Drug Class Review
on
Proton Pump Inhibitors

FINAL REPORT

Marian S. McDonagh, PharmD
Susan Carson, MPH

Produced by
Oregon Evidence-based Practice Center
Oregon Health & Science University
3181 SW Sam Jackson Park Road
Mailcode: BICC
Portland, OR 97201-3098

Mark Helfand, MD, MPH, Director

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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).

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 over-the-counter medicines. Lifestyle modifications include avoiding foods, beverages, and medicines that can aggravate heartburn, decreasing the size of portions at mealtimes, avoiding tight-fitting clothing, losing weight if overweight, and eating at least 3 hours before going to sleep. Over-the-counter medications include antacids and histamine-2 receptor antagonists (H2-RAs, commonly called "H2-blockers"), such as cimetidine or ranitidine. If these lifestyle changes and over-the-counter medications 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. Current Oregon Health Plan policy is that PPIs be used primarily in patients who have inflammation of the esophagus (esophagitis). Even though use of H2-RAs is higher (36,130 claims vs 15,829 claims from 1/1/01 to 6/30/01), usage of the PPIs in the Oregon Health Plan is also significant (see Table 1).

Table 1. OHP fee-for-service sector PPIs (1/1/01 – 6/30/01)

Brand Name	Generic Name	Total Paid	Claim Count	Avg. Paid / Claim
PRILOSEC	OMEPRAZOLE	$717,403	5,750	$124.77
PREVACID	LANSOPRAZOLE	$697,084	5,919	$117.77
PROTONIX	PANTOPRAZOLE	$261,058	3,112	$83.89
ACIPHEX	RABEPRAZOLE	$92,154	848	$108.67
NEXIUM	ESOMEPRAZOLE	$23,384	200	$116.92

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 Barretts 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 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 H2-RAs, 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 (2002, Issue 1), MEDLINE (1966-2002), EMBASE (1980-2001), 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, using a protocol issued by the State of Oregon (http://www.ohppr.state.or.us/index.htm). All citations were imported into an electronic database (EndNote 5.0).

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, 2] 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 proportion 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 identified 1799 citations: 147 from the Cochrane Library, 815 from MEDLINE, 574 from EMBASE, 231 from reference lists, and 32 from pharmaceutical company submissions. We included 91 randomized controlled trials and six systematic reviews. 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?

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?

We identified 10 randomized controlled trials comparing two PPIs for healing of esophagitis and gastroesophageal reflux symptom relief.[6-15] Omeprazole was the comparator in all but one study.[10] These studies are summarized in Table 2. Four studies compared omeprazole versus lansoprazole,[6, 11, 13, 14] two omeprazole versus rabeprazole,[8, 9] two omeprazole versus esomeprazole,[12, 15] one omeprazole versus pantoprazole,[7] and one lansoprazole versus pantoprazole.[10] The scales used to grade esophagitis in these studies are described in Appendix E.

One study[15] met all our criteria for internal validity, one was rated poor,[11] and the rest were fair. In the poor quality study, eligibility criteria were not specified, so it would be impossible to verify or reproduce the results.

Only one study[6] reported the ethnic makeup of the population; in this study, 85% of participants were white, 9% black, and 5% Hispanic. Results were not analyzed by ethnic

group, however. Pregnant and lactating women, and women of childbearing potential were excluded from all studies, and all were over 60% male. No children (i.e., under age 18) were included in these studies.

Esophagitis Healing

A recent systematic review (Caro)[16] examined esophagitis healing and relapse rates in trials of newer PPIs compared to omeprazole. This study met criteria for a good quality systematic review: it used comprehensive sources and systematic search strategies, explicit and relevant selection criteria, standard appraisal of studies, and drew valid conclusions. The review found that lansoprazole, rabeprazole, and pantoprazole had similar efficacy to omeprazole for healing. No studies of esomeprazole had been done at the time.

Our review of 10 trials confirmed this result. 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 8 weeks for the eight trials that provided this information (2 studies[8, 12] did not provide number healed/total). There was no difference between lansoprazole 30mg, omeprazole 20mg, pantoprazole 40mg, and rabeprazole 20mg in healing rates at 4 or 8 weeks. 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. One would expect that esomeprazole 40mg, an optical isomer of omeprazole, was equal in potency to omeprazole 40mg, not omeprazole 20mg. There is also no reason to expect that omeprazole 40mg and esomeprazole 40mg differ in toxicity. 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. Rates of symptom relief at 4 weeks were also comparable; neither study reported symptoms at 8 weeks.

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.

In summary, our review and a recent good quality systematic review[16] 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, or of esomeprazole versus any other PPI.

Relief of Symptoms

All 10 head-to-head comparisons of PPIs measured symptom relief as a secondary outcome. Symptoms were assessed through patient diaries, investigator-elicited reports, or both. Four studies compared symptom relief for lansoprazole versus omeprazole.[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 and 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.

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.

The earlier of two trials of esomeprazole[12] reported shorter time to relief of heartburn and 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%). 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. 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.

Prevention of Relapse

Only two randomized controlled trials comparing one PPI to another for long-term maintenance therapy for esophagitis relapse prevention have been published (Table 3).[4, 17] There were no differences in endoscopic or symptomatic relapse rates for lansoprazole versus omeprazole after 48 weeks of treatment,[4] or lansoprazole versus omeprazole after 13, 26, and 52 weeks.[17] No maintenance study has been conducted with rabeprazole or esomeprazole.

A third, shorter-term study of 36 patients with severe (Savary-Miller Grade 4) esophagitis compared omeprazole, lansoprazole, and pantoprazole for the prevention of relapse at 4 weeks.[18] Before randomization, all of the patients were treated with omeprazole. Six of these did not heal after 6 to 8 weeks of omeprazole; the remainder were randomized to omeprazole, lansoprazole, or pantoprazole. After 4 weeks, patients taking omeprazole had a lower rate of endoscopic relapse (10%) than the other lansoprazole (80%) or pantoprazole (70%). The relapse rates in the lansoprazole and pantoprazole groups are very high compared with other studies, and the study had an obvious selection bias in that all subjects had responded well to one of the study drugs (omeprazole) within the previous 2 months.

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?

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

Esophagitis Healing

In the systematic review mentioned above,[16] four PPIs were better than ranitidine at healing esophagitis, but there were no differences among them. No study of esomeprazole was included.[16]

Twenty-one randomized controlled trials compared a PPI with an H2-RA for GERD. Figure 2 shows the rates of esophagitis healing at 8 weeks in 20 of these (full text of one study[19] was unavailable). These trials compared an H2-RA to omeprazole (10 studies),[20-29] lansoprazole (five studies),[30-34] pantoprazole (four studies),[35-38] and rabeprazole (1 study).[39] 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,[16] 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

The Caro systematic review identified 15 studies of relapse prevention.[16] 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?

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?

Nine randomized controlled trials compared one PPI to another.[8, 40-47] The details of these studies are summarized in Table 4. Six of these trials compared lansoprazole 30mg to omeprazole 20mg.[40-44, 47] One study each compared pantoprazole 40mg and rabeprazole 20mg to omeprazole 20mg[8, 45] and one study comparing esomeprazole 40mg to omeprazole 40mg.[46] 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.[48]

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.[46] The pooled risk difference for lansoprazole 30mg versus omeprazole 20mg once a day was -0.2 (95% CI, -3.0-2.6). 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 study addressed maintenance, comparing two different PPIs (lansoprazole 15mg, lansoprazole 30mg and omeprazole 20mg) for up to 12 months (see Table 5).[43] 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 Table 5 compared a PPI (lansoprazole) to placebo[49, 50] or ranitidine.[51] Relapse rates at 12 months in the lansoprazole 15mg groups ranged from 23 to 30%, in the single lansoprazole 30mg group 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.

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?

Twenty-four randomized controlled trials compared a PPI with an H2-RA. Of these, 21 papers were reviewed.[52-72] (Full-text articles of three trials[19, 73, 74] were unavailable.) 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 nine 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%).

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?

Only one study compared one PPI to another in the treatment of gastric ulcer.[75] This fair quality study of 227 patients compared rabeprazole 20mg to omeprazole 20mg and is summarized in Table 6, with the other gastric ulcer studies. Timing of assessment of healing was 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.

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?

Fourteen studies compared a PPI to an H2-RA for treatment of gastric ulcer (Table 6).[44, 52, 76-87] There was one study of maintenance therapy and one followup study of relapse rates in patients healed in one of the above studies.[50, 88] No study compared esomeprazole or rabeprazole to a H2-RA. Four 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.[78] 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[89] 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. A 6-month followup study without treatment[88] of patients who had healed after 6 weeks of treatment with omeprazole or cimetidine,[77] found no significant difference in relapse rate. Both studies had high dropout rates.

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?

No study compared one PPI to another.

F. 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 NSAID-induced ulcer?

Three studies assessed PPIs compared to another drug in healing ulcers induced by NSAIDs.[90-92] The details of these studies are summarized in Table 7.

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[91] 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.

G. 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.

H. In comparisons of PPIs and H2-RAs, what is the comparative efficacy of different PPIs in preventing NSAID-induced ulcer?

One recent, good quality systematic review addressed this question.[93] 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.

Two trials published more recently[94, 95] are presented in Table 8, along with two of the treatment studies that included a prevention phase.[91, 92] 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[94] 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. The other study[95] randomized patients to pantoprazole 40mg or placebo for 3 months.

In the study of H. pylori negative patients,[94] 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,[95] 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.

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."[95] 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.[94]

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

One recent, fair quality systematic review addressed this question.[96] 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.[97] This review found no difference between lansoprazole and omeprazole in eradication rate.

Since this review, 13 studies were published that directly compared one PPI to another in combination with the same antibiotic(s).[46-48, 98-107] They made the following comparisons:

- rabeprazole 20mg versus omeprazole 40mg, plus amoxicillin (one study)[98]
- lansoprazole 60mg versus omeprazole 40mg, plus amoxicillin and metronidazole(one study)[100]
- omeprazole 40mg versus pantoprazole 40mg, plus clarithromycin and metronidazole (one study)[107]
- omeprazole 20mg versus lansoprazole 30mg, plus clarithromycin and tinidazole (one study) [47]
- various doses of lansoprazole, rabeprazole, pantoprazole and esomeprazole versus omeprazole, plus clarithromycin and amoxicillin (nine studies)[46, 48, 99, 101-106]

None of these studies was conducted in the US. Five were conducted in Japan, two in Italy, one in England, one in Germany, 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.[98] 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).[106] 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.

Seven studies included patients with documented ulcer.[46-48, 98, 100, 105, 108] Five studies included patients with ulcers or non-ulcer dyspepsia.[99, 101, 102, 104, 107] The proportion of non-ulcer patients ranged from 12%[102] to 71%.[104] One study conducted in a low-income population in Colombia included patients with "gastritis" and did not check for ulcer.[106]

As would be expected based on these differences, eradication rates varied in these studies, from a low of 62.5% (rabeprazole 20mg)[98] to a high of 100% (pantoprazole 40mg).[107] Only one study found a significantly lower eradication rate for pantoprazole (40mg) than for omeprazole 40mg or high-dose pantoprazole (80mg). No other study found a significant difference regardless of dose or specific PPI.

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?

Three fair quality systematic reviews assessed PPIs compared to H2-RA-based eradication regimens.[96, 109, 110] All three 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 long-term maintenance studies of patients with GERD, there was no difference in the number of adverse events reported or number of withdrawals due to adverse events in the different PPI treatment groups. In one study of GERD patients,[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 the other study of long-term maintenance treatment for GERD, comparing rabeprazole 10 or 20mg to omeprazole 20mg,[17] 13 of 243 (5.3%) patients withdrew because of adverse events; the numbers in each group did not differ significantly. Seven patients each in the rabeprazole 10mg and 20mg groups, and 8 patients in the omeprazole 20mg group reported serious adverse events. 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.[50]

Several reports of long-term (1 year or more) followup of individual PPIs (omeprazole, lansoprazole, and pantoprazole) have been published.[111-123] The potential adverse effects 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, and potential malabsorption syndromes. 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. 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 Table 9. 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. The exception was one study of rabeprazole 10mg or 20mg versus omeprazole 20mg that reported 5% to 7% withdrawals for adverse events.[9] The rate of attrition overall was somewhat high in this study (17%-24%).

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.[124]

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 10. 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 10: Clinically Significant Drug Interactions

	Omeprazole	Esomeprazole	Rabebrazole	Lansoprazole	Pantoprazole
Drugs with pH dependent absorption (e.g. ketoconazole, iron, digoxin, delaviradine, indinivir, enteric coated salicylates)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)
Carbamazepine	Monitor (1)				No significant

	Omeprazole	Esomeprazole	Rabebrazole	Lansoprazole	Pantoprazole
					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,[49] to a high of 60.[90] From 57% to 89% of the patients enrolled were male. The ethnicity of participants was only stated in two trials,[6, 49] both done in the US. In these studies, the patients enrolled were 76% and 85% white. Of the remaining studies, 23 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.

An age-based analysis of healing or prevention was not possible in most 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, 75] There were no differences between PPIs based on these characteristics.

In trials comparing a PPI to another drug, the same general statements can be made, but 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 equally effective in these populations,[101, 125] and that rapid metabolizers may have a higher failure rate in eradicating H. pylori.[98, 99]

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 >/= 65 years old compared to those < 65.[126] 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, similar data are not available for other PPIs.

SUMMARY AND DISCUSSION

Results for the key questions are summarized in Table 11. 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. Esomeprazole was found to be superior to omeprazole for GERD in two studies, but the relevance of this evidence is limited because the doses were not equipotent. 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. Ten head-to-head trials, 21 trials of these PPIs versus an H2-RA, and a good quality systematic review have found these four PPIs to be equally effective. The evidence for the effectiveness of esomeprazole is fair to poor. Two trials found esomeprazole 40mg to be more effective than omeprazole 20mg. The justification for using esomeprazole 40mg rather than 20mg in these studies is not clear. There are no head-to-head comparisons of omeprazole 40mg versus esomeprazole 40mg, or of esomeprazole versus any other PPI.

Duodenal Ulcer

The data regarding comparative effectiveness of various PPIs for treating duodenal ulcer is 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, -3.0-2.6). This translates to a number needed to treat of -5, meaning that for every one patient receiving omeprazole, five additional patients need to receive lansoprazole to achieve healing at 4 weeks in one patient. 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

There is little head-to-head comparative data of PPIs for the treatment of gastric ulcer, 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 three subsequently published trials compared PPIs to placebo or other drugs. None of the trials 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 data regarding comparative effectiveness of various PPIs for eradicating H. pylori is fair, with one systematic review, and nine 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. Symptom resolution was not assessed in these studies.

Complications

The comparative evidence on long-term adverse effects is limited. Two 48-month maintenance studies found no difference between omeprazole and lansoprazole in adverse events or withdrawals due to adverse effects. 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 is inadequate data to identify any difference between them.

Table 11: 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	8 head-to-head trials found no difference in healing rates between omeprazole, lansoprazole, rabeprazole, or pantoprazole. 20 trials of newer PPIs compared to H2-RAs and a previous systematic review also found no differences among these PPIs. There are no trials that compare esomeprazole to an H2-RA for GERD. Two studies by the same group found esomeprazole at 40mg better at esophagitis than omeprazole 20mg. There are no studies comparing esomeprazole 20mg to any other PPI, and no studies comparing esomeprazole to an H2-RA.
GERD symptoms	Good for (o), (l), (r), (p), Good for (e 40mg) vs (o 20mg) Poor for equivalent doses	8 head-to-head trials found no difference in relief of symptoms between omeprazole, lansoprazole, rabeprazole, or pantoprazole. 20 trials of these PPIs compared to H2-RAs, and a previous systematic review also found no differences. Two studies by the same group found esomeprazole at 40mg better at symptom relief than omeprazole 20mg. There are no studies comparing esomeprazole 20mg to any other PPI, and no studies comparing esomeprazole to an H2-RA.
GERD relapse	Fair for (o), (l), (r) Poor for (e), (p)	2 head-to-head trials found no differences in endoscopic or symptomatic relapse rates for lansoprazole versus omeprazole after 48 and rabeprazole versus omeprazole after 13, 26, and 52 weeks. No maintenance study compared lansoprazole, esomeprazole, or pantoprazole to another PPI. 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.
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 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 symptoms resolution were apparent.
Prevention of NSAID induced ulcer	Poor	No head-to-head studies. In other studies, significant heterogeneity in study design and outcome measure definitions make this evidence insufficient to identify any differences between PPIs.
Eradication of H. pylori	Fair	One fair quality systematic review and 13 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	Two comparative trials. Evidence from single-drug followup studies indicates no differences between the PPIs. No long-term studies of esomeprazole or rabeprazole 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.

**Quality of evidence ratings based on criteria developed by the Third US Preventive Services Task Force

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