 42% (o), 67% (ran)(NS)

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 5. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Number of Adverse Effects	Quality Rating	Comments
Kovacs 1999 USA Multicenter Maintenance Study	39 patients reported 1 or > adverse events reported (13 (pl), 14 (l15), 12 (l30), NS. The most common adverse events that were possibly or probably related to study drug were diarrhea (0%(pl), 0% (l15), 13.3% (l30) and constipation (12.5% (pl), 5.3% (l15), 0% (l30)). 7 patients withdrew due to adverse events (4 (pl), 1 (l15), 2 (l30)). No clinically significant lab changes, vital signs, or ECG seen. Serum Gastrin Significantly (P</= 0.003) greater changes from baseline seen in (l) groups vs (pl) 4 (l15), and 15 (l30) fasting levels > 200 pg/ml during study Increases occurred within 1 month of starting (l) and returned to baseline within 1 month of stopping drug Gastric Mucosal Biopsy Increases in Grimelius positive cell density in the corpus (from baseline) 121 cells/mm2 (pl), 146 cells/mm2 (l15), 176 cells/mm2 (l30) (P=0.001 vs (pl)). No other cell changes seen.	Fair	
Cooperative Study 1990 UK Multicenter	1 death judged to be unrelated to study. 9 patients reported adverse events (5 (o), 4 (ran)). The most common were GI symptoms.	Poor	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 5. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Walan 1989 13 countries (primarily European plus Australia and Canada), 45 centers	Mean age 55 (o20), 57 (o40), 58 (ran) % smokers 61% (o20), 60% (o40), 56% (ran) % alcohol users 60% (o20), 57% (o40), 50% (ran) NSAID use 11% (o20), 12% (o40), 11% (ran)	Omeprazole 20mg or 40mg once daily x 4 to 8 weeks	Ranitidine 150mg twice daily x 4 to 8 weeks	602 enrolled (436 gastric ulcers, 166 prepyloric ulcers)	***Healing:*** ***Gastric + prepyloric (PP analysis):*** *4 weeks:* 69% (o20), 80% (o40), 59% (ran) *8 weeks:* 89% (o20), 96% (o40), 85% (ran) ***ITT analysis reported as 'similar'*** *Prepyloric only:* (PP analysis) *2 weeks:* 33% (o20), 42% (o40), 27% (ran)(NS) ***NSAID users (PP analysis)*** *4 weeks:* 61% (o20), 81% (o40), 32% (ran) *8 weeks:* 82% (o20), 95% (o40), 53% (ran) ***Symptoms:*** *None at 2 weeks:* 62% (o20), 69% (o20), 55% (ran)((o40) vs (ran)P= 0.02) *Followup Study:* *Healing maintained at 6 months:* 59% (O40 and O20), 53% (ran) (P=0.03 (o40) vs (ran)) *No symptoms 'during followup':* 52% (O40 and O20), 48% (ran)(P=0.02 (o40) vs (ran))
Rossini 1989 Italy Single center	Data not reported – stated to be similar	Omeprazole 20mg or 40mg once daily x 4 to 8 weeks	Ranitidine 150mg twice daily x 4 to 8 weeks	18 enrolled (number per group not stated)	***Healing*** *4 weeks:* 78% (o), 50% (ran) *8 weeks:* 100% (o), 87% (ran) Pain disappeared almost completely in both groups by two weeks

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 5. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Number of Adverse Effects	Quality Rating	Comments
Walan 1989 13 countries (primarily European plus Australia and Canada), 45 centers	106 patients reported adverse events (34 (o20), 32 (o40), 40 (ran)). The most common were GI symptoms, similar in all groups. Numbers withdrawn or lost to follow up: 21 (o20), 19 (o40), 22 (ran) 3 patients died during study (all on (o40)) of causes shown to be unrelated to study drug, 2 patients withdrawn due to abnormal labs also shown to be unrelated to study drugs ((1 (o40), 1 (ran)).	Good/Fair	Patients enrolled in followup study not well described, attrition not described.
Rossini 1989 Italy Single center	None reported in either group	Fair/poor	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 5. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Classen 1985 Germany Multicenter	Data not reported – stated to be similar	Omeprazole 20mg once daily x 4 to 6 weeks	Ranitidine 150mg twice daily x 4 to 6 weeks	184 enrolled	***Healing (PP analysis only):*** *2 weeks:* 43% (o), 45% (ran) (NS) *4 weeks:* 81% (o), 80% (ran) (NS) *6 weeks:* 95% (o), 90% (ran) NS ***Symtoms:*** "equally good with either drug"
Bardhan 1994 United Kingdom and Sweden Multicenter	Mean ages 60 (l60), 59(l30), 57(r) 57% males 65% UK 35% Sweden 52% smokers 60% alcohol use 11% NSAID use	Lansoprazole 30mg or 60mg once a day x 4 to 8 weeks	Ranitidine 300mg every night x 4 to 8 weeks	250 enrolled	***Healing rates:*** *4 weeks:* *of those with endoscopy:* 78% (120), 84% (160), 61% (ran) ***ITT:*** 72% (l30), 73% (l60), 52% (ran) ***PP:*** 80% (l30), 78% (l60) 57% (ran) *8 weeks:* *of those w/endoscopy:* 99% (l30), 97% (l60), 91% (ran) ***ITT:*** not reported ***PP:*** 98% (l30), 100% (l60), 90% (ran) *Symptoms:* proportaion symtom free at 4 weeks: *Pain:* 75% (l30), 72% (l60), 65% (ran) *Nausea:* 88% (l30), 89% (l60), 76% (ran) *Vomiting:* 100% (l30), 87% (l60), 89% (ran)

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 5. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Number of Adverse Effects	Quality Rating	Comments
Classen 1985 Germany Multicenter	Not reported	Poor	This appears to be a report in English of two trials previously published in German, therefore the quality of the trials may be higher than appears from this paper.
Bardhan 1994 United Kingdom and Sweden Multicenter	69 patients experienced 91 adverse events, 26% (l30), 27% (l60), 30% (ran). The most common thought to be possibly or probably related to study drug were diarrhea and headache.	Fair	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 5. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Michel 1994 France Multicenter	Mean age 52 (l), 56 (ran) 69% male 38% smokers 52% alcohol users 42% NSAID users mean ulcer size 12mm (l), 11mm (ran)	Lansoprazole 30mg once daily x 4 to 8 weeks	Ranitidine 150mg twice daily x 4 to 8 weeks	158 enrolled	***Healing:*** *4 weeks:* ITT 68% (l), 56% (ran)NS PP: 80% (l), 62% (ran)(p<0.05) *8 weeks:* ITT 81% (l), 76% (ran)(NS) PP: 100% (l), 87% (ran)(P<0.05) *No epigastric pain:* (at baseline 26% (l), 22% (ran)) *4 weeks:* 73% (l), 72% (ran)(NS) *8 weeks:* 95% (l), 92% (ran)(NS)
Capurso 1995 Italy Multicenter	Data not reported – stated to be similar	Lansoprazole 30mg once daily x 2 to 8 weeks	Ranitidine 300mg once daily x 1 x 2 to 8 weeks	74 enrolled (34 (l), 35 (o), 5 not reported)	***Healing rates:*** *2 weeks:* 41.4% (l), 26.5% (ran) *4 weeks:* 79.3% (l), 61.8% (ran) *8 weeks:* 96.6% (l), 94.1% (ran) ***Pain:*** at 2 weeks no significant difference between groups 64% pain free

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 5. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Number of Adverse Effects	Quality Rating	Comments
Michel 1994 France Multicenter	38 patients reported adverse events. 4 withdrawn due to serious adverse events all (r)group). 3 of these were deaths (1 acute heart failure, 2 acute respiratory distress), the forth withdrawn due to femur fracture resulting from hypotension. GI symptoms (diarrhea, constipation were the most common adverse effects reported in both groups.	Fair	Numbers of subjects in PP analysis do not add up. Table 2 shows 3 patients withdrawn due to adverse events, but text reports 4. Table 2 reports 16 lost from (l) (79 - 16 = 63) but only 62 included in PP analysis. Likewise, number analyzed at 4 weeks on (ran)reported as 68, but 12 reported lost (79 - 12 = 67)
Capurso 1995 Italy Multicenter	8 adverse effects reported: 3 (ran), 3 (l), and 2 (o) No biochemistry abnormalities, no significant difference between therapies for changes in gastrin levels or changes in endocrine cells from biopsies	Fair	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 5. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Hotz 1995 Germany Multicenter (28)	Median age 55 (p), 57 (r) 60% male 45% smokers 9.7% everyday alcohol users mean ulcer diameter 10.9 (p), 11.2 (r)	Pantoprazole 40mg once daily x 2, 4 or 8 weeks depending on healing. (2:1 randomization p:r)	Ranitidine 300mg every night x 2, 4 or 8 weeks depending on healing	248 enrolled.	***Healing:*** *2 weeks:* ITT: 33% (p), 17% (ran) (P<0.01) PP: 37% (p), 19% (ran) (P<0.01) *4 weeks:* ITT 77% (p), 52% (ran) (P<0.001) PP: 87% (p), 57% (ran) (P<0.001) *8 weeks:* ITT 86% (p), 72% (ran) (P<0.01) PP: 97% (p), 80% (ran) (P<0.001) No pain:(13% (p), 8% (ran) at baseline) (PP) *2 weeks: 7*2% (p), 68% (ran) (NS) Based on diary card, no difference between groups in time to becoming pain free Other GI symptoms also improved in both groups.
Tsuji 1995	Mean age 64 81% male 50% H. pylori positive	Lansoprazole 30mg once x 4 to 8 weeks	Famotidine 40mg x 4 to 8 weeks	16	***Healing:*** *4 weeks:* 71% (l), 29% (f) *8 weeks:* 83% (l), 57% (f) Symptoms not reported
Okai 1995	Mean age 54 (range 36-86) (l30) 59 (range 39-80) (f) 75% male 71% smokers 38% ulcer size >15mm	Lansoprazole 30mg once daily x 2 to 8 weeks	Famotidine 40mg once daily x 2 to 8 weeks	24	***Healing:*** *4 weeks:* 50% (l), 0% (f) *8 weeks:* 54.5% (l), 18.2% (f) (from Kovacs, 1998) **Symptoms:** Pain free at week 1:80% (l), 60% f) (NS)

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 5. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Number of Adverse Effects	Quality Rating	Comments
Hotz 1995 Germany Multicenter (28)	26 patients reported adverse events (15 (p), 11 (ran). The most frequent was diarrhea (3) and headache (2) on (pl), and sleep disorder (2) on (ran). 4 (p) and 3 (ran) withdrew due to adverse events, 1 (r) patient had elevated serum transaminase levels, otherwise lab values were normal. Median change in serum gastrin levels at 8 weeks: 30pg.ml (pl), 12pg/ml (ran), median values at all time points were higher in the (p) group.	Good/Fair	
Tsuji 1995	None	Fair	
Okai 1995	None	Fair	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 5. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Bate 1989 UK and Republic of Ireland Multicenter	Mean age 57 47% male 59% smokers 3% ulcer size >10mm	Omeprazole 20mg once daily x 4 to 8 weeks	Cimetidine 800mg x 4 to 8 weeks	197 enrolled (105 (o), 92 (c))	***Healing (ITT):*** *4 weeks:* 73% (o), 58% (c) (P<0.05) *8 weeks:* 84% (o), 75 (c) (NS) ***Symptoms*** ***Pain free*** *4 weeks:* 81% (o), 60% (c) (P<0.01) *8 weeks:* "difference no longer significant" *4 weeks* (but not at 8 weeks) Daytime pain and heartburn less in (o) (P<0.05) data not reported. No difference in nocturnal pain or nausea Diary cards: 2 weeks: (o) better than (c) for daytime pain (P<0.01), nighttime pain (P<0.05) and antacid use (P<0.0001)
Lauritsen 1988 Denmark Multicenter	Mean age 57 45% male 74% smokers mean ulcer 9.7, 10.7 mm	Omeprazole 30mg once daily x 6 weeks	Cimetidine 1000mg x 6 weeks	179 eligible, 176 enrolled (3 chose not to participate)	***Healing:*** *2 weeks:* ITT: 54% (o), 39% (c) PP: 55% (o), 42% (c) *4 weeks:* ITT 81% (o), 73% (c) PP: 85% (o), 77% (c) *6 weeks:* ITT 86% (o), 78% (c) PP: 89% (o), 86% (c) ***No pain:*** (24% (o), 14% (c) at baseline) *2 weeks:* 48% (o), 29% (c) *4 weeks:* 57% (o), 47% (c) *6 weeks:* 62% (o), 58% (c) Number of hours of pain at 6 weeks: 7.5 (o), 10.5 (c)

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 5. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Number of Adverse Effects	Quality Rating	Comments
Bate 1989 UK and Republic of Ireland Multicenter	32 patients reported adverse events (19% (o), 15% (c)). 2 were serious, but considered unrelated to study. 7 (4 (o),3 (c)) withdrew due to adverse events (2 in (o) were due to lack of efficacy). The most common adverse events were GI and CNS system related in both groups	Fair/Poor	
Lauritsen 1988 Denmark Multicenter	12 reports of adverse events. (o): one each: headache, fatigue, transient diarrhea, gastroenteritis, muscle pain. (c): one each of headache, dry mouth, 2 each of dizziness, impotence	Fair	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 5. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Danish Omeprazole Study Group 1989	Median age 60 (range 52-71) (o) 61 (range 50-72) (c) 48% male 69% smokers	Omeprazole 30mg x 2 to 6 weeks	Cimetidine 1000mg x 2 to 6 weeks	161 enrolled 146 evaluated	***Healing:*** *2 weeks:* 41% (o), 41% (c) *4 weeks:* 77% (o), 58% (c) *6 weeks:* 88% (o), 82% (c) ***Symptoms*** ***Mean days with pain:*** *2 weeks:* 5 (o), 5.5 (c) *4 weeks:* 4.3 (o), 3.8(c) *6 weeks:* 2.4 (o), 2.4(c) (all NS) 6-month followup (untreated) no difference in relapse rate (Endo):17% (o), 19% (c)
Aoyama 1995	Data not reported – stated to be similar	Lansoprazole 30mg x 2 to 8 weeks	Cimetidine 800mg x 2 to 8 weeks	107 enrolled 84 evaluated	***Healing:*** *2 weeks: 14% (l), 6% (c)* *4 weeks:71% (l), 47% (c)* *6 weeks:* 94% (l), 75% (c)

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 5. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Number of Adverse Effects	Quality Rating	Comments
Danish Omeprazole Study Group 1989	3 withdrawals due to adverse effects in (c) group due to 'other diseases' and urticarial reaction. 19 other adverse events reported. (o) group: allergic edema, itching, diarrhea (2 cases), tremor, polyuria, shoulder pain, and pulmonary edema.. (c) group: itching, diarrhea, constipation (2), dizziness (2), fatigue (2), insomnia, and back pain (2).	Poor	
Aoyama 1995	Nor reported.	Poor	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 6. Randomized controlled trials of NSAID-induced ulcer treatment

Author Year Setting Purpose	Age, Gender, Race, Other population characteristics	Interventions	Control	Number Screened/Eligible/ Enrolled
Hawkey 1998 International (14 countries including USA) Treatment or prevention	Mean age 58 (range 20 to 85) 38% male 23% smokers 39% H. pylori positive 8% history of bleeding ulcer 41% gastric ulcer 38% rheumatoid arthritis	20 mg or 40 mg of omeprazole once daily (duration not clearly stated, assumed to be 8 weeks)	200 mcg of misoprostol four times daily	935 enrolled

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 6. Randomized controlled trials of NSAID-induced ulcer treatment (continued)

Author Year Setting Purpose	Outcomes reported (results)	Number of adverse effects	Quality rating	Comments
Hawkey 1998 International (14 countries including USA) Treatment or prevention	***Treatment Success at 8 weeks:*** 76% (o20), 75% (o40), 71% (m) (NS) ***ITT analysis:*** 75% (o20), 75% (40), 71% (m) ***GU only:*** 87% (o20), 80% (o40), 73% (m) (P=0.004 (o20) vs (m); 0.14 (o40) vs (m) ***GU and DU:*** 85% (o20), 79% (o40), 74% (m) ***DU only:*** 93% (o20), 89% (o40), 77% (m) ***Erosions only:*** 77% (o20), 79% (o40), 87% (m) ***H. pylori positive:*** 83% (o20), 83% (o40), 69% (m) ***H. pylori negative:*** 73% (o20), 70% (o40), 74% (m) ***Symptoms:*** Reduction in mod-severe dyspepsia at 4 weeks 34% (o20), 39% (o40), 27% (m) Proportion of days with abdominal pain 43% (o20), 43% (o40), 50% (m) Proportion of days with heartburn 16% (o20), 14% (o40), 29% (m) QOL (completed by 68% (o20), 66% (o40), 62% (m)) Gastrointestinal Symptom Rating Scale at 8 weeks change in total score-0.47 (o20), -0.36 (o40), -0.20 (m) change in reflux score: -0.82 (o20), -0.75 (o40), -0.33(m) change in diarrhea score: -0.24 (o20), -0.06 (o40), +0.22 (m) Nottingham Health Profile change in sleep score: -3.1 (o20), -8.6 (m), (o40 not reported)	470 patients reported adverse events (48% (o20), 46% (o40), 59% (m) Most common reported was diarrhea (4.5% (o20), 5.3% (o40), 11.4 % (m)	Fair	Patients without healing at eight weeks received open treatment with 40 mg of omeprazole daily for a further four to eight weeks.

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 6. Randomized controlled trials of NSAID-induced ulcer treatment (continued)

Author Year Setting Purpose	Age, Gender, Race, Other population characteristics	Interventions	Control	Number Screened/Eligible/ Enrolled
Yeomans 1998 International (15 countries) Traetment or prevention	Mean age 57 33% male 10% history of bleeding ulcer 39% gastric ulcer 46% H. pylori positive 44% rheumatoid arthritis	20 mg or 40 mg of omeprazole once daily for four or eight weeks	150 mg of ranitidine twice daily for four or eight weeks	541 enrolled

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 6. Randomized controlled trials of NSAID-induced ulcer treatment (continued)

Author Year Setting Purpose	Outcomes reported (results)	Number of adverse effects	Quality rating	Comments
Yeomans 1998 International (15 countries) Traetment or prevention	***Treatment Success at 8 weeks:*** 80% (o20), 79% (o40), 63% (ran) ***GU only:*** 84% (o20), 87% (o40), 64% (ran) ***DU only:*** 92% (o20), 88% (o40), 81 (ran) ***Erosions only:*** 89% (o20), 86% (o40), 77% (ran) ***H. pylori positive*** *:* 83% (o20), 82% (o40), 72% (m) *H. pylori negative:* 75% (o20), 71% (o40), 55% (m) ***Symptoms:*** *reduction of 'moderate to severe' category at 4 weeks:* 46% (o20), 38% (ran) (o40 not reported)	190 moderate to severe adverse events were reported (30% (o20), 38% (o40), 40% (r) GI effects (diarrhea, nausea, constipation, and flatulence) were the most common reported Discontinuation of therapy due to either and adverse event or lack of efficacy (not reported separately): 2.8% (o20), 3.2% (o40), 8.5% (ran)	Fair	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 6. Randomized controlled trials of NSAID-induced ulcer treatment (continued)

Author Year Setting Purpose	Age, Gender, Race, Other population characteristics	Interventions	Control	Number Screened/Eligible/ Enrolled
Agrawal 2000 USA and Canada, multicenter healing only	Mean age 60 35% male 90% white 21% smokers 31% alcohol users 29% H. pylori positive	Lansoprazole, 15 or 30 mg once daily for 8 weeks	Ranitidine 150 mg twice daily for 8 weeks	Endoscopy was performed on 669 patients, 353 met inclusion criteria.

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 6. Randomized controlled trials of NSAID-induced ulcer treatment (continued)

Author Year Setting Purpose	Outcomes reported (results)	Number of adverse effects	Quality rating	Comments
Agrawal 2000 USA and Canada, multicenter healing only	***Healing: Gastric Ulcer*** *4 weeks:* 47% (l15), 57% (l30), 30% (ran) *8 weeks:* 69% (l15), 73% (l30), 53% (ran) ***GU and DU 8 weeks****:* 93% (l15), 81% (l30), 88% (ran) ***GU or erosions 8 weeks:*** 85% (l15), 100% (l30), 86% (l30) ***H. pylori positive: 8 weeks:*** 67% (l15), 82% (l30), 60% (ran) ***H. pylori negative****:* 70% (l15), 69% (l30), 51% (ran) ***Symptoms:*** *4 weeks:* no daytime pain 66% (l15), 64% (l30), 60% (ran) no nighttime pain 67% (l15), 69% (l30), 64% (ran) % days antacids used 67% (l15), 70% (l30), 62% (ran) *8 weeks:* no daytime pain 70% (l15), 66% (l30), 63% (ran) no nighttime pain 71% (l15), 71% (l30), 69% (ran) % days antacids used 69% (l15), 71% (l30), 64% (ran)	33 patients reported an adverse event, 15 patients stopped taking study medication because of adverse events (5 (l15), 4 (l30), 6 (ran)). The most commonly reported treatment-related event was diarrhea.	Good/Fair	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Evidence Table 7. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer

Author Year	Population setting	Diagnosis	Eligibility criteria	Interventions	Control
Lai et al. 2002	123 patients, double blind, ITT. Hong Kong, mean age 70 (range 18-80), female 28%, race NR. 245 screened, 171 eligible by H. pylori, 127 treated, 4 H. pylori uneradicated.	History of cerebrovascular accident (52%) or heart disease (48%) - endo revealed gatric (74%), duodenal (21%) or gastroduodenal (5%) ulcer.	- History of stroke or ischemic heart isease requiring long-term aspirin therapy; - Ulcer developed after at least one month low-dose aspirin therapy; - H. pylori infection; - Ulcer and H. pylori successfully eradicated during initial healing phase of study; - No esophagitis, history of ulcer surgery, comcomitant treatment with NSAIDs, corticosteroids or anticoagulant agents, active cancer, or allergic to study drugs.	30 mg (l) + 100 mg aspirin bid for median 12 months	Matching placebo + 100 mg aspirin bid
Graham, 2002	US and Canada Multicenter Mean age 60 65% female 90% white, 6% black, 4% other.	No H. pylori; reason for long-term NSAID use not reported, previous GI disease: 59% reflux esophagitis, 50% duodenal ulcer, 99% gastric ulcer.	Age 18 or older, h/o endoscopically-documented gastric ulcer with or without coexisting duodenal ulcer or GI bleeding, and treatment with stable, full therapeutic doses of an NSAID (except nabumetone or aspirin >1300 mg/day) for at least the previous month.	Lansoprazole 15 or 30 mg for 12 weeks	Misoprostol 200 mcg qid for 12 weeks

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (m) = misoprostol (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations:(c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, qid - 4 times a day; Endo = all patients evaluable by endoscopy analysis

Evidence Table 7. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer (continued)

Author Year	Other Medications	Definition of Treatment Failure/Success	Outcomes Reported (Results)	Adverse Effects	Quality Rating
Chuen et al. 2002	Antacid permitted, advised to avoid other NSAIDs if possible	Primary endpoint: recurrence of ulcer complications (bleeding, outlet obstruction, perforation). Secondary endpoint: recurrence of ulcer.	Clinical Bleeding: (l) = 0, (pl) = 8 (p≤.01) Ulcer recurrence: (l) = 1, (pl) = 9 (p=.008) H. pylori recurrence: (l) = 0, (pl) = 4 (p≤.05)	Death: (l) = 1, (pl) = 0 Other adverse effects NR.	
Graham 2002	40% ibuprofen, 35% naproxen, 32% diclofenac, 22% aspirin or aspirin combinations, 17% piroxicam, 34% other NSAIDS	Occurrence of gastric ulcer (definition of gastric ulcer not specified), included analysis with withdrawals considered treatment failures (having a gastric ulcer).	***Treatment success:*** *Free of gastric ulcer by week 12 (per protocol):* *(pl)* :51% (m): 93% (l15): 80% (l30): 82% ***Treatment success:*** *Results when withdrawals classified as treatment failures:* *(pl)* :34% (m): 67% (l15): 69% (l30): 68%	Withdrawals due to adverse events: (pl) 6.7%, (m) 10.4%, (l15) 2.9%, (l30) 7.5%; Higher percentage of treatment related adverse events in misoprostol group (31% (m), 10% (pl), 7% (l15), 16% in (l30); most common diarrhea. One upper GI tract hemorrhage (l15).	Fair: randomization and allocation method not reported.

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (m) = misoprostol (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations:(c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, qid - 4 times a day; Endo = all patients evaluable by endoscopy analysis

Evidence Table 7. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer (continued)

Author Year	Population setting	Diagnosis	Eligibility criteria	Interventions	Control
Bianchi Porro 2000	Italy Single center Mean age 59.9 (range 22-80) 83% female ethnicity not given	63% rheumatoid arthritis 38% osteoarthritis.	Over age 18, with rheumatoid arthritis or osteoarthritis, treated with effective and constant doses of NSAIDs (diclofenac, ketoprofen, indomethacin) for at least 8 weeks prior to start of study. Lanza endoscopic grade 0,1, or 2.	Pantoprazole 40 mg	Placebo
Labenz et al. 2002	2264 patients screened, 832 randomized, 660 analyzed - in 3 countries in central Europe, double blind, not ITT. Mean age: 55 Male: 38%	Systemic inflammatory disease (24%), noninflammatory disease (73%), mild dyspepsia (42%), Lanza score "0" on study entry (stomach 68%; duodenum 89%).	Age >18 years with inflammatory disease of musculoskeletal system requiring NSAID treatment ≥5 weeks, and H. pylori positive. Excluded for ulcer or history of ulcer, clotting disorders, prior regular use of NSAIDS (except aspirin ≤100 mg/day), antibiotics, PPIs, misoprosol, or bismuth salts within 4 weeks; regular use of H2R antagonists, prokinetics or sucralfate; systemic corticosteroids, known or suspected intolerance to study drug, severe concomitant diseases; previous gastric surgery; pregnancy or nursing; and dyspepsia therapy.	OAC-O = omeprazole 40 mg + amoxicillin 2 g +clarithro-mycin 1000 mg for 1 week, then 20 mg ome for 4 weeks. O-O = 20 mg ome for 5 weeks.	OAC-P = OAC for 1 week, then placebo for 4 weeks. P-P = placebo for 5 weeks.

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (m) = misoprostol (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations:(c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, qid - 4 times a day; Endo = all patients evaluable by endoscopy analysis

Evidence Table 7. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer (continued)

Author Year	Other Medications	Definition of Treatment Failure/Success	Outcomes Reported (Results)	Adverse Effects	Quality Rating
Bianchi Porro 2000	37% diclofenac, 34% ketoprofen, 35% indomethacin.	Occurrence of gastric or duodenal ulcers (grade 4, Lanza classification) after 4 and 12 weeks, or patients who discontinued the study due to lack of efficacy leading to discontinuation of the study medication, an adverse event which was assessed by the study investigator as possibly or definitely related to the study medication.	***Ulcer status assigned (treatment failure):*** (p)*:* 13 with endoscopically-proven peptic ulcer, 3 due to lack of efficacy, 2 adverse events (pl)*:* 9 with endoscopically-proven peptic ulcer (1 with both gastric and duodenal ulcer), 1 lack of efficacy , 2 adverse events. ***Endoscopically proven duodenal and/or gastric ulcers:*** (p)*:* 13 (pl)*:* 9	4.3% (p) (m) unrelated to treatment, vomiting possitbly related, diarrhea definitely related), 5.9% (pl) (diarrhea possibly related, asthenia definitely related), all withdrew for adverse events.	Fair/Good: concealment of allocation not reported
Labenz et al. 2002	NSAID treatment: diclofenac 100-150 mg, and could add tramadol 200 mg. Dyspeptic therapy with an antacid.	Primary endpoint: endoscopically proved peptic ulcer. Secondary endpoints: dyspeptic complaints, signs of gastrointestinal bleeding.	OAC-O vs. O-O vs. OAC-P vs. P-P Developed peptic ulcers - Total: 2/173 (1.2%) vs. 0/155 vs. 2/161 (1.2%) vs. 10/171 (5.8%) - Duodenal: 0/173 vs. 0/155 vs. 2/161(1.2%) vs. 7/171(4.1%) - Gastric: 2/173 (1.2%)vs. 0/155 vs. 0/161 vs. 3/171 (1.8%) (Bonferroni p-value significant for all ome groups vs. pla) Dyspepsia developed requiring therapy: 10.4% vs. 12.3% vs. 10.6% vs. 19.9% (All treatment groups significantly different from pla only group - p-value NR) Negative H. pylori status: 85.3% vs. 21.9% vs. 81.3% vs. 11.8%	201 of 660 patients reported 302 adverse events (no details reported): OAC-O 31% O-O 16% OAC-P 26% P-P 26% Diarrhea more frequent in antibiotic groups: OAC-O 8.8% O-O 3.0% OAC-P 8.4% P-P 3.3%	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (m) = misoprostol (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations:(c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, qid - 4 times a day; Endo = all patients evaluable by endoscopy analysis

Evidence Table 7. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer (cont)

Author Year	Population setting	Diagnosis	Eligibility criteria	Interventions	Control
Hawkey, 1998	93 centers in 14 countries mean age 58 (range 20-85) 64% female ethnicity not given	38% rheumatoid arthritis, 47% osteoarthritis, 13% other, 2% combinations.39% gastric ulcer with or without erosions, 20% duodenal ulcer with or without erosions, 4% gastric and duodenal ulcer with or without erosions, 36% erosions only.	Patients who successfully healed during treatment phase of study. Age 18 to 85, with any condition requiring continuous treatment with oral or rectal NSAIDS above a predetermined minimal dose (no maximal dose). Minimal (and mean) daily oral doses: 50 mg (129 mg) diclofenac, 100 mg (137 mg) ketoprofen, 500 mg (844 mg) naproxen. By endoscopy, any or all of the following: ulcer, defined as a mucosal break at least 3 mm in diameter with definite depth in the stomach, duodenum, or both, more than 10 gastric erosions, and more than 10 duodenal erosions.	Omeprazole 20 mg	Misoprostol 200 mcg bid or placebo
Yeomans 1998	73 centers in 15 countries; mean age 56 (range 20-80); 69% female; ethnicity not given	44% rheumatoid arthritis, 32% osteoarthritis, 6% psoriatic arthritis, 5% anklyosing spondylitis,	Age 18 to 85, with any condition requiring continuous therapy with NSAIDs above specified therapeutic doses (no maximal dose),and not more than 10 mg prednisolone or equivalent per day. By endoscopy, any or all of the following: ulcers 3 mm of more in diameter, more than 10 erosions in stomach, more than 10 erosions in the duodenum. (Lanza scale)	Omeprazole 20 mg	Ranitidine 150 mg bid

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (m) = misoprostol (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations:(c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, qid - 4 times a day; Endo = all patients evaluable by endoscopy analysis

Evidence Table 7. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer (cont)

Author Year	Other Medications	Definition of Treatment Failure/Success	Outcomes Reported (Results)	Adverse Effects	Quality Rating
Hawkey, 1998	At baseline (all patients):most common diclofenac (23%), naproxen (22%), ketoprofen (16%).	Development of any of the following: an ulcer, more than 10 gastric erosions, more than 10 duodenal erosions, at least moderate symptoms of dyspepsia, or adverse events resulting in the discontinuation of treatment.	***In remission at 6 months:*** ***(***o20):61%(m): 48%(pl): 27%p = 0.001 for (o20) vs (m) *Gastric ulcers at relapse:(* o20):13%(m):10%(pl):32% *Duodenal ulcers at relapse:(* o20): 3%(m):10%(pl):12%	Withdrawals due to adverse events: (o20): 3.9%, (m): 7.7%, (pl): 1.9%; most common diarrhea (7.6% (o20), 8.4% (m), 4.5% (pl), abdominal pain (5.1% (o20), 4.7% (m), 5.8% (pl). One perforated duodenal ulcer after 31 days of (pl).	Fair: randomization and allocation method not reported, not intention-to-treat.
Yeomans 1998	Not reported for maintenance phase. Most common at baseline (including healing phase) diclofenac (29%), indomethacin (23%), naproxen (16%)	Remission defined as absence of a relapse of lesions, dyspeptic symptoms, and adverse events leading to the discontinuation of treatment.	***In remission at 6 months:*** **(**o20): 72%(r): 59%p = 0.004	Any adverse event: (o20): 64%, (r): 58%; withdrawals due to adverse events: 6.1% (o20), 3.2% (ran). Most common arthritis, rheumatoid arthritis, vomiting (2.9% (o20), 2.3% (ran)), abdominal pain (2.9% (o)o, 1.9% (ran)), diarrhea (3.3% (o20), 1.4% (ran)). One bleeding duodenal ulcer after 10 days of (o20).	Fair: randomization and allocation method not reported, not intention-to-treat.

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (m) = misoprostol (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations:(c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, qid - 4 times a day; Endo = all patients evaluable by endoscopy analysis

Evidence Table 8. Adverse effects in short term RCTs: PPI vs PPI

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Castell 1996 US Multicenter	GERD	Lansoprazole 15 mg or 30 mg	Omeprazole 20 mg	1070	(o20): 2% (l30): 1.7% (l15): 0.9%
Johnson et al. 2002 UK & Ireland Multicenter Crossover	Chronic PPI treatment for benign ulcers or GERD	Omeprazole 20 mg/day	rabeprazole 20 mg/day	240	30/240 (12.5%)
Hatlebakk 1993 Norway/ Sweden Multicenter	GERD	Lansoprazole 30 mg	Omeprazole 20 mg	229	(o20): 0.9%(l30):0
Mee 1996 UK and Ireland Multicenter	GERD	Lansoprazole 30 mg	Omeprazole 20 mg	604	Not reported
Howden et al. 2002	GERD	Lansoprazole 30 mg	Esomeprazole 40 mg	284	2/143 (1.4%) lansoprazole vs 5/141 (3.5%) esomeprazole

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl)

Evidence Table 8. Adverse effects in short term RCTs: PPI vs PPI (continued)

Author Year Setting	Number of adverse effects	Quality rating
Castell 1996 US Multicenter	Any adverse event:(l15) 44.5%, (l30) 55.7%, (o20) 53.4%. Most commonly reported events headache, diarrhea, nausea. More patients in (ll5) reported nausea (p<0.05). 6 severe events possibly or probably related to medication (4 in (o20) , 1 in (l15), 1 in (l30).	Fair
Johnson et al. 2002 UK & Ireland Multicenter Crossover	(o) = 115 (51%) reported 114 mild, 117 moderate, and 30 serious treatment-emergent AEs. (r) = 120 (52.6%) reported 97 mild, 118 moderate, and 28 severe treatment-emergent AEs. No significant differences in AEs between groups. No difference in general preference for (o) or (r). - More patients prefer (r) for "absence of side effects" (p=.047), among those with any preference (46%). - More patients prefer (r) for "unexpected positive side effects" (p=.019), among those with any preference (28%). - More patients prefer tablet form of (r) as "easy to swallow" (p=.0001), among those with any preference (52%). - More patients prefer capsule form of (o) as "easy to pick up and hold" (p=.0003), among those with any preference (47%).	Not assessed
Hatlebakk 1993 Norway/ Sweden Multicenter	32.8% (l30), 29.2% (o20) reported adverse event, One (o20) withdrawn for severe diarrhea. Headache in 4 pts (o20), none (l30).2 severe events (l30) (1 pharyngitis, 1 nausea, vomiting).	Poor
Mee 1996 UK and Ireland Multicenter	51% of all patients had at least one event, not broken down by treatment group. Most frequent events: headache (12% (l30), 11% (o20) diarrhea (9.4% (l30), 8% (o20) nausea (4.3% (l30), 4.7% (o20). 2 serious events (o20) (esophageal cancer (pre-existing) and vasovagal syncope and loose stools)	Good/Fair
Howden et al. 2002	Lansoprazole vs esomeprazole: Incidence of all adverse events 46.2% vs 52.5% Of these, 16.1% vs 19.1% considered "possibly", "probably", or "definitely" treatment-related. Most frequently reported treatment-related effects: diarrhea (5% vs 5%), headache (2% vs 5%), eructation (5% vs 2%), abdominal pain (2% vs 4%), flatulence (1% vs 4%), nausea (2% vs 2%). Most events mild to moderate. Esomeprazole one severe case each of eructation, dizziness, and paresthesia; lansoprzole one severe case each of abdominal pain, diarrhea, eructation, rectal disorder, and somnolence.	Fair

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl)

Evidence Table 8. Adverse effects in short term RCTs: PPI vs PPI (continued)

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Mulder 1996 Netherlands Multicenter	GERD	Lansoprazole 30 mg	Omeprazole 40 mg	211	None
Richter 2001b	GERD	Lansoprazole 30 mg	Omeprazole 20 mg	3410	40/1754 (2%) lansoprazole 33/1756 (2%) omeprazole.
Korner et al. 2003	GERD	Pantoprazole 40 mg	Omeprazole MUPS 40 mg	669	4/337 (1%) pantoprazole, 7/332 (2%) omeprazole MUPS
Scholten et al. 2003	GERD	Pantoprazole 40 mg	Esomeprazole 40 mg	217	3 (groups not reported)
Dekkers 1999 European Multicenter	GERD	Rabeprazole 20 mg	Omeprazole 20 mg	202	(r20): 1% (o20): 0
Delchier 2000 European Multicenter	GERD	Rabeprazole 20 mg or Ransoprazole 10 mg	Omeprazole 20 mg	300	(r10): 5% (r20): 5% (o20): 2%

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl)

Evidence Table 8. Adverse effects in short term RCTs: PPI vs PPI (continued)

Author Year Setting	Number of adverse effects	Quality rating
Mulder 1996 Netherlands Multicenter	19% (l), 21% (o) No difference in change in gastrin levels between groups. No other events reported.	Fair
Richter 2001b	44% in both groups, most mild or moderate. Lansoprazole vs omeprazole significant differences in incidence of diarrhea (10% vs 8%), increased appetite (0.3% vs 0%), melena (0.1% vs 0.7%), asthma (0.4% vs 0%).	Fair
Korner et al. 2003	Pantoprazole vs omeprazole 6% vs 7%, mostly mild or moderate. 2.1% vs 1.2% severe. Most frequently reported adverse event headache for pantoprazole (1%), diarrhea for omeprazole (2%).	Fair
Scholten et al. 2003	14% of patients reported an adverse event, most assessed as "not related" to the study drug. Three patients in each group had an event assessed as "likely" or "definitely" related to study drug. No significant differences beween groups in frequency or type of adverse events.	Fair
Dekkers 1999 European Multicenter	32% (r20) and 28% (o20) reported at least one adverse event. Headache, diarrhea, flatulence most common. Flatulence more common (o20) gr (4% vs 0%). One serious event (r20) (t wave changes).	Fair
Delchier 2000 European Multicenter	21% (r20), 26% (r10), and 23% (o20) reported at least one event. Abdominal pain, pharyngitis, bronchitis, headache, diarrhea most common. Four serious events, none related to medication. At week 4, incidences of elevated serum gastrin levels 16% (r20), 27% (r10), 20% (o20) (NS)	Fair

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl)

Evidence Table 8. Adverse effects in short term RCTs: PPI vs PPI (continued)

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Kahrilas 2000 US Multicenter	GERD	Esomeprazole 40 mg or 20 mg	Omeprazole 20 mg	1960	(e40): 2% (e20): 2.6% (o20): 2%
Richter 2001 US Multicenter	GERD	Esomeprazole 40 mg	Omeprazole 20 mg	2425	1% in each group
Corinaldesi 1995 European Multicenter	GERD	Pantoprazole 40 mg	Omeprazole 20 mg	241	(p40): 0.8% (o20): 1.7%
Dupas 2001 France Multicenter	GERD	Pantoprazole 40 mg	Lansoprazole 30 mg	461	(p40): 1.3% (l30): 2.5%
Dobrilla 1999 Italy Multicenter	Duodenal ulcer	Lansoprazole 30mg, then those with healed ulcer randomized to 15 or 30mg lansoprazole x 12 months	Omeprazole 40mg, then those with healed ulcer switched to omeprazole 20mg x 12 months	251 eligible (167 (l), 84 (o)) Maintenance phase: 243 enrolled (164 (l), 79(o))	Treatment:2.3% (o), 9% (l)Maintenance:4% (l15), 2.8% (l30), 1.4% (o)

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl)

Evidence Table 8. Adverse effects in short term RCTs: PPI vs PPI (continued)

Author Year Setting	Number of adverse effects	Quality rating
Kahrilas 2000 US Multicenter	Total or per group not reported. Most common: headache 8.6% (e40), 8.7% (e20), 6.9% (o20) abdominal pain 3.7% (e40), 3.7% (e20), 4.2% (o20) diarrhea (4.6% (e40), 4.7% (e20), 3.9% (o20) flatulence (1.8% (e40), 3.5% (e20), 2.5% (o20) gastritis 2.5% (e40), 3.5% (e20), 2.5% (o20) nausea 3.8% (e40), 2.9% (e20), 3.1% (o20). No differences observed according to gender, age, or race. No serious drug-related events reported.	Fair
Richter 2001 US Multicenter	At least one adverse event reported in 32.2% in(e40), 34.3% in (o20). Most common: headache 6.2% (e40), 5.8% (o20) diarrhea 3.9% (e40), 4.7% (o20) nausea 3.0% (e40), 3.0% (o20) abdominal pain 2.6% (e40) 2.7% (o20) < 1% in each group had a serious event (0 considered treatment related)	Good
Corinaldesi 1995 European Multicenter	Adverse events reported by 15% of patients in (p40), 12% in (o20). Diarrhea, abdominal pain, hyperlipemia and constipation most frequently reported in (p40) , diarrhea most frequently (o20).	Fair
Dupas 2001 France Multicenter	Adverse events reported in 28% in p40 group, 17% in l30. Most common headache, diarrhea, elevation of hepatic enzymes, abdominal pain, skin disorders. 11 serious events (5 (p40) 6 (l30)).	Fair
Dobrilla 1999 Italy Multicenter	16 during phase I (healing): 10 (6%, l), 6 (7.1%, o) 21 during Phase 2 (maintenance): 9 (12.2%, l15), 4 (5.6%, l30), and 8 (11%, o) Most common adverse event was diarrhea. 8 patients withdrew due to adverse events (3 (l15), 2 (l30), 3 (o))Serum gastrin levels were elevated in both groups at 4 weeks (increase of 23.8pg/ml (l30), 35.8pg/ml (o) NS), and continued to be elevated at 6 and 12 months of maintenance therapy. The (l15) had the least and the (l30) had the highest elevation at 6 and 12 months. At 6 months all values were returning to baseline.	Fair/Poor

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl)

Evidence Table 8. Adverse effects in short term RCTs: PPI vs PPI (continued)

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Chang 1995 Taiwan Single-center	Duodenal ulcer	Lansoprazole 30mg	Omeprazole 20mg	83 enrolled (42 (l), 41 (o))	None reported.
Ekstrom 1995 Sweden Multicenter	Duodenal ulcer	Lansoprazole 30mg	Omeprazole 20mg	279 enrolled (143 (l), 136 (o))	Not reported
Capruso 1995 Italy Multicenter	Duodenal ulcer	Lansoprazole 30mg	Omeprazole 20mg	107 enrolled, (52 (l), 55(r))	Not reported.
Chang 1995 Taiwan Single center	Duodenal ulcer	Lansoprazole 30mg once a day x 4 weeks	Omeprazole 20mg a day x 4 weeks	111 enrolled (57 (l), 54 (o)	Not stated in abstract
Fanti 2001 Italy Single center	Duodenal ulcer and H. pylori	Lansoprazole 30mg once a day x 4 weeks Plus clarithromycin 500 and tinidazole 1gm x 7 days	Omeprazole 20mg a day x 4 weeks Plus clarithromycin 500 and tinidazole 1gm x 7 days	43 enrolled (22 (l) and 21 (o))	None
Dekkers 1999 European Multicenter	Duodenal ulcer	Rabeprazole 20mg	Omeprazole 20mg	205 enrolled (102 (r), 103 (o))	1.9% (o) 0% (r)

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl)

Evidence Table 8. Adverse effects in short term RCTs: PPI vs PPI (continued)

Author Year Setting	Number of adverse effects	Quality rating
Chang 1995 Taiwan Single-center	Serum PGA was elevated in both groups (NS), and had returned to baseline at 8 weeks. In both groups, the elevation in PGA was significantly higher in those found to have H. pylori eradication	Fair
Ekstrom 1995 Sweden Multicenter	68 adverse events occurred in 57 patients (23 (l), 34 (o)) (NS). A statistically significant difference was found in the mean change in ALT concentration, but the change was minor (0.05 unit increase (l), 0.03 unit decrease (o).	Fair
Capruso 1995 Italy Multicenter	8 adverse effects reported: 3 (r), 3 (l), and 2 (o). No significant difference between therapies for changes in gastrin levels or changes in endocrine cells from biopsies	Fair
Chang 1995 Taiwan Single center	Hypergastrinemia with both agents. A few occurrences of reversible skin rash and constipation.	Not assessed
Fanti 2001 Italy Single center	“Mild and self-limiting” Total number not reported.1 (l) stomatitis and 1 (o) mild diarrhea	
Dekkers 1999 European Multicenter	43 patients reported at least one adverse event. (21 (r), 22 (o)). The most common was headache. 2 (o) withdrew due to adverse events (evaluated as unrelated to study)The mean elevations in serum gastrin levels at 4 weeks were 39.8 pg/ml (r) and 18.9 pg/ml (o).	Fair

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl)

Evidence Table 8. Adverse effects in short term RCTs: PPI vs PPI (continued)

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Dekkers 1998 European Multicenter	Gastric ulcer	Rabeprazole 20mg	Omeprazole 20 mg	227 enrolled	Not reported
Beker 1995 European Multicenter	Duodenal ulcer	Pantoprazole 40mg	Omeprazole 20mg	270 enrolled (135 each group)	0.74% (p)2.9% (o)
Lanza 1997 USA Multicenter	Duodenal ulcer maintenance	Lansoprazole 15mg once daily x 12 months or until ulcer recurrence	Placebo once daily x 12 months or until ulcer recurrence	186 enrolled 88 (pl), 92 (l))	4.5% (pl) 2.2% (l)
Kovacs 1999 USA Multicenter	Duodenal ulcer maintenance	Lansoprazole 15 or 30mg once daily for up to 12 months	Placebo once daily for up to 12 months	56 enrolled19 (pl),18 (l15), 19 (l30)	21.5%(pl)17% (l15)5.3% (l30)
Russo 1997 Italy Multicenter	Duodenal ulcer maintenance	If (l30) during healing trial: Lansoprazole 15 mg or Placebo once daily x 12 months or until recurrence	If (r) during healing trial: Ranitidine or placebo 150mg once daily x 12 months or recurrence	108 enrolled 30 (l30/l15)28 (l30/p), 24 (ran/ran),26 (ran/p)	Not reported

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl)

Evidence Table 8. Adverse effects in short term RCTs: PPI vs PPI (continued)

Author Year Setting	Number of adverse effects	Quality rating
Dekkers 1998 European Multicenter	60 patients reported at least one adverse event. (25 (r), 35 (o)). The most common was headache. No difference by sex, age, race.Slightly elevated creatine phosphokinase at 6 weeks was found in 6 (o) patients. The mean elevations in serum gastrin levels at 6 weeks were 12.7 pg/ml (r) and 10.0 pg/ml (o).	Fair
Beker 1995 European Multicenter	21 patients reported adverse events (10, 7% (p), 11, 8% (o)), with a total of 23 events reported. Diarrhea was the most common adverse event reported. 5 were considered serious (1 (p), GI hemorrhage and 4 (o), angina pectoris, hypertension, vertigo and abdominal pain. These patients were withdrawn from study. Serum gastrin levels rose in both groups at both 2 and 4 weeks, the change was statistically significant within but not between groups.	Fair
Lanza 1997 USA Multicenter	9 adverse events possibly or probably related to study drug. The most common was diarrhea. No significant differences between groups. Serum gastrin levels were significantly higher in (l) group than (pl), median 92pg.ml vs 52 pg/ml (P0.001). Values reached a plateau after one month of treatment and returned to baseline one month after treatment stopped. Gastric biopsies: significant increase in Gastrin cell density in (l) group compared to (pl) group (707cells/mm2 vs 556 cells.mm2), no other differences found.	Fair
Kovacs 1999 USA Multicenter	40 patients reported adverse events (11 (pl), 15 (l15), 14 (l30)). Adverse events possibly or probably related to study drug: 2 (pl), 2 (l15), 6 (l30). None were severe. Serum gastrin levels increased significantly in both (l) groups compared to (pl) (P<0.001). Elevations occurred within 1 month of starting study. 8 patients (3(l15), 5 (l30)) had levels >200pg/ml during study. All returned to baseline within 1 month of stopping study drug.	Fair
Russo 1997 Italy Multicenter	Maintenance: 3% (l/l), 18% (l/pl), 0% (ran/ran). (ran/pl) not reported.	Fair/Poor

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl)

Appendix A. Search Strategy

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1 Gastroesophageal reflux/ or "gerd".mp.
2 exp peptic ulcer/ or "peptic ulcer".mp.
3 1 or 2 (24054)
4 Proton pump/ai [Antagonists & Inhibitors]
5 proton pump inhibitor$.mp.
6 (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp.
7 4 or 5 or 6
8 3 and 7
9 limit 8 to (human and english language)
10 limit 9 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial)
11 exp clinical trials/ or clinical trial$.mp.
12 exp epidemiologic research design/
13 observational stud$.mp.
14 11 or 12 or 13
15 9 and 14
16 10 or 15

Appendix B. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project

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)

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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.

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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.

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.

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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) [abstract]. Gastroenterology 2000;118:A1210.

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4. 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.
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Appendix E. Esophagitis grading scales used in randomized controlled trials

Savary-Miller (used in Mulder, 1996, Mee, 1996, and Mulder, 2002):

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 (used in Delchier, 2000 and Dekkers, 1999):

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(used in Kahrilas, 2000 Richter, 2001, and Castell, 2002):

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.