Drug Class Review

Proton Pump Inhibitors

Final Report Update 5

May 2009

Update 4: May 2006
Update 3: May 2005
Update 2: April 2004
Update 1: April 2003
Original Report: November 2002

The literature on this topic is scanned periodically.

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Published in a separate document

The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

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INTRODUCTION

Proton pump inhibitors decrease secretion of gastric acid. They act by blocking the last enzyme in the system that actively transports acid from gastric parietal cells into the gastrointestinal lumen, hydrogen–potassium adenosine triphosphatase, also known as the proton pump. Omeprazole, the first drug in this class, was introduced in 1989. Since then, 4 other proton pump inhibitors have been introduced: lansoprazole (1995), rabeprazole (1999), pantoprazole (2000), and esomeprazole (2001). In 2003 omeprazole became available over-the-counter in the United States. The formulation for the over-the-counter product is omeprazole magnesium, available in other countries as omeprazole multiple unit pellet system. Omeprazole is also available in combination with sodium bicarbonate (Zegerid). Table 1 provides an accounting of indications of different proton pump inhibitors.

Proton pump inhibitors are mainly used to treat symptoms of gastroesophageal reflux disease and gastritis. Often, they are used only after therapy with histamine-2 (H2) receptor antagonists, commonly called H2 blockers, has been unsuccessful for symptoms of reflux. Proton pump inhibitors also are used to treat peptic ulcers (duodenal and gastric) and drug-induced ulcers, such as those associated with nonsteroidal anti-inflammatory drugs; the bacterium that causes ulcers, *Helicobacter pylori,* is eradicated by treatment with a proton pump inhibitor and antibiotics. Proton pump inhibitors also are used to promote healing of erosive esophagitis. Esophagitis can lead to scarring and narrowing of the esophagus (stricture) or to Barrett esophagus, which is a risk factor for esophageal cancer.

Evidence-based reviews usually emphasize health outcomes—events or conditions that patients can feel or experience. Heartburn, waking at night, acid regurgitation, and quality of life are health outcomes. But severity of symptoms is not a reliable indicator of esophagitis; patients without esophagitis can experience severe heartburn, and some patients who have esophagitis have no symptoms. Consequently, esophagitis is diagnosed by direct visualization via endoscopy. Esophagitis appears as a tear, break, or ulceration in the lining of the esophagus. When esophagitis has healed, the ulceration has been completely reepithelialized, as viewed during endoscopy. This endoscopically verified healing often is used as an intermediate outcome measure for esophagitis.

For ulcer disease, quick relief of symptoms is an important health outcome. But in the long run, the most important determinant of functional status and quality of life is prevention of recurrence of ulcers and their complications (bleeding, hospitalization, and death). Historically, studies of proton pump inhibitors for ulcer disease have been too short to address these outcomes directly. So instead, they report intermediate outcome measures. In the past the most common intermediate outcome measure was endoscopic healing, meaning that on endoscopy after treatment the ulcer is gone. But because ulcer disease tends to recur even when the initial ulcer has completely healed, endoscopic healing, while important as a predictor of relapse, is an imperfect indicator of long-term morbidity from ulcer disease. Since the discovery that *Helicobacter pylori* causes many peptic ulcers, eradication of *Helicobacter pylori* has emerged as a more important indicator of the long-term outcome of treatment. Long-term studies have shown that eradication reduces the risk of ulcers and ulcer complications for several years.

Table 1. Proton pump inhibitors and their US Food and Drug Administration-approved indications

Active ingredient	Trade name	Dosage form	Duodenal or gastric ulcer	GERD	Erosive esophagitis maintenance	Erosive esophagitis treatment	NSAID-induced ulcer
Omeprazole	Prilosec®	Oral capsule	X	XX	X	XX	X
		Oral suspension	X	XX	X	XX	X
	Losec® (Canada)	Oral capsule	X	X	-	-	X
	Prilosec OTC®[a]	Oral tablet	-	X[a]	-	-	-
Omeprazole/ sodium bicarbonate	Zegerid®[a]	Oral suspension	-	X	X	X	-
		Oral capsule	X	X	X	X	-
		Oral chewable tablet	X	X	X	X	-
Lansoprazole	Prevacid®	Oral capsule	X	XX	X	XX	X
		Oral suspension	X	XX	X	XX	X
		Oral tablet	X	X	X	XX	X
	Prevacid FasTab® (Canada)	Oral tablet	X	XX	-	XX	X
Pantoprazole	Protonix®	Oral tablet	-	-	X	X	-
		Oral suspension	-	-	X	X	-
	Pantoloc® (Canada)	Oral tablet	X	X	-	-	X
Rabeprazole	Aciphex®	Oral tablet	X[b]	XX[c]	X	X	-
	Pariet® (Canada)	Oral tablet	X	X	-	-	-
Esomeprazole	Nexium®	Oral capsule	-	XX	X	X	X
		Oral suspension	-	XX	X	X	X

Abbreviations: GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug.
X: Adults; XX: Pediatrics and adults.
[a] Not available in Canada. Indication = treatment of frequent heartburn (>2 times weekly). Heartburn is listed as the only "use" for Prilosec OTC per product labeling description.
[b] Duodenal ulcers only.
[c] For patients 12 years and over.

Purpose and Limitations of Systematic Reviews

Systematic reviews, also called evidence reviews, are the foundation of evidence-based practice. They focus on the strength and limits of evidence from studies about the effectiveness of a clinical intervention. Systematic reviews begin with careful formulation of research questions. The goal is to select questions that are important to patients and clinicians then to examine how well the scientific literature answers those questions. Terms commonly used in systematic reviews, such as statistical terms, are provided in Appendix A and are defined as they apply to reports produced by the Drug Effectiveness Review Project.

Systematic reviews emphasize the patient's perspective in the choice of outcome measures used to answer research questions. Studies that measure health outcomes (events or conditions that the patient can feel, such as fractures, functional status, and quality of life) are preferred over studies of intermediate outcomes (such as change in bone density). Reviews also emphasize measures that are easily interpreted in a clinical context. Specifically, measures of *absolute risk* or the probability of disease are preferred to measures such as relative risk. The difference in absolute risk between interventions depends on the number of events in each group, such that the difference (absolute risk reduction) is smaller when there are fewer events. In contrast, the difference in relative risk is fairly constant between groups with different baseline risk for the event, such that the difference (relative risk reduction) is similar across these groups. Relative risk reduction is often more impressive than absolute risk reduction. Another useful measure is the *number needed to treat* (or harm). The number needed to treat is the number of patients who would need be treated with an intervention for 1 additional patient to benefit (experience a positive outcome or avoid a negative outcome). The absolute risk reduction is used to calculate the number needed to treat.

Systematic reviews weigh the quality of the evidence, allowing a greater contribution from studies that meet high methodological standards and, thereby, reducing the likelihood of biased results. In general, for questions about the relative benefit of a drug, the results of well-executed randomized controlled trials are considered better evidence than results of cohort, case-control, and cross-sectional studies. In turn, these studies provide better evidence than uncontrolled trials and case series. For questions about tolerability and harms, observational study designs may provide important information that is not available from controlled trials. Within the hierarchy of observational studies, well-conducted cohort designs are preferred for assessing a common outcome. Case-control studies are preferred only when the outcome measure is rare and the study is well conducted.

Systematic reviews pay particular attention to whether results of *efficacy studies* can be generalized to broader applications. Efficacy studies provide the best information about how a drug performs in a controlled setting. These studies attempt to tightly control potential confounding factors and bias; however, for this reason the results of efficacy studies may not be applicable to many, and sometimes to most, patients seen in everyday practice. Most efficacy studies use strict eligibility criteria that may exclude patients based on their age, sex, adherence to treatment, or severity of illness. For many drug classes, including the antipsychotics, unstable or severely impaired patients are often excluded from trials. In addition, efficacy studies frequently exclude patients who have comorbid disease, meaning disease other than the one under study. Efficacy studies may also use dosing regimens and follow-up protocols that are impractical in typical practice settings. These studies often restrict options that are of value in actual practice, such as combination therapies and switching to other drugs. Efficacy studies also

often examine the short-term effects of drugs that in practice are used for much longer periods. Finally, efficacy studies tend to assess effects by using objective measures that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

Systematic reviews highlight studies that reflect actual clinical *effectiveness* in unselected patients and community practice settings. Effectiveness studies conducted in primary care or office-based settings use less stringent eligibility criteria, more often assess health outcomes, and have longer follow-up periods than most efficacy studies. The results of effectiveness studies are more applicable to the "average" patient than results from the highly selected populations in efficacy studies. Examples of effectiveness outcomes include quality of life, frequency or duration of hospitalizations, social function, and the ability to work. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures, such as scores based on psychometric scales.

Efficacy and effectiveness studies overlap. For example, a study might use very narrow inclusion criteria like an efficacy study, but, like an effectiveness study, might examine flexible dosing regimens, have a long follow-up period, and measure quality of life and functional outcomes. For this report we sought evidence about outcomes that are important to patients and would normally be considered appropriate for an effectiveness study. However, many of the studies that reported these outcomes were short-term and used strict inclusion criteria to select eligible patients. For these reasons, it was neither possible nor desirable to exclude evidence based on these characteristics. Labeling a study as either an efficacy or an effectiveness study, although convenient, is of limited value; it is more useful to consider whether the patient population, interventions, time frame, and outcomes are relevant to one's practice or to a particular patient.

Studies anywhere on the continuum from efficacy to effectiveness can be useful in comparing the clinical value of different drugs. Effectiveness studies are more applicable to practice, but efficacy studies are a useful scientific standard for determining whether characteristics of different drugs are related to their effects on disease. Systematic reviews thoroughly cover the efficacy data in order to ensure that decision makers can assess the scope, quality, and relevance of the available data. This thoroughness is not intended to obscure the fact that efficacy data, no matter how large the quantity, may have limited applicability to practice. Clinicians can judge the relevance of studies' results to their practice and should note where there are gaps in the available scientific information.

Unfortunately, for many drugs there exist few or no effectiveness studies and many efficacy studies. Yet clinicians must decide on treatment for patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. Systematic reviews indicate whether or not there exists evidence that drugs differ in their effects in various subgroups of patients, but they do not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these decisions must be informed by clinical judgment.

In the context of development of recommendations for clinical practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of an intervention are based on strong evidence from clinical studies. By themselves, they do not say what to do. Judgment, reasoning, and applying one's values under conditions of uncertainty must also play a role in decision making. Users of an

evidence report must also keep in mind that *not proven* does not mean *proven not*; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is untrue. The quality of the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policy. Additional criteria include acceptability to physicians and patients, potential for unrecognized harm, applicability of the evidence to practice, and consideration of equity and justice.

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different proton pump inhibitors. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and, based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project. The participating organizations of the Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide Update 5 of this review:

1. What is the comparative effectiveness of different proton pump inhibitors in patients with symptoms of gastroesophageal reflux disease?

2. What is the comparative effectiveness of different proton pump inhibitors in treating peptic ulcer and nonsteroidal anti-inflammatory drug-induced ulcer?

3. What is the comparative effectiveness of different proton pump inhibitors in preventing ulcer in patients taking a nonsteroidal anti-inflammatory drug?

4. What is the comparative effectiveness of different proton pump inhibitors in eradicating *Helicobacter pylori* infection?

5. Is there evidence that a particular treatment strategy is more effective or safer than another (for example, stepping down to a lower dose, treatment as needed compared with daily treatment, high dose compared with standard dose, or switching to an H2 antagonist) for treatment longer than 8 weeks in patients with gastroesophageal reflux disease or ulcer?

6. What are the comparative safety and adverse events of different proton pump inhibitors in patients being treated for symptoms of gastroesophageal reflux disease, peptic ulcer, and nonsteroidal anti-inflammatory drug-induced ulcer?

7. Are there subgroups of patients based on demographics, other medications, or comorbidities (including nasogastric tubes and inability to swallow solid oral medication) for which a particular proton pump inhibitor or preparation is more effective or associated with fewer adverse effects?

METHODS

Literature Search

To identify articles relevant to each key question, we searched the Cochrane Library (4th Quarter 2008), Medline (1966- week 2 of November 2008), Embase (1980-3rd Quarter 2004), and reference lists of review articles. In electronic searches, we combined terms for gastroesophageal reflux and peptic ulcer with terms for proton pump inhibitors and particular research designs. (See Appendix B for complete search strategy.) Pharmaceutical manufacturers were invited to submit dossiers, including citations. All citations were imported into an electronic database (EndNote X1).

Update 5 added a key question (Key Question 5) addressing different treatment strategies. To identify citations relevant to the new question but published before the literature search for this update, we searched the EndNote library of citations from all previous versions of this report, looking for citations that met criteria for this new question.

Study Selection

The abstracts of all citations identified in literature searches and dossiers were assessed for inclusion using the predetermined criteria specified in the key questions. For abstracts that met these criteria, full-text articles were retrieved and inclusion criteria reapplied. Citation and full-text review were conducted by one reviewer and checked by a second. Disagreements were resolved by consensus.

We included English-language reports of randomized controlled trials of at least 4 weeks' duration in adult outpatients with symptoms of gastroesophageal reflux, peptic ulcer, or nonsteroidal anti-inflammatory drug-induced ulcer. Included interventions were a proton pump inhibitor (omeprazole, lansoprazole, pantoprazole, rabeprazole, or esomeprazole) compared with proton pump inhibitor, other ulcer drug (H2 receptor antagonist, prokinetic agent, or antacid), placebo, surgery, or antibiotics. For adverse effects, we also included observational studies. Outcomes measured were symptoms, functional outcomes, endoscopic healing, eradication of *Helicobacter pylori*, quality of life, and adverse effects. We excluded reports that were published as only abstracts (see Appendix C).

To evaluate *efficacy* we included only randomized controlled 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 compared one proton pump inhibitor with another provided direct evidence of comparative efficacy and adverse event rates. We did not examine in detail placebo-controlled or active-control trials when head-to-head trials were available. In theory, trials that compare proton pump inhibitors with H2 receptor antagonists or placebos also can provide evidence about efficacy. However, the efficacy of proton pump inhibitors in different trials can be difficult to interpret because of differences between patients.

To supplement our analyses of published results, we requested and received from the trial funders additional data for 2 published trials[4, 5] and 1 trial[6] that was submitted to the US Food and Drug Administration but not published.

To evaluate *adverse events*, we included clinical trials and observational cohort studies. Clinical trials are often not designed to assess adverse events and may select only low-risk patients (in order to minimize drop-out rate) or use 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 period, use higher quality methodological techniques for assessing adverse events, or examine larger sample sizes.

Data Abstraction

The following data were abstracted from included studies: 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 follow-up; method of outcome ascertainment; and results for each outcome. We recorded intention-to-treat results if they were available and the trial did not report high overall loss to follow-up. Data were abstracted by one reviewer and checked for accuracy by a second; disagreements were resolved by consensus.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix D. These criteria are based on criteria developed by the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom) for assessing study quality.[2, 7] We rated the internal validity of each trial on the basis of 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 follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw in 1 or more categories were rated poor quality. Trials that 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 a true difference between the compared drugs. External validity of trials was assessed based on whether the publication adequately described the study population, whether patients in the study were similar to patients in 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 D 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 6 or more of the 7 predefined criteria, fair if they met 3 to 5 criteria, and poor if they met 2 or fewer criteria.

Overall quality rating for an individual study was based on ratings of internal and external validity of the trial. A particular randomized trial might receive 2 quality ratings, 1 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

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. We reviewed studies using a hierarchy-of-evidence approach, in which the best evidence was the focus of our synthesis for each question, population, intervention, and outcome addressed. Meta-analyses were conducted where possible. *Differences* in healing rates (ulcers and esophagitis) between drugs based on head-to-head trials are expressed as the percent risk difference, defined as the difference between the proportions healed in 2 groups of patients at a specified time-point. For example, if at 4 weeks 80% of patients in group A have only healed lesions and 75% in group B have only healed lesions, then the risk difference between the groups is 5%. A measure of the variance around these estimates, the 95% confidence interval (CI) is also reported. If the 95% CI includes 0, then the difference is not statistically significant. Meta-analysis was done using RevMan software using a random-effects model. (RevMan, Version 5.0, The Cochrane Collaboration, 2008).

To determine healing and symptom resolution *rates* for *individual* drugs, we performed a meta-analysis by using a random-effects model controlling for the effect of the study. For example, the healing rate for Drug A might be calculated as 81% based on 7 head-to-head trials, and Drug B might have a rate of 83% based on 4 head-to-head trials.. This analysis was conducted using SAS 9.1 (SAS Institute Inc., Cary, NC, USA using data on each individual drug from head-to-head trials.

Similarly, we conducted random-effects logistic meta-regression to estimate rates of healing associated with *individual* drugs based on studies comparing a proton pump inhibitor with a H2 receptor antagonist. The rate of healing with the proton pump inhibitor was adjusted for healing rate with H2 receptor antagonist within the same study. The model stratified by type of proton pump inhibitor (lansoprazole, omeprazole, pantoprazole, and rabeprazole). Posterior distributions were simulated using WinBUGS software version 1.4.3 (Medical Research Council and Imperial College School of Medicine at St Mary's, London).[8]

Peer and Public Review

The Original report underwent a review process that involved solicited peer review from clinical experts. Their comments were reviewed and, where possible, incorporated into the final document. The comments received and the author's proposed actions were reviewed by the representatives of the participating organizations of the Drug Effectiveness Review Project prior to finalization of the report. Names of peer reviewers for Drug Effectiveness Review Project reports are listed at www.ohsu.edu/drugeffectiveness. Peer reviewers have a maximum of 3 weeks for review and comment. They are asked to submit their comments in a standardized form in order to maintain consistent handling of comments across reports and to allow the Drug Effectiveness Review Project team to address all comments adequately.

The Drug Effectiveness Review Project process allows for a 2-week public comment period prior to finalization of the current report. Draft reports are posted on the Drug Effectiveness Review Project web site and interested individuals or organizations have the ability to review the complete draft report and submit comments. For Update 5 of this report, we received comments from 2 pharmaceutical companies.

RESULTS

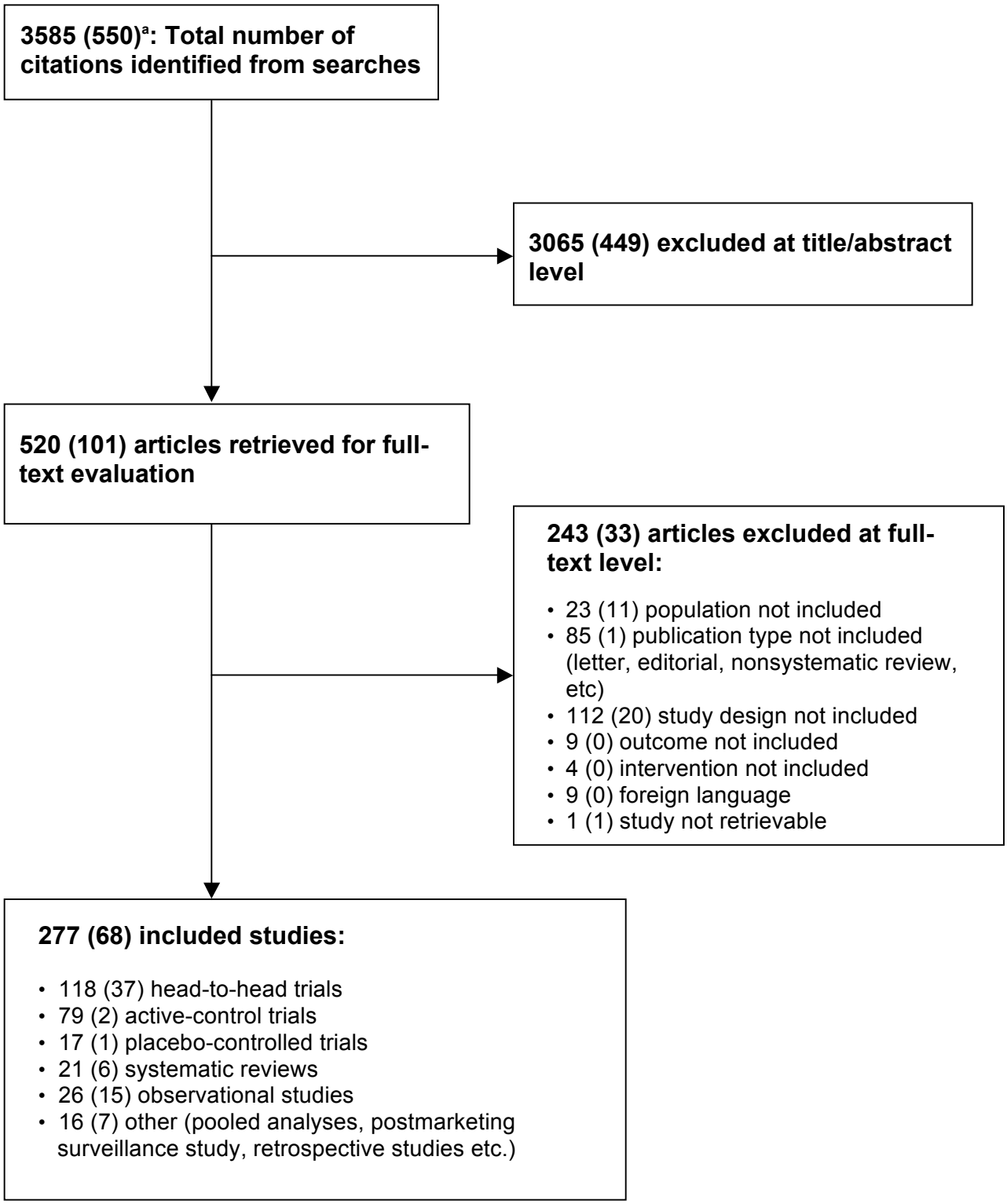
Overview

Our literature searches identified 550 new citations for Update 5: 376 from Medline, 57 from Cochrane Central Register of Controlled Trials, 45 from dossiers submitted by the manufacturers of esomeprazole and rabeprazole, 31 from Cochrane Database of Systematic Reviews, 29 from Database of Abstracts of Reviews of Effects, 7 from public comment on the draft of this report, and 5 from reference lists of included review articles. Of these 68 were ultimately included (see Figure 1).

We excluded trials when the study was reported only as an abstract, contained no original data, contained no included outcome measure, did not have an included study design, did not use an included drug or used combined drug therapy where the effect of the proton pump inhibitor could not be distinguished, did not evaluate an included patient population, or was reported in a language other than English. Figure 1 summarizes the flow of study inclusion and exclusion. No study of omeprazole in combination with sodium bicarbonate (Zegerid) met inclusion criteria.

There is controversy about the appropriateness of dose comparisons in head-to-head trials comparing esomeprazole with omeprazole. The US Food and Drug Administration's clinical review of esomeprazole indicates that esomeprazole 40 mg is "pharmacodynamically thrice that of the s-isomer" in omeprazole 20 mg (see US Food and Drug Administration Medical Review, executive summary, page 4).[9] While the doses approved by the US Food and Drug Administration for treatment of erosive esophagitis are 20 to 40 mg daily for esomeprazole, and 20 mg daily for omeprazole (both for 4 to 8 weeks), because of differences in drug chemistry and pharmacology, there is no clear equivalent dose of omeprazole and esomeprazole.

Figure 1. Results of literature search



[a] Numbers in parentheses are results of the literature search new to Update 5.

Key Question 1. What is the comparative efficacy of different proton pump inhibitors in patients with symptoms of gastroesophageal reflux disease?

Summary

Symptom relief and healing in patients with erosive esophagitis

- Among 16 head-to-head trials, those with comparable doses did not find differences in symptom relief or healing of esophagitis.
- The only difference between proton pump inhibitors on the outcome of complete symptom relief at 4 weeks was in the comparison of esomeprazole 40 mg with omeprazole 20 mg; the pooled risk difference in 3 trials was 8% (95% CI 3 to 13), with a number needed to treat of 13.
- Time to relief of heartburn was similar for all proton pump inhibitors in head-to-head trials, but the methods used to measure and report this outcome varied in the 14 studies.
- Good evidence showed no difference between omeprazole, lansoprazole, pantoprazole, and rabeprazole for healing of esophagitis. Thirteen head-to-head trials found these 4 proton pump inhibitors to be equally effective in healing at 4 and 8 weeks.
- Pooled analysis of 4- and 8-week healing rates from 4 trials of esomeprazole 40 mg compared to omeprazole 20 mg indicated esomeprazole to be superior; risk difference 7% (95% CI 1 to 12) and a number needed to treat of 14 and 5% (95% CI 1 to 9), number needed to treat = 20, respectively.
- Three trials compared esomeprazole 40 mg with lansoprazole 30 mg. The pooled difference in healing rate was significantly greater with esomeprazole at 4 and 8 weeks, risk differences 5% (95% CI 2 to 7) and 3% (95% CI 1 to 5), respectively.
- Evidence on the comparison of esomeprazole 40 mg and pantoprazole 40 mg was mixed, with 2 studies finding esomeprazole superior and 2 finding no difference in healing rates. Pooled analysis of 3 trials with similar populations finds that esomeprazole was superior to pantoprazole at 4 weeks (risk difference 5%, 95% CI 2 to 8), but not at 8 weeks (risk difference 1%, 95% CI –3 to 5).

Healing in moderate to severe erosive esophagitis

- Esomeprazole 40 mg was more effective at healing esophagitis at 4 and 8 weeks than omeprazole 20 mg and lansoprazole 30 mg.
- The pooled risk difference in 3 studies comparing omeprazole 20 mg with esomeprazole 40 mg was 16% at 4 weeks and 13% at 8 weeks (number needed to treat = 6 at 4 weeks, 8 at 8 weeks).
- The pooled risk difference in 2 studies comparing lansoprazole 30 mg with esomeprazole 40 mg was 8% at 4 weeks and 9% at 8 weeks (number needed to treat = 13 at 4 weeks, 11 at 8 weeks).
- Evidence was mixed on differences between esomeprazole 40 mg and pantoprazole 40 mg.
    - At 4 weeks, esomeprazole 40 mg had a higher healing rate than pantoprazole 40 mg; pooled risk difference (2 studies) 14% (95% CI 7 to 20)
    - At 8 weeks, no difference was found in a single small study of patients with mild to moderate esophagitis.
- Lansoprazole 30 mg (2 studies) and esomeprazole 20 mg (1 study) were no different to omeprazole 20 mg at 4 or 8 weeks.

Prevention of relapse in patients with erosive esophagitis

- For maintenance of healed esophagitis, there was good evidence that no difference exists between omeprazole, lansoprazole, and rabeprazole. The longest study (over 5 years) compared omeprazole with rabeprazole.
- Two 6-month studies found lower relapse rates for esomeprazole 20 mg than for lansoprazole 15 mg or pantoprazole 20 mg.
- No difference was found between esomeprazole 20 mg and pantoprazole 20 mg in combined symptomatic and endoscopic remission rates after 6 months.

Symptom relief in patients with nonerosive gastroesophageal reflux disease or presumptively treated symptoms of gastroesophageal reflux disease

- Three head-to-head trials in patients with gastroesophageal reflux disease but without erosive esophagitis on endoscopy found no difference between esomeprazole 20 mg and omeprazole 20 mg, pantoprazole 20 mg, or rabeprazole 10 mg. These studies used different outcome measures.
- Limited indirect evidence from placebo-controlled and active-control trials suggested similar efficacy for heartburn resolution and complete symptom relief for all 5 proton pump inhibitors.

Evidence in children

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

Detailed Assessment

Erosive esophagitis

We identified 31 randomized controlled trials comparing 2 or more proton pump inhibitors in patients with gastroesophageal reflux disease with endoscopically-proven erosive esophagitis (Evidence Table 1).[4-6, 10-38] Two publications are supplemented with additional data provided by the manufacturer.[4, 5] Most studies used omeprazole. No study of omeprazole in combination with sodium bicarbonate met inclusion criteria. The scales used to grade esophagitis in these studies are described in Appendix E.

In most studies of proton pump inhibitors, patients who have esophagitis before treatment undergo another endoscopy for assessment of healing 4 or 8 weeks after starting treatment. There is no evidence that rate of esophageal healing after 4 or 8 weeks of treatment is associated with risk of stricture or esophageal cancer in the long run. As distinct from symptom relief, the benefit of quicker esophageal healing is also uncertain.

The clinical importance of small differences in healing rates at 4 or 8 weeks is not known. In addition, patients who have clinically significant improvements but who are not completely healed (for example, patients whose esophagitis improves from LA classification scale grade D to grade B) are considered unhealed. Studies do not report the esophagitis grade for patients “not healed” at follow-up.

Resolution of symptoms

Five head-to-head comparisons of proton pump inhibitors measured symptom relief as a primary outcome, [10, 11, 13, 16, 37] and 14 reported symptoms as a secondary outcome.[4, 5, 12, 14, 15, 17, 21-26, 30, 32, 35] Symptoms in these studies were assessed through patient diaries, investigator-elicited reports, or both.

Sixteen head-to-head trials reported the proportion of patients with resolution of symptoms at 4 weeks.[4, 5, 10, 12-14, 16, 17, 20, 23, 24, 26, 27, 29, 33, 36] We performed a random-effects meta-analysis of data from these studies to determine an estimate of the proportion who were symptom-free at 4 weeks for each drug. Results are shown in Table 2. Proportions ranged from 65% to 77%, and 95% confidence intervals overlapped, indicating the drugs are similarly efficacious for resolution of symptoms at 4 weeks.

A systematic review of most of these trials, with search dates through 2004, evaluated the proton pump inhibitors as a group and compared to one another.[39] This meta-analysis found omeprazole 20 mg daily to be inferior to esomeprazole 40 mg or lansoprazole 30 mg daily in heartburn relief at day 1, with relative risks of 0.78 (95% CI 0.71 to 0.85) and 0.82 (95% CI 0.75 to 0.88), respectively. Lansoprazole and esomeprazole were not found statistically different (relative risk 1.03; 95% CI 0.87 to 1.22). Our analysis includes more recently published trials.

Table 2. Symptom resolution in head-to-head trials in patients with erosive gastroesophageal reflux disease

Proton pump inhibitor and daily dose	Resolution of symptoms at 4 weeks (95% CI)	Reference number
Esomeprazole 40 mg	73% (65 to 82)	4, 5, 10, 12, 16, 20, 29
Lansoprazole 30 mg	70% (61 to 80)	4, 13-15, 23, 29
Omeprazole 20 mg	65% (54 to 76)	5, 12, 13, 16, 24, 26, 27
Omeprazole 40 mg	76% (65 to 87)	14, 17
Pantoprazole 20 mg	77% (70 to 84)	27
Pantoprazole 40 mg	72% (62 to 83)	10, 13, 17, 20, 23, 26
Rabeprazole 20 mg	69% (52 to 86)	24

Figure 2 shows risk differences in rates of symptom resolution at 4 weeks in these trials.[4, 5, 10, 12-14, 16, 17, 20, 23, 24, 26, 27, 29, 33, 36] In Table 3 we report the difference in symptom resolution for esomeprazole compared with other proton pump inhibitors. The pooled data on the comparison of esomeprazole 40 mg with omeprazole 20 mg significantly favored esomeprazole; for every 13 persons treated with esomeprazole 40 mg instead of omeprazole 20 mg, 1 additional patient would be symptom-free at 4 weeks in the esomeprazole group. The pooled data for comparison of esomeprazole 40 mg with either lansoprazole 30 mg or pantoprazole 40 mg did not indicate a significant difference between drugs.

Figure 2. Resolution of symptoms at 4 weeks in head-to-head trials of proton pump inhibitors

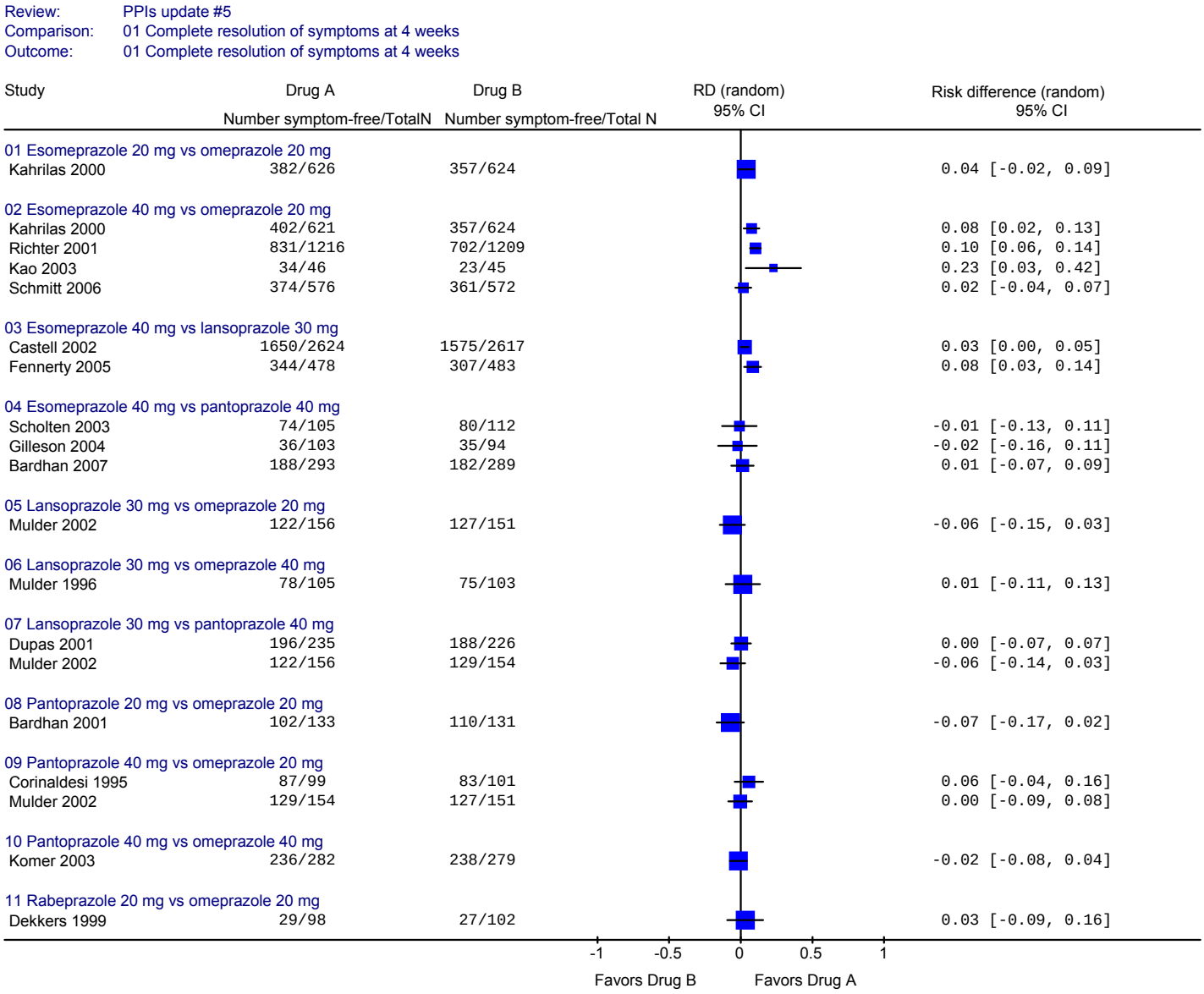


Table 3. Symptom resolution at 4 weeks in trials of esomeprazole compared with another proton pump inhibitor in erosive gastroesophageal reflux disease

Study	Portion of group with resolution of symptoms at 4 weeks	Risk difference (95% CI)	Pooled estimate
Esomeprazole 40 mg compared with omeprazole 20 mg			
Kahrilas 2000[5]	65% vs. 57%	8% (2 to 13)	**8% (3% to 13%) number needed to treat=13**
Kao 2003[16]	74% vs. 51%	23% (3 to 42)	
Richter 2001[12]	68% vs. 58%	10% (6 to 14)	
Schmitt 2006[36]	65% vs. 63%	2% (–4 to 7)	
Esomeprazole 40 mg compared with lansoprazole 30 mg			
Castell 2002[4]	63% vs. 60%	3% (0 to 5)	**5% (0% to 9%)**
Fennerty 2005[29] (ITT[a])	69% vs. 61%	8% (2 to 14)	
Esomeprazole 40 mg compared with pantoprazole 40 mg			
Bardhan 2007[33]	64% vs. 63%	1% (–7 to 9)	**0% (–6% to 6%)**
Gillessen 2004[20]	35% vs. 37%	–2% (–16 to 11)	
Sholten 2003[10]	70% vs. 71%	–1% (–13 to 11)	

[a] Intention-to-treat analysis performed for this report.

A single study reported resolution of symptoms after 1 week of therapy,[32] finding rabeprazole 20 mg daily superior to omeprazole 20 mg daily (resolution in 27.9% of patients compared with 16.6%, *P*=0.0013 as calculated from number randomized and using chi square analysis).

A head-to-head trial of pantoprazole 40 mg compared with esomeprazole 40 mg used the ReQuest Score to assess symptoms.[35] ReQuest is a validated self-assessment scale used to measure symptoms in erosive and nonerosive gastroesophageal reflux disease. Measured on the last 3 days of a 4-week treatment period, the median ReQuest-GI score in patients taking pantoprazole was found to be non-inferior to the median score in patients taking esomeprazole.

Time to relief of symptoms

Fourteen studies reported the time to resolution of symptoms (no heartburn). This outcome usually was reported as the percentage of patients with symptom resolution by a given time point, such as 1 day or 7 days), the median number of days to resolution, or both. One study reported this outcome as the number of days needed for 50% and 75% of patients to achieve resolution of symptoms.[10]

Another measure was the time to sustained resolution of heartburn, defined as the first of 7 consecutive days without heartburn. This outcome was used only in studies funded by the maker of esomeprazole, so it is not possible to compare this outcome with studies funded by others.

Esomeprazole compared with omeprazole. In 4 studies that compared esomeprazole 40 mg with omeprazole 20 mg, the median number of days to the *first* resolution of symptoms was similar; however, the median number of days to sustained resolution of symptoms favored esomeprazole in the 2 studies reporting this measure (Table 4).[5, 12, 16] More patients taking esomeprazole 40 mg reached *first* of resolution of symptoms by day 1 and day 7 in absolute proportions than patients taking omeprazole 20 mg. These findings were statistically significant in 1 study,[12] nonsignificant in 2 others,[16, 31] and not assessed in the fourth.[5] The time to *sustained* resolution of heartburn was statistically superior with esomeprazole 40 mg compared to omeprazole 20 mg at day 14 in 2 studies.[12, 16] The differences at other time points were mixed or not statistically assessed. One of these studies used a tablet formulation of esomeprazole that is not available in the US or Canada.[31]

In a comparison of esomeprazole 20 mg with omeprazole 20 mg,[5] a higher proportion of omeprazole patients started 7 consecutive days without heartburn at day 1; esomeprazole had a higher proportion of patients with sustained relief by day 28. Neither comparison was statistically significant. The median number of days to sustained resolution was similar. This pattern was also seen in the time to first resolution of symptoms.

Table 4. Time to symptom relief in trials comparing esomeprazole with omeprazole in erosive gastroesophageal reflux disease

Study	Proportion with first resolution of heartburn		Proportion that has begun sustained resolution of heartburn (7 consecutive days)			
Esomeprazole 20 mg compared with omeprazole 20 mg						
Kahrilas 2000	Day 1: 38% vs. 37% *P*=0.76	Day 7: 81% vs. 80% *P*=0.81	Day 1: 22% vs. 23% *P*=0.60		Day 28: 70% vs. 67% *P*=0.18	
Esomeprazole 40 mg compared with omeprazole 20 mg						
Kahrilas 2000	**Day 1: 47% vs. 37% *P*=0.0006**	Day 7: 83% vs. 80% *P*=0.12	**Day 1: 30% vs. 23% *P*=0.01**		**Day 28: 74% vs. 67% *P*=0.003**	
Kao 2003	Day 1: 28% vs. 26% NS	Before day 7: 56% vs. 56% NS	Day 7: 15% vs. 15.6% NS	Day 14: 50% vs. 20% *P*<0.05	Day 21: 72% vs. 40% *P*<0.01	Day 28: 74% vs. 51% *P*<0.05
Richter 2001	**Day 1: 45% vs. 32% *P*≤0.0005**	**Day 7: 86% vs. 82% *P*≤0.0005**	Day 1: 29% vs. 20% *P*≤0.0005		Day 14: 68% vs. 63% *P*≤0.0005	
Chen 2005	Day 1: 77.3% vs. 65% NS		Not reported			

Esomeprazole compared with lansoprazole. In 3 studies comparing esomeprazole 40 mg with lansoprazole 30 mg, results were mixed and outcomes were reported differently (Table 4). Overall, results did not favor one drug over another.

Esomeprazole compared with pantoprazole. The 2 trials comparing esomeprazole with pantoprazole reported time to symptom resolution differently and found conflicting results. In 1

trial comparing esomeprazole 40 mg with pantoprazole 40 mg, 4% more esomeprazole patients began sustained resolution of heartburn (7 consecutive days) after 1 day of treatment: 24% compared with 20% (*P* value not reported).[30] The median time to sustained resolution was 6 days with esomeprazole, compared with 8 days (*P*<0.001). Based on this same life-table analysis, the Cumulative proportion of patients reporting sustained resolution of heartburn was 78% with esomeprazole and 77% with pantoprazole, again a small difference but found to be statistically significant (*P*<0.001). A second trial comparing esomeprazole 40 mg with pantoprazole 40 mg looked at the number of days required for relief of heartburn in 50% and 75% of patients.[10] In both groups, 50% of patients had no heartburn after 2 days. But it took 3 days for 75% of the pantoprazole group to be relieved of symptoms and 8 days for the esomeprazole group. Confidence intervals overlapped, (95% CI for pantoprazole, 2 to 7 days; for esomeprazole, 3 to14 days) suggesting a significant difference between the drugs is unlikely but not proven.

Lansoprazole compared with omeprazole. Three studies reported time to relief of heartburn with lansoprazole compared with omeprazole.[14, 15, 25] Although lansoprazole improved some symptoms more quickly, there was no strong or consistent pattern suggesting that lansoprazole provides faster symptom relief than omeprazole. Time to sustained resolution of heartburn (defined as 3 consecutive days without heartburn) was measured in 1 study and was similar for the drugs (median 3 days for both drugs, *P*=0.285).[14] In another study, daytime and nighttime heartburn were reported separately.[25] After 1 day of treatment, more lansoprazole patients were free of day heartburn (48.7% compared with 37.6%, *P*<0.05) and night heartburn (62% compared with 52%, *P*<0.05). The third comparison of these drugs used a visual analogue scale to measure heartburn and reported the time to relief only for daytime heartburn.[15] After 3 days, there was a significant decrease in symptom score in lansoprazole patients (–20.2 compared with –15.3, *P*=0.05); the difference was not significant after 7 days (scores not reported).

Rabeprazole compared with omeprazole. One study reported similar mean time to complete relief of heartburn for rabeprazole and omeprazole 20 mg daily (7 and 8 days, respectively).[32] A second study reported median time to achieve heartburn control, defined as the first day heartburn score was below 3 on a 5-point Likert scale.[34] The median time to heartburn control was 1.5 days for both rabeprazole and omeprazole (*P*<0.43).

Healing of esophagitis

All the proton pump inhibitors allowed esophagitis to heal. Healing rates at 4 weeks ranged from 49% to 91% and at 8 weeks ranged from 71% to 99% (see Evidence Table 1). One small, fair-quality study conducted at a single center in China had a lower 8-week healing rate than other studies (64% for esomeprazole 40 mg, 45.5% for omeprazole 20 mg).[31]

To estimate healing rates for each drug, we pooled data from head-to-head trials, using a random-effects model to control for the effect of the study. Table 5 shows results of this analysis. (Note that data for lansoprazole 15 mg, pantoprazole 20 mg, and rabeprazole 10 mg are available from only 1 study). Healing rates were similar and confidence intervals overlapped, indicating no significant differences between proton pump inhibitors.

Table 5. Pooled estimates of healing rates for esophagitis in head-to-head trials of proton pump inhibitors

Drug	Proportion of group whose esophagitis has healed at 4 weeks (95% CI)	Proportion of group whose esophagitis has healed at 8 weeks (95% CI)
Esomeprazole 20 mg	73% (66-79)[5, 6]	87% (84-91)[5, 6]
Esomeprazole 40 mg	78% (73-83)[4, 5, 12, 20, 29, 30, 36, 38]	90% (88-92)[4, 5, 12, 18, 20, 29-31, 38]
Lansoprazole 15 mg	63% (52-73)[25]	73% (63-82)[25]
Lansoprazole 30 mg	73% (67-79)[4, 14, 15, 21, 23, 25, 29]	86% (83-90)[4, 14, 15, 18, 21, 23, 25, 29]
Omeprazole 20 mg	70% (64-76)[5, 6, 12, 15, 21, 22, 25-27, 38]	85% (81-88)[5, 6, 12, 15, 21, 22, 25-27, 31, 38]
Omeprazole 40 mg	68% (59-78)[14, 17]	87% (76-99)[14]
Pantoprazole 20 mg	67% (54-81)[27]	77% (65-88)[27]
Pantoprazole 40 mg	71% (65-78)[17, 20, 23, 26, 30]	89% (86-92)[20, 23, 26, 30]
Rabeprazole 10 mg	65% (47-83)[22]	84% (71-96)[22]
Rabeprazole 20 mg	69% (59-79)[22, 40]	82% (76-89)[22, 40]

Data from the cited studies were pooled using a random-effect model.

We also calculated the risk difference for healing in head-to-head comparisons. Figures 3 and 4 show the differences in healing rates at 4 and/or 8 weeks for the 23 trials that provided the number healed/total patients.[4-6, 12, 14, 15, 17, 18, 20-23, 25-27, 29-33, 36, 37] Seven head-to-head trials are not represented in Figures 3 and 4: Three studies (2 comparing rabeprazole with omeprazole, 1 comparing omeprazole with both lansoprazole and rabeprazole)[19, 28, 41] did not provide number healed/total and 4 trials[10, 11, 13, 16] reported only symptom relief, not esophagitis healing. For 1 trial comparing rabeprazole 20 mg with omeprazole 20 mg the figures show calculated intention-to-treat numbers, rather than those from the article, which are not intention-to-treat.[32]

Although some published studies present results according to life-table analysis, only crude rates are included in Figure 3. For published studies that do not provide crude rates, we requested and received these data from the manufacturer. Results of life-table analyses cannot be directly compared with crude rates reported in other studies, and using life-table analysis may overestimate results by excluding patients who are lost to follow-up or have withdrawn from the study.

Omeprazole 20 mg, the first proton pump inhibitor to be marketed, was the proton pump inhibitor used most often in head-to-head trials. Table 6 summarizes the risk differences in healing rate in 9 trials[12, 15, 21, 22, 25-27, 31, 36] that compared daily omeprazole 20 mg with another proton pump inhibitor. Risk difference at 4 and 8 weeks was significant in only 1 comparison, esomeprazole 40 mg compared with omeprazole 20 mg. The pooled risk difference for 3 studies at 4 weeks was 8% and for 4 studies at 8 weeks was 6%. These risk differences translate to numbers needed to treat to heal 1 additional patient of 13 at 4 weeks and 17 at 8 weeks.

Figure 3. Esophagitis healing at 4 weeks in head-to-head trials of proton pump inhibitors

Review: PPIs update #5
Comparison: 02 Esophagitis healing at 4 weeks
Outcome: 01 Esophagitis healing at 4 weeks

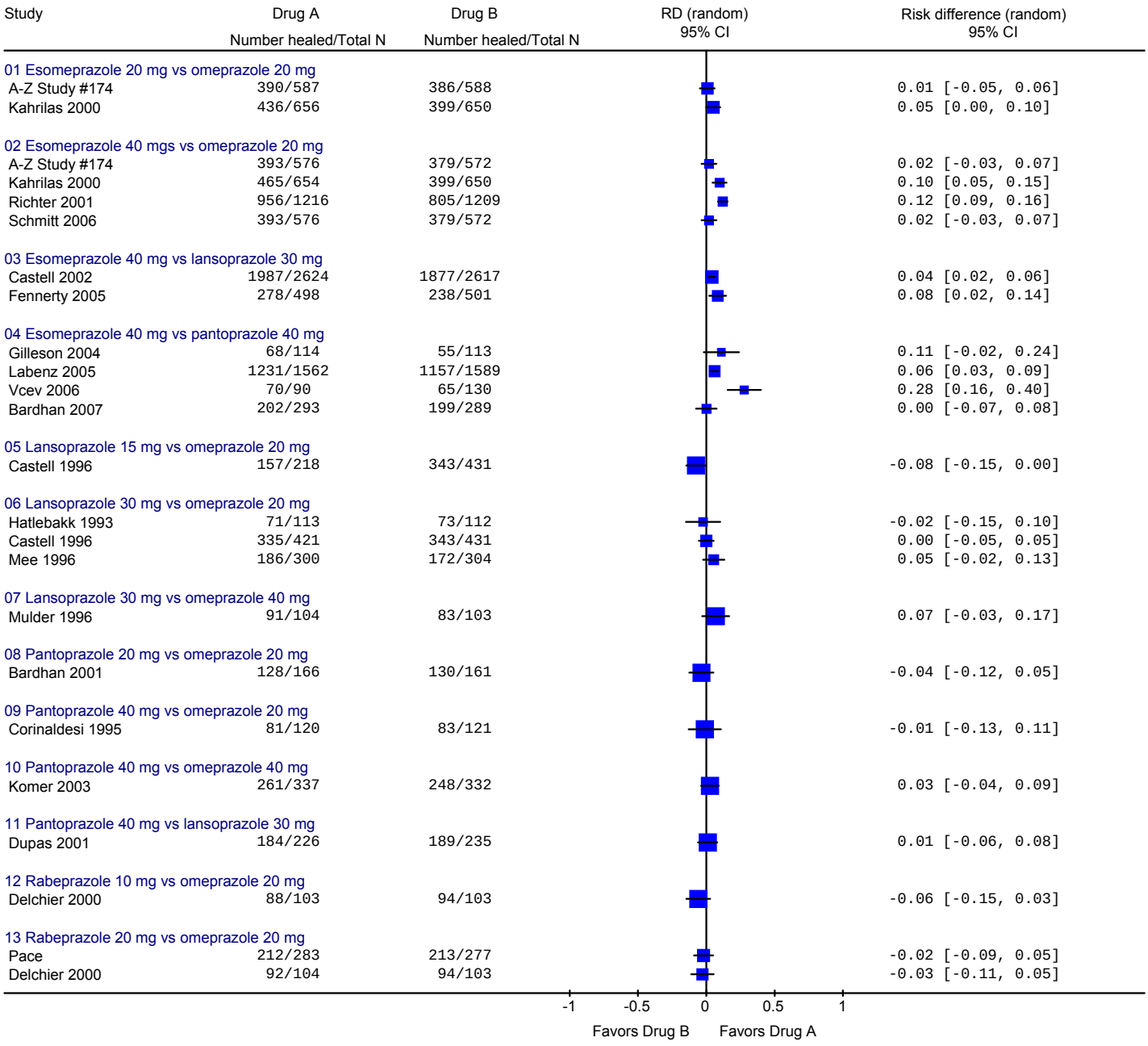


Figure 4. Esophagitis healing at 8 weeks in head-to-head trials of proton pump inhibitors

Review: PPIs update #5
Comparison: 03 Esophagitis healing at 8 weeks
Outcome: 01 Esophagitis healing at 8 weeks

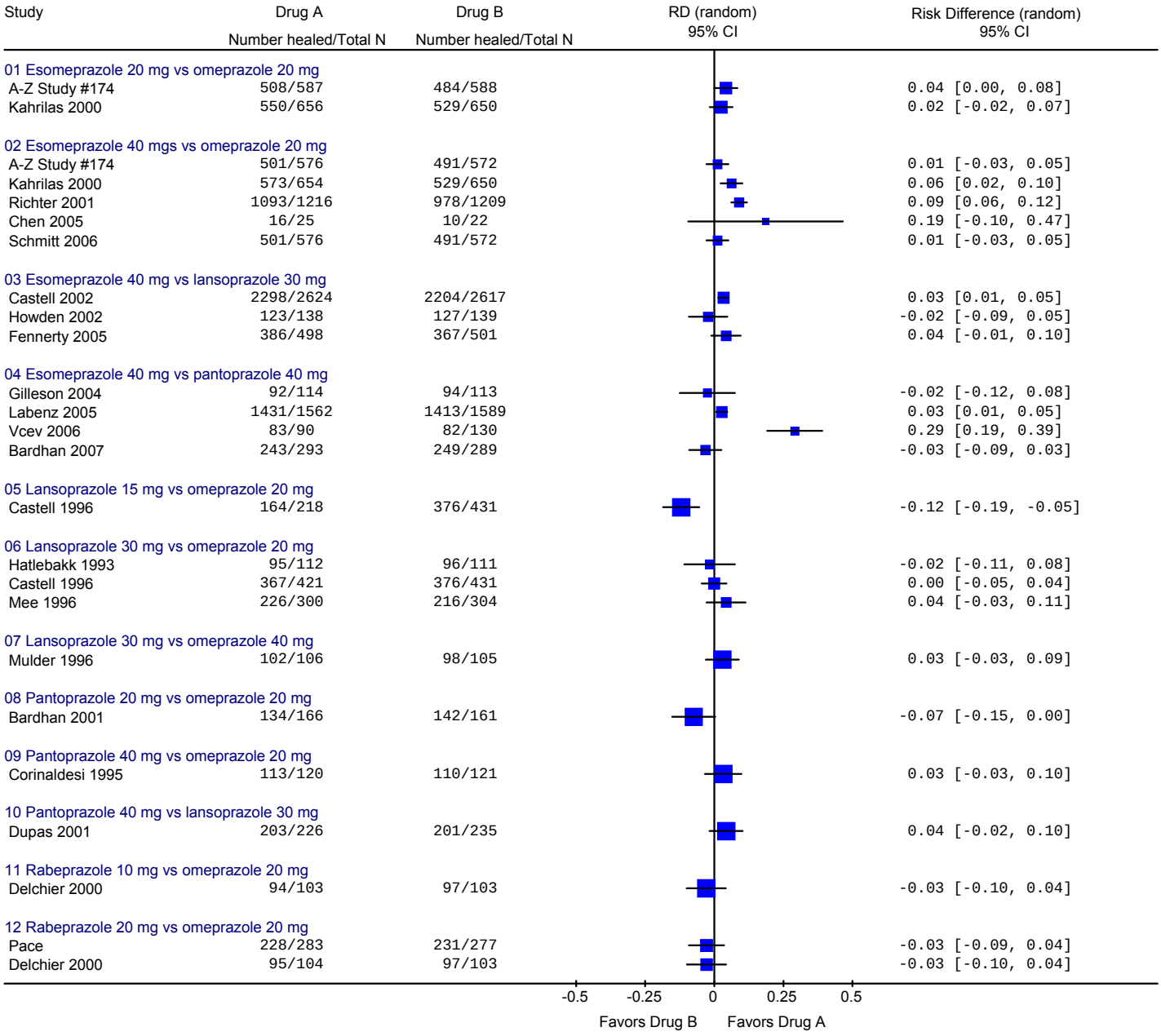


Table 6. Risk differences in healing of esophagitis in trials of omeprazole 20 mg compared with another proton pump inhibitor

Drug, daily dose	Risk difference[a] at 4 weeks in comparison with omeprazole (95% CI)	Risk difference[a] at 8 weeks in comparison with omeprazole (95% CI)
Esomeprazole 20 mg	3% (–1 to 7)[5, 6]	3% (0 to 6)[5, 6]
Esomeprazole 40 mg	7% (1 to 12), pooled[5, 12, 36, 38 36] **number needed to treat = 14**	5% (1 to 9), pooled[5, 12, 31, 36, 38] **number needed to treat = 20**
Lansoprazole 30 mg	2% (–3 to 6), pooled [15, 21, 25]	1% (–2 to –5), pooled [15, 21, 25]
Pantoprazole 20 mg	–4% (–12 to 5)[27]	–7% (–15 to 0)[27]
Pantoprazole 40 mg	–1% (–13 to 11)[26]	3% (–3 to 10)[26]
Rabeprazole 10 mg	–6% (–15 to 3)[22]	–3% (–10 to 4)[22]
Rabeprazole 20 mg	–2% (–8 to 3)[22, 32]	–3% (–8 to 2)[22, 32]

[a] Risk difference was calculated as the difference between the percent of the group on the test proton pump inhibitor in which esophagitis healed and the percent of the group on omeprazole 20 mg daily in which esophagitis healed.

Two published trials comparing esomeprazole 40 mg with omeprazole 20 mg found a statistically significantly higher healing rate in the esomeprazole group.[5, 12] Two others[36, 38] found no difference between groups at 4 and 8 weeks. A small study (N=48) not included in Table 5 found a higher healing rate for esomeprazole at 8 weeks (64% compared with 46%), but the difference was not statistically significant.[31] The study may not have had sufficient power to detect a difference between treatment groups; no power calculation was reported. This study did not measure 4-week healing rates.

The pooled risk difference for 4 studies at 4 weeks was 7% and for 5 studies at 8 weeks was 5%, favoring esomeprazole (see Table 6). This translates to a number needed to treat with esomeprazole to heal 1 additional patient at 4 weeks of 14, and a number needed to treat at 8 weeks of 20.

Three studies compared esomeprazole 40 mg with lansoprazole 30 mg.[4, 18, 29] In a large, good-quality trial in 5241 patients at multiple centers in the United States,[4] healing rates were higher in the esomeprazole group at 4 and 8 weeks. A smaller, fair-quality trial[18] in patients with mostly mild to moderate esophagitis found the drugs to have equivalent healing rates at 8 weeks; results at 4 weeks were also similar between drugs. The third study, rated good quality,[29] was conducted in patients with moderate to severe esophagitis. At 4 weeks, the esomeprazole group had a higher healing rate, but at 8 weeks the difference was not significant.

Pooled estimates show that with esomeprazole, healing rate is higher by 5% at 4 weeks and by 3% at 8 weeks (Table 6). With a random-effects analysis the difference at 8 weeks is not significant, but in fixed-effects analysis, the difference is significant (see table 6). The fixed-effect estimates of risk difference correspond to a number of patients needed to treat with esomeprazole instead of lansoprazole to heal 1 additional patient at 4 weeks equal to 20 and at 8 weeks equal to 33.

Table 7. Risk differences in healing of esophagitis in head-to-head trials of esomeprazole 40 mg compared with lansoprazole 30 mg

Study	Difference in healing[a] at 4 weeks (95% CI)	Difference in healing[a] at 8 weeks (95% CI)
Castell 2002[4]	4% (2 to 6)	3% (1 to 5)
Fennerty 2005[29]	8% (2 to 14)	4% (–1 to 10)
Howden 2002[18]	Not reported	–2% (–9 to 5)
Pooled estimates		
Random effects	5% (1 to 9)	3% (0 to 5)
Fixed effects	**5% (2 to 7)** **number needed to treat = 20**	**3% (1 to 5)** **number needed to treat = 33**

[a] Difference in healing was calculated as the difference between the esomeprazole group and the lansoprazole group in the percent in which esophagitis was healed.

Four trials compared esomeprazole 40 mg with pantoprazole 40 mg.[20, 30, 33, 37] Two studies find esomeprazole superior, while 2 do not. One[30] large study (N=3171) found that healing at 4 weeks was 6% higher in the esomeprazole group (95% CI 3 to 9). At 8 weeks, the difference was smaller but statistically significant (risk difference, 3%; 95% CI 1 to 5). We rated this study fair quality. A much smaller study (N=180) was also rated fair to poor because numbers of patients enrolled and analyzed in tables did not match the numbers discussed in the text (apparently a typographical error was made in Table 1), the study was apparently open-label, and no details on randomization or allocation concealment procedures were given.[37] This study also found esomeprazole 40 mg to have significantly higher rates of healing at 4 weeks (78% compared with 72%; $P<0.05$). Rates at 8 weeks were not statistically significantly different (92% compared with 91%). No patients with Grade D esophagitis were enrolled in this study, although they were not excluded

Two studies (N=227 and 581) found no differences in healing rates between the drugs[20, 33] at early time points (4 to 6 weeks in 1 study, 4 weeks in the other) or later time points (8 to 10 weeks in 1 study, 8 and 12 weeks in the other). The smaller of these studies included only patients with Grade B or C esophagitis.[20]

The 2 largest of these studies also examined the impact of *Helicobacter pylori* status on healing rates with the 2 drugs. One found that healing rates with esomeprazole were not different based on *Helicobacter pylori* status, but that *Helicobacter pylori* negative patients had lower healing rates with pantoprazole compared to those who were *Helicobacter pylori* positive.[30] The other study, however did not find any associated differences in healing rate, symptom relief or 'complete remission' when using intention to treat analyses.[33]

The largest study[30] reports only life-table analysis results, while the other studies report raw rates of number of patients healed. However, data on the crude rates of healing were provided by AstraZeneca through public comment on this report; the data used in the analysis below for this study are not published data. Using these data to conduct a pooled analysis of the 3 studies that included patients with all grades of esophagitis indicates that esomeprazole 40 mg is superior to pantoprazole 40 mg in rates of patients with healed erosions at 4 weeks, but not at 8 weeks (Table 8 below). Sensitivity analysis including the fourth study which included only patients with Grades B and C esophagitis,[20] or only the 2 highest quality studies, did not change these results.[30, 33]

Table 8. Risk differences in healing of esophagitis in trials of esomeprazole 40 mg compared with another proton pump inhibitor

Drug, daily dose	Risk difference[a] at 4 weeks in comparison with esomeprazole 40 mg (95% CI)	Risk difference[a] at 8 weeks in comparison with esomeprazole 40 mg (95% CI)
Lansoprazole 30 mg[4, 18, 29]		
Pooled estimates Random effects	5% (1% to 9%)	3% (0% to 5%)
Fixed effects	**5% (2% to 7%)** **number needed to treat = 20**	**3% (1% to 5%)** **number needed to treat = 33**
Pantoprazole 40 mg[20, 30, 33, 37]		
Pooled estimates Random effects	5% (2% to 8%) **number needed to treat = 20**	1% (-3% to 5%)
Fixed effects	5% (2% to 8%) **number needed to treat = 20**	2% (-0.2% to 4%)

[a] Risk difference was calculated as the difference between the percent of the group on the test proton pump inhibitor in which esophagitis healed and the percent of the group on esomeprazole 40 mg daily in which esophagitis healed.

Analysis of healing rates by baseline severity of esophagitis

Nineteen head-to-head trials reported information about esophagitis healing rates by baseline severity of esophagitis.[4-6, 12-15, 18-23, 25, 27, 29, 30, 37, 38] These results are shown in Evidence Table 1. Ten trials stratify by baseline severity the ratio of number of patients with healed esophagitis to total number patients (Figures 5 and 6).[4-6, 12, 15, 25, 29, 30, 37, 38] To estimate healing rate for each drug at 4 and 8 weeks for patients with moderate to severe esophagitis (that is, grades C-D or 3-4; see Appendix E for grading scales), we conducted a random-effects meta-analysis of data from these 9 studies[4-6, 12, 15, 25, 29, 30, 38] (Table 9). An additional study[18] reports a combined outcome of improved by 2 grades or healed; those data were not included in the meta-analysis.

Figure 5. Healing of moderate to severe esophagitis at 4 weeks in head-to-head trials of proton pump inhibitors

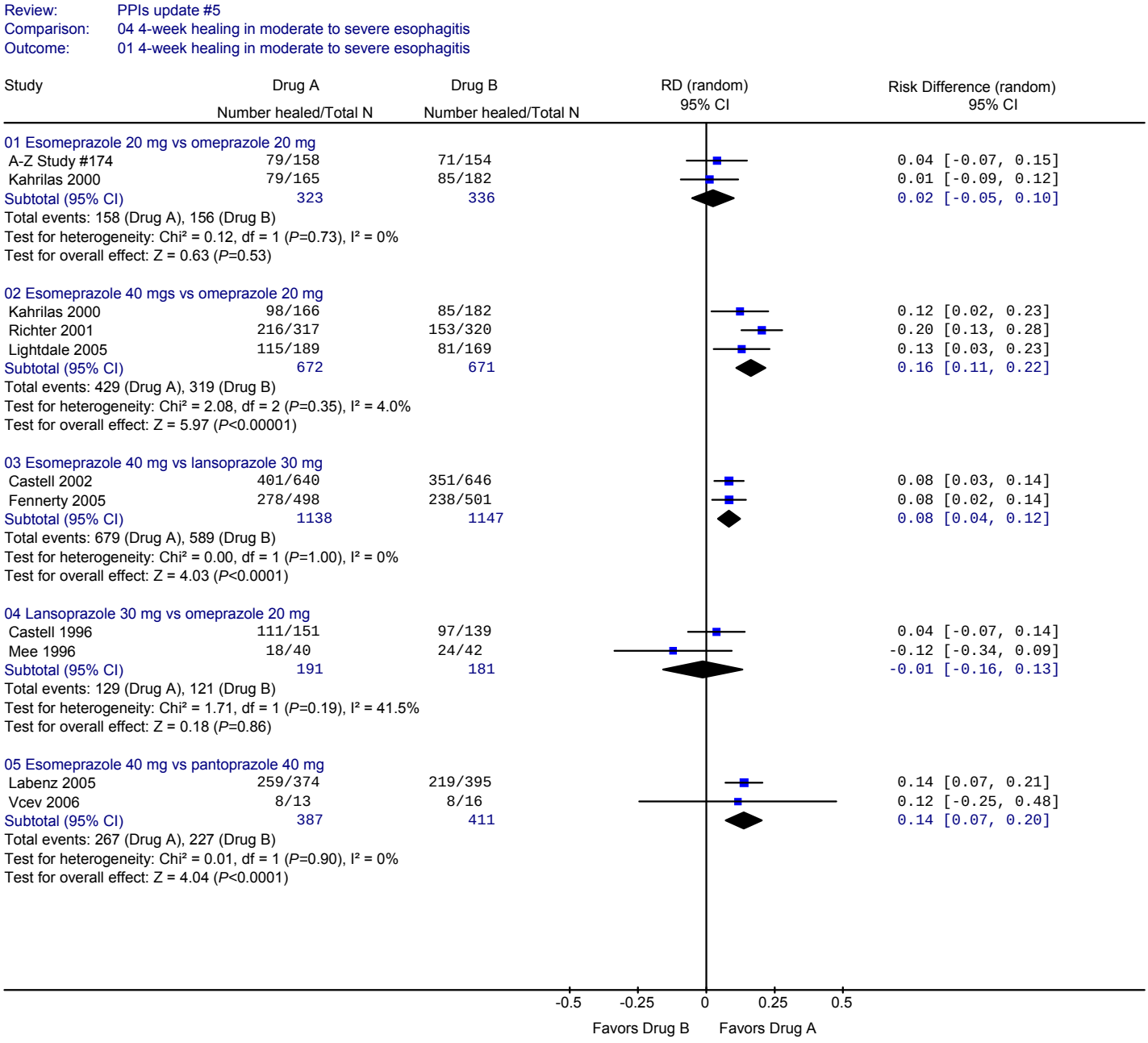


Figure 6. Healing of moderate to severe esophagitis at 8 weeks in head-to-head trials of proton pump inhibitors

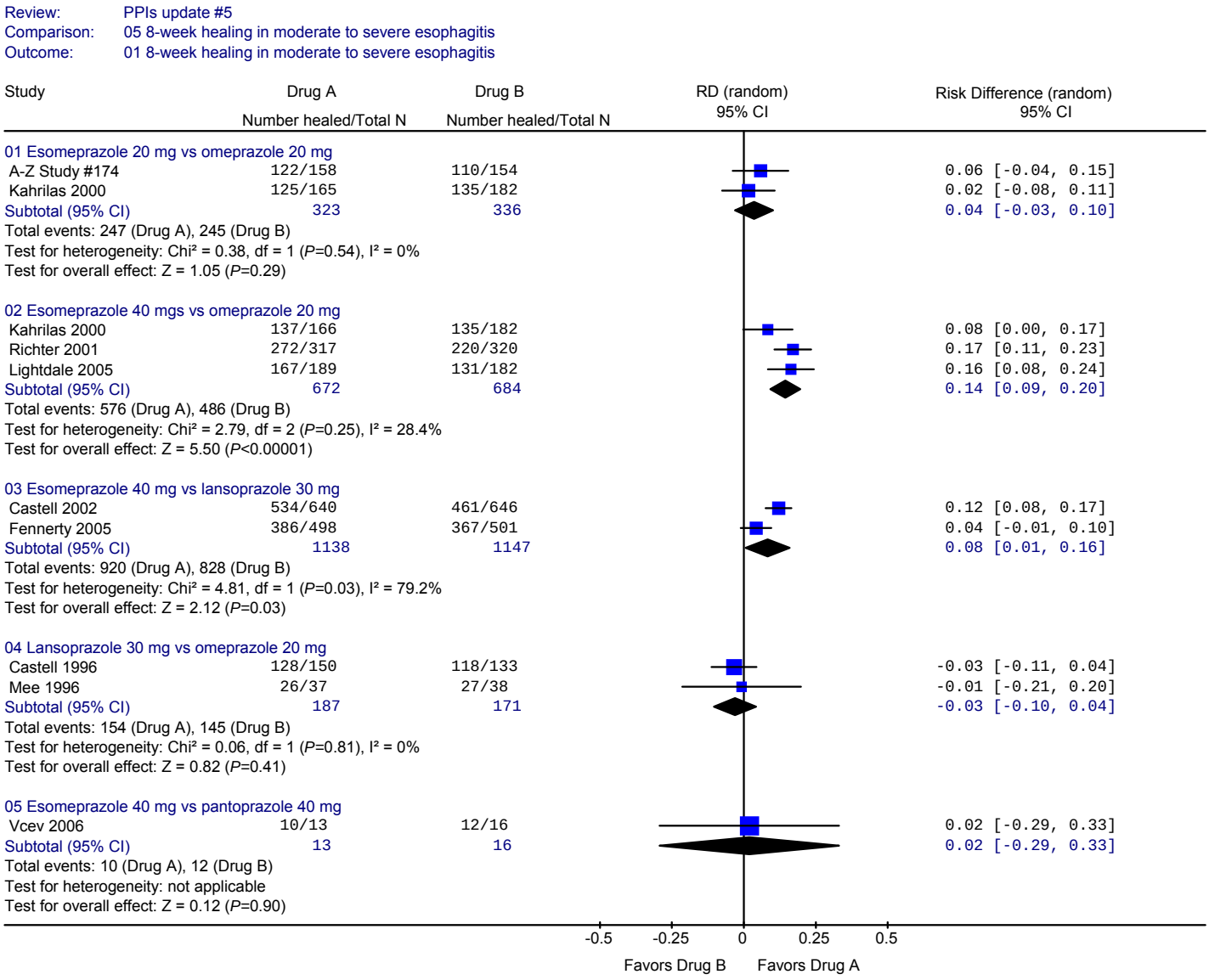


Table 9. Estimated healing rates in patients with moderate to severe esophagitis at baseline

Drug and daily dose	Percent patients with healed esophagitis at 4 weeks (95% CI)	Percent patients with healed esophagitis at 8 weeks (95% CI)
Esomeprazole 20 mg	49% (37-61)[5, 6]	77% (70-85)[5, 6]
Esomeprazole 40 mg	64% (57-71)[4, 5, 12, 29, 30, 38]	85% (81-89)[4, 5, 12, 29, 38]
Lansoprazole 30 mg	56% (48-64)[4, 15, 25, 29]	77% (71-82)[4, 15, 25, 29]
Omeprazole 20 mg	52% (45-59)[5, 6, 12, 15, 25, 38]	74% (68-80)[5, 6, 12, 15, 25, 38]

Esomeprazole compared with omeprazole. Four studies comparing daily esomeprazole 40 mg with omeprazole 20 mg[5, 12, 36, 38] reported healing rate in patients with moderate to severe esophagitis at baseline (Figures 5 and 6). The pooled risk difference at 4 weeks was 16% (95% CI 11 to 22) and at 8 weeks was 13% (95% CI 9 to 17).

In 2 studies comparing esomeprazole 20 mg with omeprazole 20 mg[5, 6] there was no difference in healing rate at 4 weeks (pooled risk difference 2%; 95% CI –5 to 10) or 8 weeks (pooled risk difference 4%; 95% CI –3 to 10). Estimates of healing rates with esomeprazole 20 mg were similar to omeprazole 20 mg (see Table 7). There were no comparisons of esomeprazole (any dose) with omeprazole 40 mg.

Esomeprazole compared with lansoprazole. Two studies comparing esomeprazole 40 mg with lansoprazole 30 mg reported healing rates in patients with moderate to severe esophagitis at baseline.[4, 29] The pooled risk difference at 4 weeks was 8% (95%, CI 4 to12) and at 8 weeks was 9% (95% CI 5 to 12). These correspond to a number needed to treat of 13 at 4 weeks and 11 at 8 weeks.

A third study, published by the maker of lansoprazole, reported only the combined outcome of healing or improvement of at least 2 grades in the subgroup of patients with moderate to severe esophagitis.[18] In this small (N=109) subanalysis lansoprazole had a statistically nonsignificant higher rate of healing/improvement at 8 weeks (10%; 95% CI –2 to 22); results at 4 weeks were not reported.

Esomeprazole compared with pantoprazole. In 1 study patients with moderate (Grade C) esophagitis at baseline who were taking pantoprazole 40 mg had a higher healing rate at "later" time points (8 to 10 weeks) than patients on esomeprazole 40 mg (67% compared with 45%).[20] Esophagitis in 100% of patients with Grade C esophagitis on pantoprazole and 91% of patients on esomeprazole improved by 1 or 2 grades (to Grade B or A) by the final visit (10 weeks). Rates at 4 weeks are not reported, and no patients with Grade D esophagitis were enrolled.

In 2 trials of esomeprazole 40 mg compared with pantoprazole 40 mg in patients with moderate to severe esophagitis, there was a 14% risk difference favoring esomeprazole after 4 weeks (95% CI 7 to 21).[30, 37] At 8 weeks, there was no difference between the drugs in healing rate, although the 1 study that reported this outcome was small (N=29). [37]

Lansoprazole compared with omeprazole. Three studies comparing lansoprazole with omeprazole reported healing rate in patients with moderate to severe (Grades 3 and 4) esophagitis.[14, 15, 25] Two of these compared lansoprazole 30 mg with omeprazole 20 mg.[15, 25] There was no difference in healing rate at 4 weeks (pooled risk difference 1%; 95% CI –13 to 16) or 8 weeks (pooled risk difference 3%; 95% CI –4 to 10). The third study compared lansoprazole 30 mg with omeprazole 40 mg and reported healing rates as percentages only.[14] There was no significant difference between groups at 4 or 8 weeks. The distribution of the severity of esophagitis among patients in this study is not reported.

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

Seven recent systematic reviews have been published comparing proton pump inhibitors for healing of esophagitis and relief of gastroesophageal reflux disease symptoms.[42-48] Five of the 7 reviews included studies of esomeprazole, and all concluded that esomeprazole is superior to other proton pump inhibitors for gastroesophageal reflux disease, based on the same studies

included in this report.[43, 44, 46-48] One of these 3 concluded that the better healing rate in patients taking esomeprazole 40 mg than those taking omeprazole 20 mg or lansoprazole 30 mg is attributable to increased efficacy of esomeprazole in patients with more severe esophagitis.[46] Another of these reviews was designed to compare the efficacy of esomeprazole compared with lansoprazole; it concluded that esomeprazole provides an additional benefit of 5% at 4 weeks and 4% at 8 weeks compared with lansoprazole 30 mg.[48] Both of these reviews were funded by the manufacturer of esomeprazole. The third of these systematic reviews,[47] for which the funding source is not reported, concluded that esomeprazole 40 mg was superior to omeprazole 20 mg for esophagitis healing after 4 weeks (relative risk, 1.18; 95% CI 1.14 to 1.23), but that this result was due to the nonequivalent, higher dose of esomeprazole. There were no differences among the other proton pump inhibitors.

A Cochrane review of short term management of reflux esophagitis found focused on the proton pump inhibitors as a group, with minimal emphasis on comparing the drugs.[42] A systematic review conducted in 2001[45] found that lansoprazole, rabeprazole, and pantoprazole had efficacy similar to omeprazole for healing. No study of esomeprazole had been done at the time.

Indirect evidence

Comparisons of proton pump inhibitors across studies are difficult because patient populations and healing rates in control groups were dissimilar.

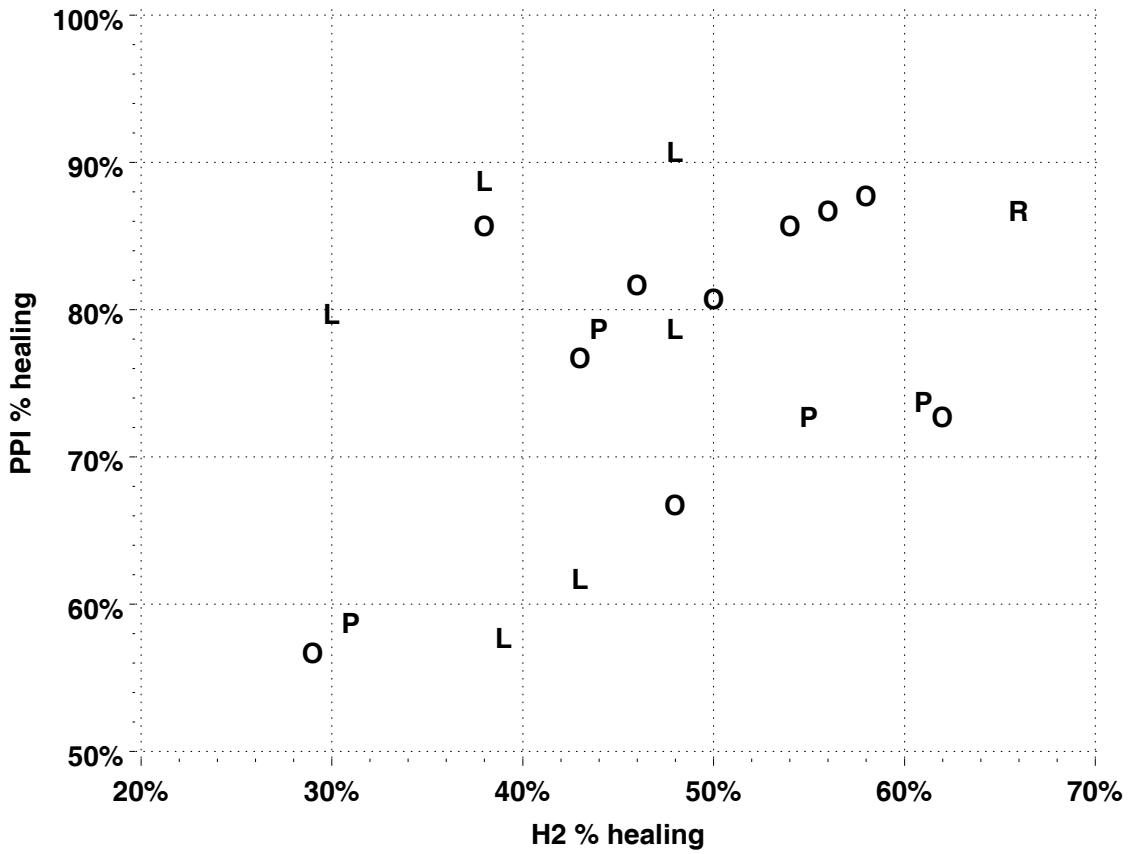
Esophagitis healing

In the systematic review mentioned above,[45] 4 proton pump inhibitors were better than ranitidine at healing esophagitis, but there were no differences among them. No study of esomeprazole was included.[45]

We reviewed 22 randomized controlled trials published through 2001 that compared a proton pump inhibitor with an H2 receptor antagonist for esophagitis healing. Figure 7 shows the rates of esophagitis healing at 8 weeks. These trials compared an H2 receptor antagonist with omeprazole (11 studies),[49-59] lansoprazole (5 studies),[60-64] pantoprazole (5 studies),[65-69] and rabeprazole (1 study).[70]

We did not create evidence tables of these studies or rate their quality, because after graphing their results we found no indication that the proton pump inhibitors 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, proton pump inhibitors were more effective at healing than H2 receptor antagonists, but there was no difference in healing rate among the proton pump inhibitors for any comparison. Healing rate ranged from 71.2% to 85.6%.

Figure 7. Esophagitis healing at 8 weeks in 22 randomized controlled trials comparing proton pump inhibitor with H2 receptor antagonist



Estimated healing rate	Mean percent patients with healed esophagitis (95% CI)
Lansoprazole	78.8% (69.7 to 86.4)
Omeprazole	79.3% (72.2 to 85.3)
Pantoprazole	71.2% (59.0 to 81.4)
Rabeprazole	85.6% (67.9 to 95.4)

Difference between proton pump inhibitors	Mean difference in percent patients with healed esophagitis (95% CI)
Lansoprazole vs. omeprazole	(–11.6 to 10.0)
Lansoprazole vs. pantoprazole	(–5.9 to 22.1)
Lansoprazole vs. rabeprazole	(–20.5 to 12.2)
Omeprazole vs. pantoprazole	(–4.3 to 21.7)
Omeprazole vs. rabeprazole	(–18.9 to 12.2)
Pantoprazole vs. rabeprazole	(–30.4 to 5.5)

Relief of symptoms

In 1 systematic review,[45] the pooled relative risk of studies that reported resolution of heartburn at 4 weeks was 1.02 (95% CI 0.94 to 1.11) for newer proton pump inhibitors (pantoprazole, rabeprazole, and lansoprazole) compared with omeprazole. For all 4 proton pump inhibitors compared with ranitidine the pooled relative risk was 1.53 (95% CI 1.37 to 1.72).

Prevention of relapse

Nine randomized controlled trials compared proton pump inhibitors in long-term (6 months or more) maintenance therapy to prevent relapse of esophagitis in patients with endoscopically-proven erosive gastroesophageal reflux disease (Evidence Table 4).[30, 71-78] Two of these found no differences in endoscopic or symptomatic relapse rates; 1 with lansoprazole compared with omeprazole after 48 weeks of treatment[71] and one with rabeprazole compared with omeprazole after 13 weeks, 26 weeks, 1 year, and 5 years.[77, 78]

Two studies compared esomeprazole 20 mg with pantoprazole 20 mg.[73, 76] In one,[76] patients took their proton pump inhibitor when needed, and in the other,[73] the proton pump inhibitor was taken daily. The study of daily treatment found no differences between treatment groups on the combined outcome of symptomatic and endoscopic remission.[73] The study of treatment on-demand measured efficacy using patient reports of the intensity of gastroesophageal reflux disease-related symptoms (0=none, 1=mild, 2=moderate, 3=severe). The mean intensity of heartburn was significantly higher (worse) in the esomeprazole group during the 6-month maintenance phase (1.32 for esomeprazole compared with 1.12 for pantoprazole; P=0.012). Pantoprazole patients took an average of 52.6 tablets (0.31 daily) and esomeprazole patients took an average of 59.9 tablets (0.36 daily); the difference between groups was not significant. Similarly, use of antacids as rescue medications was not statistically different between the groups (mean number of tablets in the esomeprazole group = 38, and in pantoprazole group = 53).

Two similar 6-month trials conducted by the same investigators compared esomeprazole 20 mg daily (a dose approved by the US Food and Drug Administration for healing or maintenance of erosive esophagitis) with lansoprazole 15 mg daily (approved dose for maintenance of healed erosive esophagitis)[75] or pantoprazole 20 mg daily (lower than the approved dose for maintenance of healed erosive esophagitis).[74] These studies randomized patients whose esophagitis had healed after 4 to 8 weeks of treatment and compared relapse rates at 6 months. According to life-table analysis, the esophagus of a higher proportion of patients in the esomeprazole groups remained healed over 6 months: 83% compared with 74% for esomeprazole compared with lansoprazole, respectively, and 87% compared with 74.9% for esomeprazole compared with pantoprazole. The authors also present data by baseline severity. The esophagus of more patients in the esomeprazole groups remained healed across all grades of disease severity in both studies. The efficacy of lansoprazole and pantoprazole decreased with increasing severity of disease in these studies. Esomeprazole showed lower rates of efficacy in preventing relapse in patients who started out with grade D esophagitis in only 1 study.[74] No crude rates or numbers of patients whose esophagitis remained healed were presented. Crude rates provide a more conservative estimate of effectiveness due to the manner in which dropouts are handled in life-table analyses. Because all patients enrolled in the study of esomeprazole and lansoprazole[75] had responded to esomeprazole for initial healing of esophagitis, the study may be biased towards esomeprazole. Both studies were funded by the manufacturer of esomeprazole and the publications were coauthored by representatives of the company.

A more recent study also compared daily esomeprazole 20 mg with lansoprazole 15 mg.[72] The primary outcome was remission, defined as no detectable erosive esophagitis and no study discontinuation due to reflux symptoms. After 6 months, remission was significantly greater in the esomeprazole group compared with the lansoprazole group (84.8% compared with 75.9%; P=0.0007). Remission rates were higher for esomeprazole in patients with either grade A and B or C and D esophagitis at baseline. Considering remission as measured by endoscopy alone, esomeprazole was superior to lansoprazole (86.9% compared with 77.8%; P=0.003). However, there were no significant differences between groups in the proportion of patients without symptoms at 6 months.

A shorter trial of 36 patients with severe (Savary-Miller Grade 4) esophagitis compared omeprazole, lansoprazole, and pantoprazole for the prevention of relapse at 4 weeks.[79] Before randomization, all patients were treated with omeprazole. Six patients did not heal after 6 to 8 weeks of omeprazole; the rest (83%) were randomized to omeprazole, lansoprazole, or pantoprazole. After 4 weeks, patients taking omeprazole had a lower rate of endoscopic relapse (10%) than those randomized to either lansoprazole (80%) or pantoprazole (70%). The relapse rates in the lansoprazole and pantoprazole groups were very high compared with other studies and, as in the study comparing esomeprazole with lansoprazole, discussed above, had a selection bias: All subjects had responded well to a study drug before enrollment in the maintenance phase.

Nonerosive and endoscopically unexamined gastroesophageal reflux disease

We identified 3 fair-quality head-to-head trials of proton pump inhibitors in short-term treatment of patients with nonerosive or empirically treated reflux disease. They compared esomeprazole with omeprazole,[80] rabeprazole,[81] or pantoprazole.[82] The 3 studies used different outcome measures, but all found esomeprazole to be similar in efficacy to the compared drug (Evidence Table 3). A fourth head-to-head trial (lansoprazole compared with omeprazole) included patients with erosive and nonerosive gastroesophageal reflux disease but did not separate results by these patient populations.[83] Three identically designed 4-week trials comparing omeprazole 20 mg and esomeprazole 20 mg and 40 mg were conducted simultaneously and were described in 1 publication.[80] There was no difference in the resolution of heartburn at 14 days (secondary outcome) or 28 days (primary outcome) between patients taking omeprazole 20 mg or esomeprazole 20 mg or 40 mg. At 2 weeks, proportions of patients with resolution ranged from 35% to 44%, and at 4 weeks ranged from 57% to 70%. Results for adequate control of symptoms were similar, with no significant differences between drugs.

A head-to-head trial comparing pantoprazole 20 mg with esomeprazole 20 mg measured time to first and sustained relief of symptoms.[84] This trial was designed to test for noninferiority of pantoprazole compared with esomeprazole. The noninferiority margin was set at –2 days for the primary outcome of time to first symptom relief (that is, a lower boundary of the 95% confidence interval greater than 2 days would indicate noninferiority). Symptom assessment was based on patient report using a validated questionnaire (ReQuest). The questionnaire includes items on the 7 dimensions of gastroesophageal reflux disease symptoms (general well-being, acid complaints, upper abdominal/stomach complaints, lower abdominal/digestive complaints, nausea, sleep disturbances, and other complaints). Results showed that pantoprazole was not inferior to esomeprazole for first and sustained relief of symptoms.

A 4-week trial comparing rabeprazole 10 mg with esomeprazole 20 mg was conducted in 134 patients in Singapore.[81] The primary outcome was time to first 24-hour period without

symptoms of heartburn or regurgitation. There was no difference between groups on this endpoint (for heartburn, 8.5 days for rabeprazole compared with 9.0 days for esomeprazole; for regurgitation, 6.0 days for rabeprazole compared with 7.5 days for esomeprazole; *P*=NS). There was also no significant difference between groups on secondary outcomes, including complete and satisfactory relief of heartburn symptoms at weeks 1 and 4, and symptom severity score in the first 5 days.

A good-quality Cochrane systematic review of literature through 2003 addressed the efficacy of proton pump inhibitors, H2 receptor antagonists, and prokinetics in adults with endoscopically verified nonerosive or empirically treated symptoms of reflux disease.[85] *This review was not designed to compare the efficacy of different proton pump inhibitors.* The primary efficacy outcome of the review was heartburn remission, defined as mild heartburn on no more than 1 day per week. Proton pump inhibitors were superior to placebo for heartburn remission and overall symptom improvement. Proton pump inhibitors also were more effective than H2 receptor antagonists for heartburn remission in empirically treated patients (pooled relative risk 0.69; 95% CI 0.61 to 0.77), but not in patients with nonerosive gastroesophageal reflux disease (pooled relative risk 0.74; 95% CI 0.53 to 1.03). However, only 3 trials compared proton pump inhibitors with H2 receptor antagonists in nonerosive gastroesophageal reflux disease.

Another systematic review evaluated the efficacy of proton pump inhibitors for resolution of heartburn in patients with nonerosive gastroesophageal reflux disease.[86] This review searched literature through 2002, including the US Food and Drug Administration website. 7 placebo-controlled trials (3 published and 4 unpublished) were included: 2 rabeprazole, 2 esomeprazole, and 3 omeprazole. In patients with nonerosive gastroesophageal reflux disease, the risk difference in comparisons with placebo for resolution of heartburn at 4 weeks was 25% (95% CI 18 to 31). The review does not provide evidence about comparative efficacy of different proton pump inhibitors in patients with nonerosive gastroesophageal reflux disease.

Table 10 shows rates of heartburn remission rates and complete symptom relief calculated from data provided in the Cochrane review.[85] Similar proportions of patients experienced heartburn resolution or complete symptom relief across the drugs.

Table 10. Percent patients with resolution of heartburn at 4 weeks from Cochrane review[40]

	Endoscopically verified nonerosive gastroesophageal reflux disease		Presumptive treatment of symptoms	
Drug, dose	Number of trials	%, range	Number of trials	%, range
Esomeprazole 20 mg	2	61% to 62%		
Esomeprazole 40 mg	2	57% to 71%		
Esomeprazole 40 mg			1	84%
Omeprazole 10 mg or 20 mg			1	75%
Omeprazole 10 mg or 20 mg	4	56% to 95%		
Omeprazole 20 mg	5	58% to 84%	4	60% to 70%
Omeprazole 40 mg	1	95%		
Pantoprazole 20 mg			1	81%
Pantoprazole 40 mg	1	57%	1	66%
Rabeprazole 10 mg or 20 mg	1	98%		

We identified 1 additional placebo-controlled[87] and 1 active-control (ranitidine) trial[88] published since this review (Evidence Table 3). In a fair-quality trial of empiric treatment of patients with symptoms of gastroesophageal reflux disease, more patients taking pantoprazole 20 mg than ranitidine 300 mg were free of gastroesophageal reflux disease symptoms (heartburn, acid eructation, and pain on swallowing) at 4 weeks (68% compared with 43%).[88] In a fair- to poor-quality, 8-week, placebo-controlled trial of patients with endoscopically verified nonerosive gastroesophageal reflux disease whose primary symptom was upper abdominal discomfort, patients taking lansoprazole 15 mg had fewer days with upper abdominal discomfort and reduced severity of average daily pain.[87] Patients whose predominant symptom was heartburn were not included. It is not clear what proportion of patients was analyzed; patients were excluded from analysis for a specific endpoint if there were no data available for that endpoint.

Prevention of relapse

We identified only 1 head-to-head trial of maintenance treatment in patients with nonerosive gastroesophageal reflux disease.[89] We also included 2 placebo-controlled trials of on-demand rabeprazole[90] and esomeprazole[91] and a placebo-controlled trial of scheduled of omeprazole.[92] Details of these trials are shown in Evidence Table 5. Three other trials included patients with endoscopically verified nonerosive and erosive gastroesophageal reflux disease, but did not report results separately by group.[40, 93, 94]

A head-to-head trial compared on-demand esomeprazole 20 mg with scheduled lansoprazole 15 mg for 6 months in patients with endoscopically verified nonerosive gastroesophageal reflux disease who had experienced complete relief of heartburn with esomeprazole 20 mg during an acute treatment phase (2 to 4 weeks).[89] Patients were not blinded to treatment and the primary outcome measure was time to discontinuation from the maintenance phase due to unwillingness to continue. Patients also recorded heartburn and other symptoms on diary cards and were asked about their satisfaction with treatment during scheduled clinic visits.

By 6 months, significantly more patients receiving lansoprazole 15 mg were unwilling to continue than patients receiving esomeprazole 20 mg on demand (13% compared with 6%, $P=0.001$). More patients in the lansoprazole group said they discontinued because of adverse events (7.4% compared with 2.3%, $P=0.0028$), but discontinuations because of heartburn were not significantly different between treatment groups (4.8% for lansoprazole and 2.9% for esomeprazole, *P* value reported as NS). At 1 month, more esomeprazole patients were satisfied with their treatment, but at 3 and 6 months there was no difference between treatment groups on this measure. During the maintenance phase, the mean frequency of heartburn symptoms was higher in the on-demand esomeprazole group than the scheduled lansoprazole group.

Two 6-month placebo-controlled studies reported efficacy of on-demand therapy with rabeprazole 10 mg[90] or esomeprazole 20 mg[91] in patients with endoscopically verified nonerosive gastroesophageal reflux disease. In both studies, only patients who experienced complete symptom relief during an acute treatment phase were enrolled in the maintenance phase. In the study of rabeprazole 10 mg, rate of discontinuation due to inadequate heartburn control was 20% for placebo and 6% for rabeprazole ($P<0.00001$). Although mean length of heartburn-free periods was similar between groups, the time required for resolution of an episode of heartburn was significantly shorter with rabeprazole than placebo. In the study of esomeprazole 20 mg, 14% of patients taking esomeprazole discontinued the study drug compared with 51% taking placebo. Discontinuation was mainly due to inadequate control of heartburn ($P<0.0001$).[91]

In a placebo-controlled trial of daily omeprazole 10 mg, 27% of patients taking omeprazole discontinued the drug due to inadequate control of heartburn over 6 months compared with 52% of patients taking placebo.[92]

Children

There were no head-to-head trials of proton pump inhibitors in children. Placebo-controlled and active-control trials in children are shown in Evidence Table 6.

A fair-quality placebo-controlled trial of omeprazole (10 to 20 mg daily) in infants (3 to 12 months old) with gastroesophageal reflux defined as a gastric pH <4 for 5% of the monitoring time (unspecified) and/or abnormal esophageal histology found no difference in the cry/fuss time or visual analog scale scores of parent-assessed irritability between placebo and omeprazole.[95] Histologic and pH measures improved significantly with omeprazole but not placebo.

A poor-quality trial comparing omeprazole (40 mg daily per 1.73 square meters body surface area) with high-dose ranitidine (20 mg/kg daily) in children with reflux refractory to standard-dose ranitidine found both drugs to be effective; but, high dropout rate (19%), lack of intention-to-treat analysis, and inadequate reporting of baseline characteristics make these results unreliable.[96]

Key Question 2. What is the comparative effectiveness of different proton pump inhibitors in treating patients with peptic ulcer and nonsteroidal anti-inflammatory drug-induced ulcer?

Summary

Duodenal ulcer

- The data on comparative effectiveness of various proton pump inhibitors for treating duodenal ulcer were strong, with 10 head-to-head trials. Omeprazole 20 mg daily was typically the comparison.
- The evidence was strong for omeprazole and lansoprazole having similar effectiveness in both symptom relief and endoscopically verified healing. The pooled risk difference for 5 trials comparing daily lansoprazole 30 mg with omeprazole 20 mg was –0.2 (95% CI –3.0 to +2.6).
- The evidence for pantoprazole, rabeprazole, and esomeprazole was less strong because there are only single studies for each newer drug compared with omeprazole and no comparisons to other proton pump inhibitors.
- No evidence of a difference in healing rate among proton pump inhibitors.
- Symptom relief was an important measure in ulcer disease and did not always correlate with healing confirmed by endoscopy. Method of assessing symptom relief varied across studies and reporting of findings was often limited to early time points and 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 from later time points may indicate that symptom relief at those time points was equivalent for different proton pump inhibitors.

Gastric ulcer

- Comparative data about proton pump inhibitors for the treatment of gastric ulcer was very limited, with 3 studies comparing rabeprazole with omeprazole. No significant difference in healing rates was found.
- Symptom relief was better with rabeprazole 20 mg than omeprazole 20 mg in 3 of 12 measures at 3 weeks and in 2 measures at 6 weeks but no difference in symptom relief was found between rabeprazole 10 mg and omeprazole 20 mg daily.

Nonsteroidal anti-inflammatory drug-induced ulcer

- There were no head-to-head trials.
- Only 4 trials compared a proton pump inhibitor with another drug: 2 with omeprazole, 1 with esomeprazole, and 1 with lansoprazole. No differences between proton pump inhibitors could be discerned from these studies; confidence intervals for healing rates overlapped.

Detailed Assessment

Direct evidence

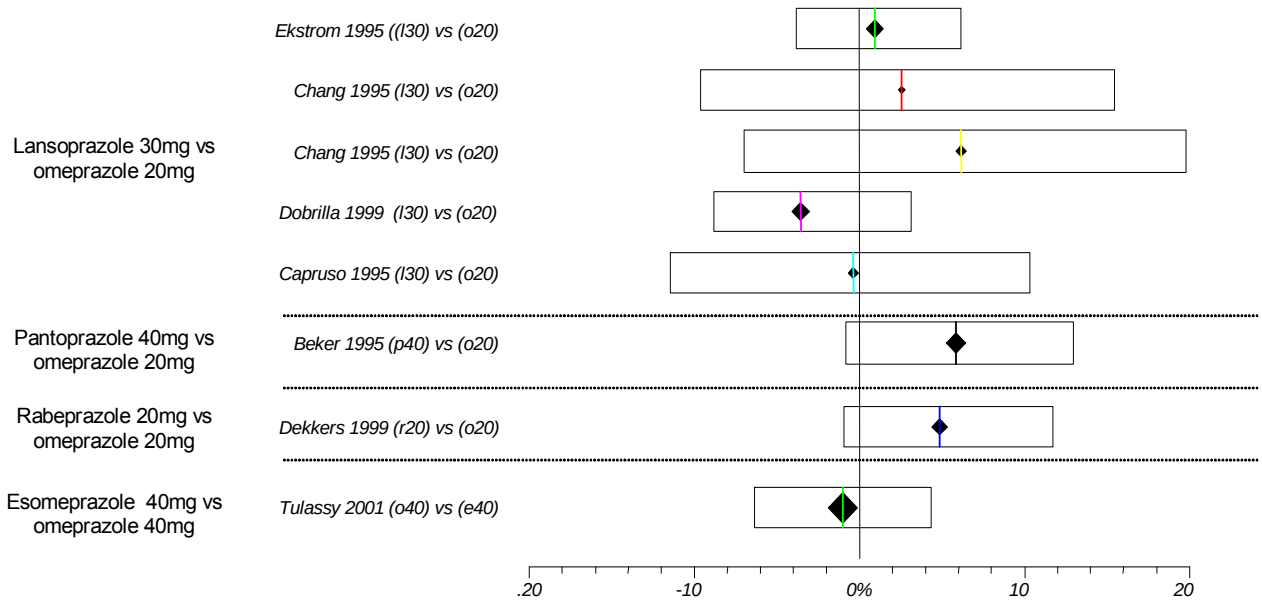
Duodenal ulcer

Ten randomized controlled trials compared one proton pump inhibitor with an equipotent dose of another.[41, 97-105] The details of these studies are summarized in Evidence Table 7. Six of these trials compared lansoprazole 30 mg with omeprazole 20 mg.[97-101, 104] One study each compared pantoprazole 40 mg and rabeprazole 20 mg with omeprazole 20 mg,[41, 102] 1 study compared esomeprazole 40 mg with omeprazole 40 mg daily (20 mg twice daily for each),[103] and 1 small study compared omeprazole enteric coated capsules with omeprazole magnesium.[105]

The studies were fair quality. They were generally similar with respect to design and demographics, with the following exceptions: One study was unusual in that as a part of an *Helicobacter 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 (only) for another 3 weeks.[103]

As shown in Figure 8, omeprazole 20 mg, lansoprazole 30 mg, rabeprazole 20 mg, and pantoprazole 40 mg did not differ in the percentage of patients with duodenal ulcer that was healed by 4 weeks compared with omeprazole 20 mg daily. The pooled risk difference for daily lansoprazole 30 mg compared with omeprazole 20 mg was –0.2 (95% CI –3.0 to +2.6). The risk differences found between esomeprazole 40 mg, pantoprazole 40 mg, and rabeprazole 20 mg and omeprazole were approximately –0.97%, 6%, and 5%, respectively; however, these estimates were based on single studies and were not statistically significant. Similarly, no difference in healing rate was found between omeprazole enteric coated capsules and omeprazole magnesium both at 40 mg daily with all 57 patients being healed at 4 weeks.[105] Results from a large multicenter trial comparing esomeprazole 20 mg twice daily with omeprazole 20 mg twice daily also showed no difference in healing rate.[103] The results for healing at 2 weeks were similar for all comparisons.

Figure 8. Duodenal ulcer healing at 4 weeks in trials comparing proton pump inhibitors



(Note: size of diamond corresponds to study sample size)

Study	Percent risk difference (95% CI)
Lansoprazole 30 mg vs. omeprazole 20 mg once daily	
Ekstrom 1995	0.96 (–3.80 to 6.15)
Chang 1995	2.55 (–9.62 to 15.5)
Chang 1995	6.14 (–7.0 to 20)
Dobrilla 1999	–3.57 (–8.84 to 3.14)
Capruso 1995	–0.34 (–11.41 to 10.32)
	Pooled risk difference = –0.2 (–3.0 to 2.6)
Pantoprazole 40 mg vs. omeprazole 20 mg once daily	
Beker 1995	5.85 (–0.84 to 12.95)
Rabeprazole 20 mg vs. omeprazole 20 mg once daily	
Dekkers 1999	4.84 (–0.96 to 11.70)
Esomeprazole 40 mg vs. omeprazole 40 mg once daily	
Tullassay 2001	–0.97 (–6.4 to 4.35)
Omeprazole enteric-coated capsule 40 mg vs. omeprazole magnesium 40 mg once daily	
Liang 2008	0 (100% healed in both groups)

Symptoms (pain, nausea, vomiting, antacid use, and overall well-being) were assessed by investigators at visits and through patient diaries in 8 studies. Only 1 study found a significant difference between proton pump inhibitors.[41] Daytime pain was "improved" in 92% of the rabeprazole group and 83% of the omeprazole group at 4 weeks (P=0.038), however, no difference was found in nighttime pain or in the number of patients without pain. Antacid use, gastrointestinal symptoms, and overall well-being were not different in any of the studies.

Only 1 head-to-head study addressed maintenance, comparing lansoprazole 15 mg, lansoprazole 30 mg, and omeprazole 20 mg for up to 12 months (see Evidence Table 8).[100] At 6 months after 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.

Gastric ulcer

Four studies directly compared proton pump inhibitors in treating gastric ulcer.[106-109] Three fair-quality trials compared rabeprazole 10 or 20 mg to omeprazole 20 mg daily.[106, 108, 109] Early healing was measured at 1 to 3 weeks and final healing was measured at 6 or 8 weeks. All 3 trials found no difference in endoscopically verified healing at 6 or 8 weeks. A fair-quality study of 227 patients compared rabeprazole 20 mg with omeprazole 20 mg (Evidence Table 9).[106] The percent risk difference in the rate of healing at 3 weeks was –3% (95% CI –16 to +9.7) and was reported as the same at 6 weeks. Twelve different comparisons of symptom resolution or improvement were made. No significant differences were found in pain resolution or improvement (frequency, severity, night, or daytime) at 3 or 6 weeks for 9 of these comparisons. Rabeprazole was statistically superior in 3 comparisons: improvement of severity of pain at 3 weeks, improvement in the frequency of daytime pain at 3 weeks, and resolution of nighttime pain at 6 weeks. No difference in change in overall well-being or in antacid use was found.

The 2 small fair quality trials comparing the lower dose of rabeprazole (10 mg) also found no difference, with a pooled relative risk of 1.0 (95% CI 0.9 to 1.2) using a random effects model and intention to treat analysis (assuming missing values to be unhealed).[108, 109] In 1 of these trials symptom resolution was also found to be similar between groups at 6 weeks (64% each; P=0.958).[109] Analysis of patient CYP2C19 genotype in both studies did not indicate a difference in healing rate at 6 or 8 weeks among those who were categorized as extensive or poor metabolizers. However, the 2 studies found different results for the ulcer size reduction at early time points. The first study (80 patients) found rabeprazole to result in similar reductions in ulcer size at 2 weeks regardless of CYP2C19 genotype but omeprazole resulted in smaller improvements among those who were categorized as homozygous extensive metabolizers.[108] The second study (112 patients) found no differences.[109]

A poor-quality trial compared lansoprazole 30 mg daily with omeprazole 20 mg daily.[107] This study did not conduct an intent-to-treat analysis and more patients in the omeprazole group (15%) were excluded from analysis than the lansoprazole group (7%). Although the authors state there were no differences between groups at baseline, 4% of patients in the omeprazole group were smokers, compared with 1% in the lansoprazole group. The results of this study found lansoprazole superior in cumulative healing rate at 8 weeks (93% compared with 82%, P=0.04); the difference at 4 weeks was not statistically significant. It is not clear from the publication which patients were included in this analysis and our statistical analyses based on differing assumptions did not result in statistically significant differences between the groups at either time point. Differences in symptom relief were not statistically significant.

Treatment of nonsteroidal anti-inflammatory drug-induced ulcer

No study compared one proton pump inhibitor with another.

Indirect evidence

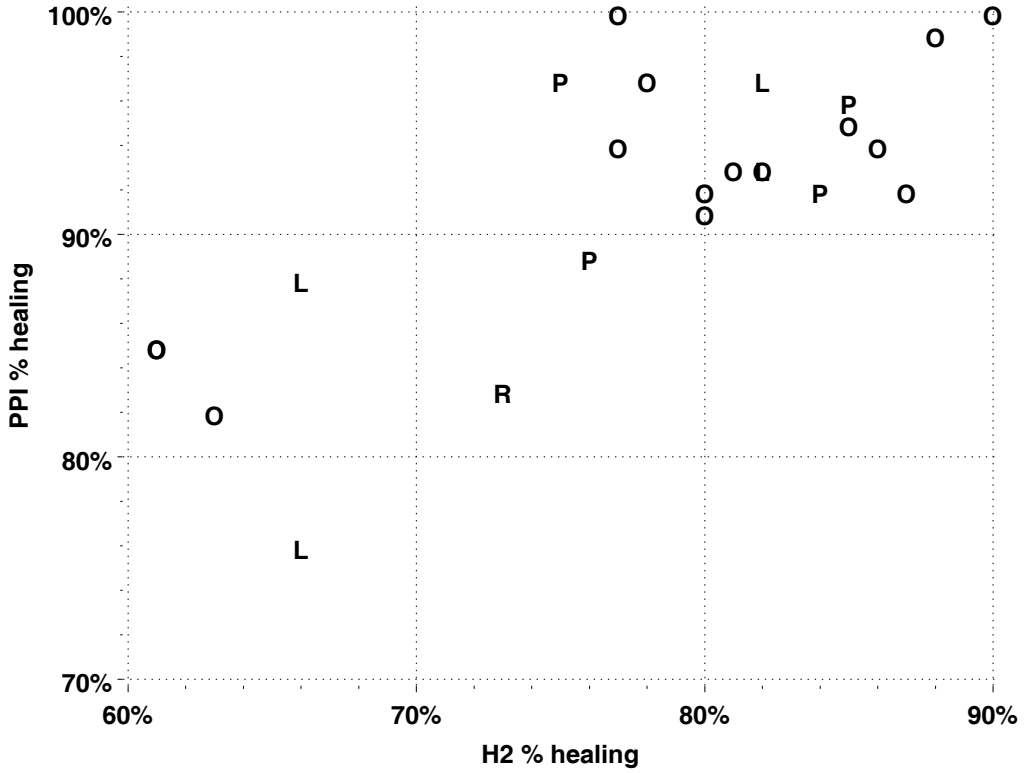
Duodenal ulcer

Twenty-five randomized controlled trials compared a proton pump inhibitor with an H2 receptor antagonist. Of these, 22 papers were reviewed.[110-135] Since these studies could only be used to make indirect comparisons of the effectiveness of the various proton pump inhibitors, we presented a limited analysis. The most common H2 receptor antagonist used in comparisons was ranitidine 300 mg daily, with 10 studies comparing omeprazole 20 mg. There were no studies comparing esomeprazole with an H2 receptor antagonist.

Figure 9 shows rates of healing at 4 weeks in 21 studies comparing a proton pump inhibitor with an H2 receptor antagonist for treatment of duodenal ulcer. Proton pump inhibitors were more effective than H2 receptor antagonists, but there was no significant difference in healing rate among the proton pump inhibitors. With omeprazole and lansoprazole, healing rate was correlated with H2 receptor antagonists' healing. That is, as the healing rate in the H2 receptor antagonist group increased, proton pump inhibitor healing rate increased. One comparison showed pantoprazole to have a significantly higher healing rate than rabeprazole (risk difference 11.3%), but this comparison was made in only 1 study, and the confidence interval is large (95% CI 2.4 to 23.2).

Another study[132] examined the added benefit of continuing omeprazole 20 mg for 3 additional weeks after 1 week of eradication therapy with omeprazole 20 mg plus amoxicillin 1000 mg and clarithromycin 500 mg. At 4 weeks, there was no difference in healing rates in patients assigned to omeprazole (89%) and placebo (87%). Another reported symptom relief only.[131]

Figure 9. Duodenal ulcer healing at 4 weeks in comparisons of proton pump inhibitor with H2 receptor antagonist



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%
Rabeprazole	—	82.6%	70.9%	91.1%
Difference between proton pump inhibitors	**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%

Gastric ulcer

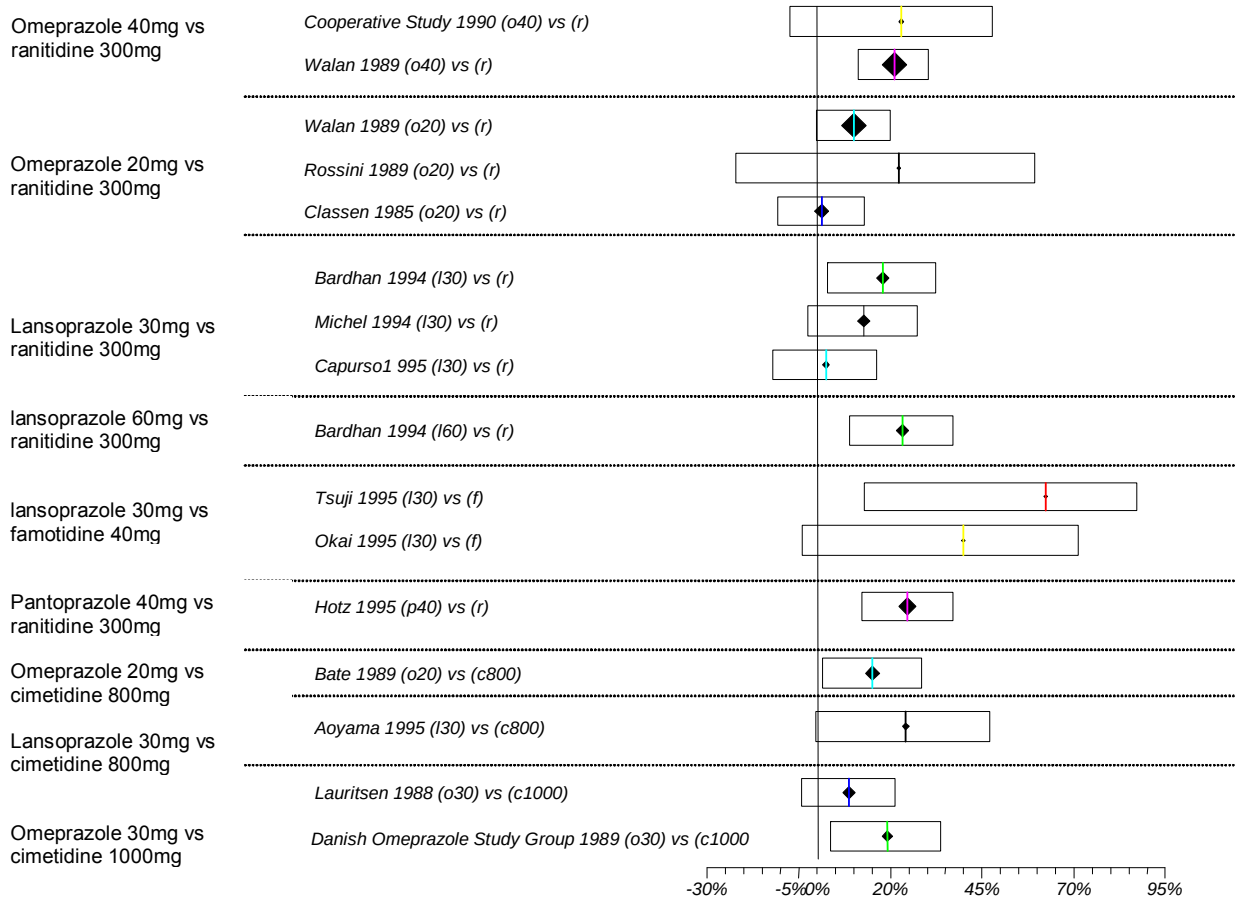
Fifteen studies compared a proton pump inhibitor with an H2 receptor antagonist for treatment of gastric ulcer (Evidence Table 9).[101, 110, 136-148] Two looked at maintenance therapy[149-151] and 1 was a follow-up of healed patients from another study.[98] One of the maintenance studies included patients with either gastric or duodenal ulcer, all of which were resistant to H2 receptor antagonist therapy.[151] The other evaluated healing of gastric ulcer with esomeprazole compared with ranitidine in patients who continued to take a nonsteroidal anti-inflammatory drug.[136] This study is examined under Key Question 3. No study compared rabeprazole with a H2 receptor antagonist. Of the 15 trials, 5 compared omeprazole with ranitidine; 3 compared lansoprazole with ranitidine; 1 compared pantoprazole with ranitidine; 2 compared lansoprazole with famotidine; 3 compared omeprazole with cimetidine, and 1compared lansoprazole with cimetidine.

The total follow-up times varied, but healing rates at 4 weeks were available from all studies. Differences in the percentages of patients healed with different proton pump inhibitors at 4 weeks are plotted in Figure 10. The pooled risk differences range from 1.1% to 62.5%, with the smallest studies showing larger effects. The confidence intervals of the risk differences for healing with proton pump inhibitors compared with H2 receptor antagonists all overlap.

Symptoms were assessed by investigators at visits and through patient diaries in 13 studies. One did not report symptoms.[139] Pain was the most commonly assessed symptom. The pain scales differed among studies (0 to 3 in some, 0 to 4 in others) and sometimes were not described. Most studies found that the proton pump inhibitor relieved symptoms somewhat more quickly, with no difference later on between groups in percentage of patients without pain. However, only 3 studies found statistically significant differences on symptom measures, and then only in some of the many measures assessed.

One study[152] reported maintenance therapy for the comparison of lansoprazole 15 mg or 30 mg with placebo. Lansoprazole was effective for preventing endoscopically verified recurrence, eliminating symptoms, and reducing antacid use. A 6-month open study reported that omeprazole 20 mg daily as more effective than ranitidine in preventing relapse in patients with refractory ulcer (unhealed after 8 weeks of treatment with an H2 receptor antagonist).[151] In this study only 12 patients of 102 enrolled were assigned to ranitidine, and patients with either gastric or duodenal ulcer were included. A 6-month follow-up study without treatment[149] looked at patients who had healed with 6 weeks of treatment with omeprazole or cimetidine;[138] no significant difference was found in relapse rate. All of these studies had high or differential dropout rates.

Figure 10. Gastric ulcer healing at 4 weeks in comparisons of proton pump inhibitor with H2 receptor antagonist



(Note: size of diamond corresponds to study sample size)

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

Treatment of nonsteroidal anti-inflammatory drug-induced ulcer

Four studies compared proton pump inhibitors (omeprazole, esomeprazole, and lansoprazole) with another drug in healing ulcers induced by nonsteroidal anti-inflammatory drugs.[136, 153-155] The details of these studies are summarized in Evidence Table 10. A good-quality systematic review of prevention and treatment of nonsteroidal anti-inflammatory drug-induced ulcers was also found.[156]

Comparisons of ranitidine 150 mg twice daily with omeprazole 20 and 40 mg daily, lansoprazole 15 and 30 mg daily, and esomeprazole 20 and 40 mg once daily showed higher rates of healed ulcer at 8 weeks for the proton pump inhibitors.[136, 153, 155] The risk difference in percent healed ranged from 14% to 22% favoring the proton pump inhibitor; in all comparisons the difference was statistically significant. While there is no direct comparison of the proton pump inhibitors, all confidence intervals overlap, suggesting it is unlikely that a difference would be found. Direct comparisons would be needed to confirm this suggestion. A single study found that omeprazole 20 mg was superior to misoprostol in healing rate at 8 weeks, but 40 mg was not superior.[154]

One study[154, 157] assessed quality of life using the Gastrointestinal Symptom Rating Scale and the Nottingham Health Profile. On the Gastrointestinal Symptom Rating Scale, omeprazole was better than misoprostol in the change in score on the total scale and on the reflux and diarrhea subscales. Although the improvement in score was greater with 20 mg omeprazole than 40 mg, the differences were not statistically significant. Only the sleep score of the Nottingham Health Profile was reported, which also showed omeprazole 20 mg to be superior to misoprostol, but the change in score for omeprazole 40 mg was not reported.

Key Question 3. What is the comparative effectiveness of different proton pump inhibitors in preventing ulcer in patients taking a nonsteroidal anti-inflammatory drug?

Summary

- Direct comparison of pantoprazole 20 mg, 40 mg, and omeprazole 20 mg daily did not indicate statistically significant differences in rates of therapeutic or endoscopic failure at 6 months in a group of patients taking nonsteroidal anti-inflammatory drugs regularly for arthritic conditions.
- A good-quality systematic review and 7 subsequently published trials compared proton pump inhibitors with placebo or other drugs. Only 1 trial included outcome measures for serious complications; for some of the endoscopic findings, patients were asymptomatic.
- For development of symptoms, new ulcers, or serious erosions, the studied proton pump inhibitors (omeprazole, lansoprazole, and pantoprazole) showed no difference. However, confidence in this finding is low because of differences in patient populations, comparison groups, and outcome measures.

Detailed Assessment

Direct evidence

In a study of 595 patients with arthritic diseases, continuously taking an nonsteroidal anti-inflammatory drug (not including COX-2 Inhibitors), and considered at high risk for

gastrointestinal injury (previous ulcer or taking anticoagulants), patients were randomized to 6 months of pantoprazole 20 mg or 40 mg or omeprazole 20 mg daily.[158] Using life-table analysis methods, remission rates were compared across and between groups. The primary outcome, therapeutic failure, was defined as peptic ulcer, >10 erosions, reflux esophagitis, and discontinuations of study drug due to an adverse event or severe gastrointestinal symptoms. Examination of baseline risk characteristics revealed that the pantoprazole 40 mg group had fewer patients taking anticoagulants (1% compared with 4%), experiencing a change in nonsteroidal anti-inflammatory drug in the last month (6% compared with 9% or 10%), and fewer with a history of endoscopically proven peptic ulcer (20% compared with 24% or 25%). These differences are small but may have biased the risk level in favor of the pantoprazole 40 mg group. Patients were censored from the analyses (considered lost to follow up) if they had low adherence to the nonsteroidal anti-inflammatory drug regimen, found to not meet inclusion after randomization, failed to adhere to the protocol, or withdrew from the study due to an adverse event not considered related to study drugs or due to "refusal to continue". The numbers of patients censored for these reasons were greater in the omeprazole group (N=42) and lowest in the pantoprazole 40 mg group (N=29). With these issues in mind, we rate this trial as fair quality (rather than poor quality, as it does meet other aspects of internal validity) and suggest caution in interpreting the results. There was no statistically significant difference between the groups in remission rates based on either therapeutic failure or failure limited to endoscopic findings, with more than 90% of patients remaining in remission in all groups at 3 and 6 months.

Indirect evidence

One good-quality systematic review addressed the question of proton pump inhibitors for treatment of nonsteroidal anti-inflammatory drug-induced ulcer.[159] Its 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). The review found 5 randomized trials that assessed omeprazole 20 mg with 40 mg in prevention of nonsteroidal anti-inflammatory drug-induced gastroduodenal toxicity. None of the studies were designed to evaluate the effectiveness of proton pump inhibitors in preventing serious complications of ulcers (hemorrhage, perforation, or death). The review showed that omeprazole is superior to the H2 receptor antagonists but provided no data on any other proton pump inhibitor.

Eight trials published more recently[154, 155, 160-165] than the omeprazole review are presented in Evidence Table 11. None of these studies was a head-to-head comparison and there were important differences in treatment regimens and follow-up, making comparisons across studies impossible. All the trials enrolled patients who were regular users of nonsteroidal anti-inflammatory drugs, with 1 including COX-2 Inhibitors.[165] Symptom assessment and reporting varied among these studies.

One study[160] included only patients *without Helicobacter pylori* who were randomized to received placebo, misoprostol 800 µg, lansoprazole 15 mg, or 30 mg with follow-up at 1, 2, and 3 months, while another study[162] included patients with *Helicobacter pylori* who developed ulcer complications (bleeding, perforation, or obstruction) after a month of daily low-dose aspirin. After ulcers were healed and *Helicobacter pylori* were eradicated, patients continued with aspirin 100 mg and were randomized to lansoprazole 30 mg or placebo. In the last study of *Helicobacter pylori* and prevention of nonsteroidal anti-inflammatory drug-induced ulcers,[163] patients with *Helicobacter pylori* but without past or current ulcer were assigned to 1 of 4 treatment groups:

omeprazole 20 mg plus clarithromycin 500 mg and amoxicillin 1 gram for 1 week; placebo or omeprazole 20 mg daily for 4 weeks; omeprazole 20 mg once daily for 5 weeks; or placebo for 5 weeks.

In the study of *Helicobacter pylori* negative patients,[160] 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 15 mg, and 18% for lansoprazole 30 mg, with no significant difference between lansoprazole doses. However, when adverse effects were included as failures, the failure rate for all 3 treatment groups was 31%. A post hoc subgroup analysis of patients taking nonsteroidal anti-inflammatory drugs and low dose aspirin found no significant difference among treatments at 12 weeks.[166] Symptoms (antacid use and day and nighttime abdominal pain) were assessed by patient diary and were found to be significantly better in the lansoprazole groups than the misoprostol group, but comparisons between the 2 lansoprazole doses were not made.[160]

In the study of *Helicobacter pylori* positive patients with ulcer complications (bleeding, perforation, or obstruction),[162] the primary endpoint was prevention of ulcer complications and the secondary endpoint was recurrence. The rate of recurrence of ulcer complications at a median follow-up of 12 months was 1.6% in the lansoprazole group compared with 14.8% in the placebo group. Two patients in the placebo group (N=61) were also taking nonsteroidal anti-inflammatory drugs.

In patients with *Helicobacter 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. There were no significant differences between the treatment groups.

A study comparing pantoprazole with placebo[161] presented a life-table analysis rather than simple proportions of patients without ulcer, making comparison with other placebo-controlled studies of proton pump inhibitors difficult. The pantoprazole group had 17% fewer ulcers at 4 weeks and 27% at 12 weeks. Patients who dropped out due to adverse events were included in the 4 week data as treatment failures. The methods or scales used to assess symptoms were not described but reported just "symptoms."[161] Presence of gastrointestinal symptoms differed at baseline in the 2 groups: They were present in 43% of the pantoprazole group and 18% of the placebo group. At 4 and 12 weeks presence of gastrointestinal symptoms improved in the pantoprazole group (to 17% and 20%, respectively), while in the placebo group remained stable (20% and 19%, respectively).

The only evidence on prevention of ulcers related to COX-2 inhibitors came from a combined report of 2 similar fair quality trials that enrolled patients who were regularly taking a nonselective nonsteroidal anti-inflammatory drug or a COX-2 inhibitor and were at risk of peptic ulcer (age > 60 years or documented peptic ulcer in last 5 years).[165] Combined, the studies randomized 1429 patients to esomeprazole 20 mg, esomeprazole 40 mg, or placebo daily for 6 months. Using pooled and separate life-table analyses, the overall analysis indicated that both esomeprazole groups prevented peptic ulcer statistically significantly more often than placebo for all nonsteroidal anti-inflammatory drugs. While no statistical analyses were undertaken comparing the 2 doses of esomeprazole, the rates of ulcer development were very similar (5.2% with 20 mg and 4.6% with 40 mg). The rates of ulcer development among the subgroup taking a COX-2 inhibitor were also statistically significantly lower with either dose of esomeprazole compared to placebo (16.5% with placebo compared with 0.9% and 4.1% with 20 mg and 40 mg of esomeprazole, respectively). The separate study analyses of the subgroup taking nonselective nonsteroidal anti-inflammatory drugs indicated that esomeprazole was superior to placebo in one

trial (N=844) but not in the other (N=585), while the pooled analysis indicated statistically significant benefit with either dose of esomeprazole compared to placebo.

Key Question 4. What is the comparative effectiveness of different proton pump inhibitors in eradicating *Helicobacter pylori* infection?

Summary

- The evidence on comparative effectiveness of various proton pump inhibitors was fair, despite 5 systematic reviews and 29 head-to-head trials. The significant heterogeneity in design, participants, and method of measuring outcomes among studies lessen the strength of the evidence.
- Pooled analysis of eradication rates stratified by number of days of treatment and dose comparison did not find statistically significant differences in eradication rate among the proton pump inhibitors.
- In children evidence was extremely limited, with only 2 trials, both of which compared lansoprazole with placebo. Neither trial found the addition of lansoprazole to result in higher eradication rates than antibiotic therapy alone.

Detailed Assessment

Direct evidence

Five systematic reviews have evaluated the efficacy of proton pump inhibitors in eradication of *Helicobacter pylori,* however because these reviews focused on comparisons to H2 receptor antagonists, were out of date (literature searches conducted prior to 2001), or included non-randomized studies or studies published only as abstracts, they were not sufficient to evaluate this question.[47, 167-171]

Twenty-nine studies directly compared one proton pump inhibitor with another, in combination with the same antibiotic(s), and reported *Helicobacter pylori* eradication rates.[98, 104, 172-198] They were fair-quality with the exception of 5 poor-quality studies that were not blinded or provided inadequate data to compare eradication rates directly.[183, 187, 192, 197, 199] Several studies included antibiotic regimens that are no longer standard.[187, 104, 178, 183, 190, 198, 200]

Of these, 23 trials compared proton pump inhibitors using identical regimens of antibiotics (within study) and reported eradication rates in a way that allowed statistical pooling (Table 11).[68, 104, 173, 175-180, 183-187, 189-191, 193-197, 201] All of these trials included treatment with 2 antibiotics and assessed *Helicobacter pylori* eradication at 4 to 6 weeks after treatment. While most of these trials used a 7 day proton pump inhibitor regimen in combination with 2 antibiotics, 3 trials used longer proton pump inhibitor regimens, a 14 day[190, 202] and a 30 day regimen.[175] Interestingly, these regimens resulted in lower eradication rates at follow-up. Overall, eradication rates ranged from 67% in a trial of lansoprazole 60 mg daily for 30 days to 100% in a trial of pantoprazole 40 mg daily for 7 days. Pooled rates of eradication from these trials vary (see Table 11 below), but pooled relative risks of these rates did not identify statistically significant differences between groups when stratified by number of days of treatment and dose comparison (Table 11 below). Several trials examined different dose levels (high compared to usual and low compared to usual) of proton pump inhibitors without finding statistically significant differences in eradication rates.

In 1 additional study, patients who had failed a 1 week regimen of amoxicillin, clarithromycin, and a proton pump inhibitor were randomized to rabeprazole 20 mg, lansoprazole 60 mg, or omeprazole 40 mg daily each plus amoxicillin and metronidazole.[188] No differences were found among the proton pump inhibitors in eradication rates, with 91% eradication in each group.

Table 11. Rates of eradication of *Helicobacter pylori*

Duration of proton pump inhibitor treatment Number of trials	Group A	Eradication rate (pooled)	Group B	Eradication rate (pooled)
Lansoprazole compared with omeprazole				
7 Days 4 trials	Lansoprazole 60 mg	83%	Omeprazole 40 mg	84%
14 Days 3 trials	Lansoprazole 60 mg	74%	Omeprazole 40 mg	77%
30 days 1 trial	Lansoprazole 60 mg	67%	Omeprazole 40 mg	76%
7 days 2 trials	Lansoprazole 30 mg	85%	Omeprazole 40 mg	84%
7 days 1 trial	Lansoprazole 30 mg	71%	Omeprazole 20 mg	78%
Pantoprazole compared with omeprazole				
7 days 2 trials	Pantoprazole 40 mg	85%	Omeprazole 40 mg	93%
7 days 3 trials	Pantoprazole 80 mg	78%	Omeprazole 40 mg	78%
Esomeprazole compared with omeprazole				
7 days 2 trials	Esomeprazole 40 mg	84%	Omeprazole 40 mg	79%
7 days 1 trial	Esomeprazole 80 mg	70%	Omeprazole 40 mg	65%
Rabeprazole compared with omeprazole				
7 days 1 trial	Rabeprazole 10 mg	71%	Omeprazole 20 mg	70%
7 days 2 trials	Rabeprazole 20 mg	72%	Omeprazole 40 mg	72%
7 -10 days 3 trials	Rabeprazole 40 mg	75%	Omeprazole 40 mg	72%
Rabeprazole compared with lansoprazole				
7 days 2 trials	Rabeprazole 20 mg	81%	Lansoprazole 60 mg	78%
7 days 2 trials	Rabeprazole 40 mg	89%	Lansoprazole 60 mg	84%
Rabeprazole compared with esomeprazole				
7 days 1 trial	Rabeprazole 40 mg	91%	Esomeprazole 40 mg	89%

Two systematic reviews addressed similar questions, 1 focusing on the comparison of esomeprazole to other proton pump inhibitors[203] and the other directly comparing proton pump inhibitors.[204] Both of these reviews were fair to poor quality because they pooled studies with differing proton pump inhibitor regimens (for example drug A given for 7 days compared to drug B given for 14 days) with those comparing similar regimens or provided inadequate details of studies included to determine the comparisons being made.

Indirect evidence in children

Two trials evaluated lansoprazole in eradication of *Helicobacter pylori* in children.[205, 206] Both studies used antibiotic regimens of amoxicillin and tinidazole, given for 6 or 7 days, in combination with lansoprazole or placebo. The 2 protocols were very similar, but not identical; in 1 the dose of lansoprazole was 30 mg daily with children 10 to 21 years eligible for enrollment,[205] while in the other dosing was based on weight (<20 kg, 15 mg daily; ≥20 kg, 30 mg daily)[206] and the age range was 8 to 14 years. However, the mean age for participants in both trials was 11 years. Neither trial resulted in significantly different eradication rates between placebo (58%[206] and 71%[205]) and lansoprazole (67%[206] and 68%[205]).

Key Question 5. Is there evidence that a particular treatment strategy is more effective or safer than another for longer-term treatment (more than 8 weeks) in patients with gastroesophageal reflux disease?

Summary

Standard dose compared with low-dose proton pump inhibitor

- Time in remission was longer for higher doses compared with lower doses for omeprazole and rabeprazole, but the same for higher and lower doses of lansoprazole. Evidence on esomeprazole was inconclusive.
- Rates of endoscopically verified remission at study end were greater with the higher dose of rabeprazole compared with the lower dose, but were not different between dose strategies for omeprazole and lansoprazole.
- Rates of relapse of symptoms were generally higher with lower doses of omeprazole, lansoprazole, and rabeprazole.

Standard dose compared with intermittent or on-demand proton pump inhibitor

- For patients with healed erosive esophagitis, a regimen of daily proton pump inhibitor was superior in preventing relapse of esophagitis or recurrence of symptoms compared with 3 days a week or on-demand regimens at 6 months.
- For patients with nonerosive esophagitis, assessments of symptom severity or relapse of symptoms was not different between daily and on-demand regimens. Patient satisfaction and quality of life ratings at study end were also not different, although the mean change in quality of life score from baseline was better with daily therapy.
- For patients presenting with symptoms of gastroesophageal reflux disease, but without endoscopic assessment, evidence is mixed.

Proton pump inhibitor compared with H2 receptor antagonist

- Daily proton pump inhibitor therapy was found superior to daily H2 antagonist therapy in preventing relapse of erosive esophagitis, or symptoms of gastroesophageal reflux disease.

Detailed Assessment

Standard-dose proton pump inhibitor compared with low-dose proton pump inhibitor

Eleven trials compared a standard dose of a proton pump inhibitor with a lower dose of the same proton pump inhibitor for longer-term treatment of gastroesophageal reflux disease (Evidence Table 13). Five trials compared lansoprazole 30 mg with lansoprazole 15 mg;[21, 207-210] 2 compared omeprazole 20 mg with omeprazole 10 mg;[211, 212]1 compared pantoprazole 40 mg with pantoprazole 20 mg;[213] 2 compared rabeprazole 20 mg with rabeprazole 10 mg; [214, 215] and 2 compared esomeprazole 40 mg with esomeprazole 20 mg and esomeprazole 10 mg.[216, 217] Eight trials also included a placebo arm. In most of the trials, the drug and dose used for acute treatment before maintenance treatment began was the same as the higher dose used in the maintenance phase. The studies' follow-up periods were 6 months in 4 trials, 12 months in 6 trials, and 5 years in 1 trial.[214] Of these, 2 were poor quality. One had significant differences in prognostic factors at baseline combined with other flaws relating to assignment of group.[209] In the other, patients with adverse events thought to possibly be or probably be related to the study drug were counted as having a relapse, the margin allowed for noninferiority was very large (20%), and there were flaws related to assignment of group.[213] These studies are not discussed below, and the remainder were fair quality.

All trials reported recurrence rate of endoscopically verified disease (either as relapse rates or remission rates) and the time in remission. Remission was considered grade 0 on any esophagitis scale in most studies, although some allowed grade 1 as well. All but 1 trial[212] also reported recurrence rate of symptoms or the number of patients with mild or no symptoms at study end. Study characteristics are summarized in Table 12 and results are shown in Table 13.

Time in remission

The duration of remission was statistically significantly greater with higher compared with lower doses of omeprazole at 6 months ($P<0.002$),[212] and rabeprazole at both 1 year ($P=0.016$) and 5 years ($P< 0.007$).[214, 215] Differences were not found between doses of lansoprazole in 3 studies.[21, 207, 208, 210] Additionally, 2 studies of esomeprazole and 1 of omeprazole did not make statistical comparisons between the doses.[211, 216, 217]

Endoscopically verified remission

Examining Table 13, the higher doses resulted in greater numbers of patients being relapse-free at 6 or 12 months but differences between the higher and lower proton pump inhibitor dose strategies were examined statistically in only 5 studies. All 3 studies of lansoprazole found no difference between the 15 mg daily and 30 mg daily doses at 12 months,[21, 207, 208] and a single trial found no difference in relapse rates between the standard dose of omeprazole (20 mg) compared with the lower dose (10 mg) at 12 months.[211] However, 1 study of rabeprazole found that patients taking the standard dose (20 mg) had a higher remission rate than patients taking a lower dose (10 mg) at 1 year[215] and 5 years[214] of follow-up.

Remission of symptoms

Remission of symptoms was defined as no symptoms in most studies, although some allowed mild symptoms. Higher doses of a proton pump inhibitor compared to a lower dose of the same drug resulted in more patients being symptom-free at study end, but again statistical analyses were not undertaken to compare the doses in most studies. Two studies of lansoprazole[207, 208] and 1 of omeprazole found no difference between the lower and higher doses.[211] With rabeprazole, the 1-year follow-up did not find a statistically significant difference between the doses, but the 5-year follow-up found the higher dose (30 mg daily) to be superior to the lower dose (15 mg daily).

Withdrawals

Differences in withdrawal (for any reason) rates were not apparent between the higher and lower doses in any of the studies.

Table 12. Proton pump inhibitors and treatment durations in longer-term studies of gastroesophageal reflux disease: Comparisons of standard doses with lower doses

Study	N	Duration	Initial short-term treatment (for healing)	Strategy 1	Strategy 2	Strategy 3
Robinson 1996	173	12 months	Lansoprazole 30 mg	Lansoprazole 30 mg	Lansoprazole 15 mg	Placebo
Sontag 1997	163	12 months	Lansoprazole 30 mg	Lansoprazole 30 mg	Lansoprazole 15 mg	Placebo
Hatlebakk 1997	103	12 months	Lansoprazole 30 mg	Lansoprazole 30 mg	Lansoprazole 15 mg	
Bate 1995	193	12 months	Omeprazole 20-40 mg	Omeprazole 20 mg	Omeprazole 10 mg	Placebo
Laursen 1995	168	6 months	Omeprazole 20-40 mg	Omeprazole 20 mg	Omeprazole 10 mg	Placebo
Caos 2000	209	12 months	Rabeprazole 10 or 20 mg	Rabeprazole 20 mg	Rabeprazole 10 mg	Placebo
Caos 2005[a]	497	5 years	Rabeprazole 10 or 20 mg	Rabeprazole 20 mg	Rabeprazole 10 mg	Placebo
Johnson 2001	318	6 months	Not reported	Esomeprazole 40 mg	Esomeprazole 20 mg	Esomeprazole 10 mg
Vakil 2001	375	6 months	Omeprazole 20 mg or esomeprazole 20 or 40 mg	Esomeprazole 40 mg	Esomeprazole 20 mg	Omeprazole 20 mg

[a] Extension of Caos 2000 and Birbara 2000.

Table 13. Remission of gastroesophageal reflux disease erosions and symptoms in longer-term studies of proton pump inhibitors: Comparisons of standard doses with lower doses

Study Year	Proton pump inhibitor	Percent of treatment group in remission (standard dose vs. low dose vs. placebo)[a]		
		Endoscopically confirmed remission	Symptom remission	Withdrawals
Robinson 1996	Lansoprazole	98% vs. 93% vs. 45% NS	67% vs. 72% vs. 35% NS	16% vs. 18% vs. 37%
Sontag 1996	Lansoprazole	94% vs. 86% vs. 13% NS	66% vs. 64% vs. 20% NS	30% vs. 70% placebo
Hatlebakk 1997	Lansoprazole	85% vs. 72% *P*=0.149	91.1% vs. 75% *P* value not reported	NR
Bate 1995	Omeprazole	74% vs. 50% vs. 14% NS	83% vs. 77% vs. 34% NS	NR
Laursen 1995	Omeprazole	59% vs. 35% vs. 0% *P* value NR	NR	3% vs. 6% vs. 12%
Caos 2000	Rabeprazole	**90% vs. 73% vs. 29%** ***P*<0.04**	90% vs. 73% vs. 29% NS	43% vs. 23% vs. 79%
Caos 2005	Rabeprazole	**89% vs. 77% vs. 37%** ***P*=0.005**	**61% vs. 52% vs. 22%** ***P*<0.05**	28% vs. 33% vs. 33%
Johnson 2001	Esomeprazole	93.6% vs. 93.2% vs. 57.1% vs. 29.0% *P* value not reported[a]	77.8% vs. 72.5% vs. 70.5% vs. 66.7% *P* value not reported	24% vs. 16% vs. 44% vs. 83%
Vakil 2001	Esomeprazole	88% vs. 79% vs. 54% vs. 29% *P* value NR	95% vs. 88% vs. 86% vs. 33% *P* value NR	27% in 40 mg group vs. 79% in placebo group; others NR

Abbreviations: NR, not reported; NS, not significant.
[a] Doses are listed in Table 9.
[a] *P* values for drug-drug comparisons not reported, *P* values for drug-placebo comparisons reported as *P*<0.001.

Standard-dose proton pump inhibitor compared with intermittent or 'on-demand' proton pump inhibitor

We identified 2 systematic reviews that compared intermittent or on-demand treatment to daily treatment for patients with gastroesophageal reflux disease.[218, 219] These reviews included studies of H2 receptor antagonists, studies comparing different doses of a proton pump inhibitor to one another, and different proton pump inhibitors with differing regimens (e.g. omeprazole given daily compared with esomeprazole given intermittently). Additionally, quality assessments of included studies were not undertaken. Most of the studies included in these reviews did not make a comparison between continuous (daily) proton pump inhibitor therapy and intermittent (3 times a week) or on-demand (taken daily when symptoms occur, discontinue when symptoms resolve) and were not included here. We have used these reviews only to identify additional studies not found in our literature searches.

Eight trials compared daily treatment with a proton pump inhibitor with intermittent or on-demand treatment of the same proton pump inhibitor.[208, 220-225, 226] One study followed patients for 1 year,[225] the rest followed patients for 6 months. Details of the study patients and

treatment strategies are presented in Table 14. In patients with healed endoscopically proven gastroesophageal reflux disease (Table 15), a regimen of daily proton pump inhibitor was superior to either 3 days a week or on-demand proton pump inhibitors of the same daily dose in preventing recurrence of erosive esophagitis based on endoscopy.[208, 221, 225] A 3-day-a-week regimen was also inferior to a daily regimen in preventing relapse of overall symptoms but no difference was found between daily treatment and on-demand treatment, although 1 study found that severity of heartburn was lower with the daily regimen.[221]

Table 14. Proton pump inhibitors and treatment durations in longer-term studies of gastroesophageal reflux disease: Comparisons of daily treatment with intermittent or on-demand treatment

Study	N	Diagnosis	Strategy 1	Strategy 2	Strategy 3
Sontag 1997	406	Healed erosive esophagitis	Omeprazole 20 mg daily	Omeprazole 20 mg 3 days a week	Placebo
Dent 1994	204	Healed erosive esophagitis	Omeprazole 20 mg daily	Omeprazole 20 mg 3 days a week	Ranitidine 300 mg daily
Sjostedt 2005	477	Healed erosive esophagitis	Esomeprazole 20 mg daily	Esomeprazole 20 mg on-demand	
Cibor 2006	65	NERD[a]	Lansoprazole 15 mg daily	Lansoprazole 30 mg on-demand	Lansoprazole 30 mg intermittent (4 weeks)
Bour 2005	181	NERD[a]	Rabeprazole 10 mg daily	Rabeprazole 10 mg on-demand	
Janssen 2005	432	NERD[a]	Pantoprazole 20 mg daily	Pantoprazole 20 mg on-demand	
Morgan 2007	268	Symptoms of gastroesophageal reflux disease	Rabeprazole 20 mg daily	Rabeprazole 20 mg on-demand	
Hansen 2005, 2006	1902	Symptoms of gastroesophageal reflux disease	Esomeprazole 20 mg daily	Esomeprazole 20 mg on-demand	Ranitidine 300 mg daily

Abbreviations: NERD, non-erosive reflux disease.
[a] Includes mild esophagitis grades 1 or A.

Table 15. Remission of gastroesophageal reflux disease erosions and symptoms in longer-term studies of proton pump inhibitors: Comparisons of daily treatment with intermittent or on-demand treatment

Study Year	Proton pump inhibitor	Comparison regimen	Percent of treatment group with result (daily vs. intermittent or on-demand regimen)	
			Endoscopically verified remission	Remission of symptoms
Healed erosive esophagitis				
Sontag 1997	Omeprazole	3 days a week	70% vs. 34% (*P*<0.001)	92% vs. 59% (*P*<0.001)
Dent 1994	Omeprazole	3 days a week	89% vs. 32% (*P*<0.001)	NR
Sjostedt 2005	Esomeprazole	On-demand	81% vs. 58% (*P*<0.0001)	95% vs. 94.3 (*P*=0.77)

In 3 studies of patients with endoscopically proven non-erosive esophagitis, no significant difference was found between daily and on-demand treatment with proton pump inhibitors rabeprazole or lansoprazole, in the severity of symptoms as measured on a visual analog scale at 3, 6, and 12 months,[222] or in the proportion with symptom relapse at 6 months.[224] Assessment of overall satisfaction with treatment was not different between regimens in 1 study[222] and final quality of life scores were also not different between groups in the other study.[224] However, the mean change in quality of life scores from baseline to 6 months was significantly better in the daily treatment group compared to the on-demand group (P=0.03).[224] The third study of pantoprazole 20 mg found the on-demand regimen to be noninferior to the daily regimen, based on the rates of 'treatment failure' defined as moderate symptoms for 3 or more days, use of > 1 dose of study medication on > 3 consecutive days, or withdrawal from study due to lack of efficacy.[226]

In patients presenting with symptoms of gastroesophageal reflux disease (but with no endoscopic examination), 2 studies found mixed results.[220, 227] In a study of on-demand esomeprazole, the results differ by which symptom-based outcome measure is used.[228] Statistical analyses of the results were not undertaken in the study, but here we have used a Yates corrected chi-square test. Using an outcome of "no heartburn" at 6 months, daily therapy is superior to on-demand treatment with 72% compared with 62% (P=0.002 using Yates corrected chi-square). However, the percentage of patients with no regurgitation at 6 months was 78% with daily therapy and 91% with on-demand treatment (P<0.001002 using Yates corrected chi-square). The other study found that daily treatment with rabeprazole resulted in statistically significantly more heartburn-free days (90%) compared with on-demand treatment (65%; P<0.0001) and fewer heartburn episodes (N=7 and 26, respectively; P<0.0001).These 2 studies also report different findings in quality of life. Again, the study of esomeprazole found the daily regimen superior to the on-demand regimen in both change from baseline in quality of life and patient satisfaction. However, data (including P values) supporting these claims are not clearly presented.[228] The other study found that on-demand treatment with rabeprazole resulted in greater improvement in quality of life at 6 months compared to the daily regimen.[220]

Standard-dose proton pump inhibitor compared with H2 receptor antagonist or placebo

Four studies found proton pump inhibitors to be superior to ranitidine 150 mg twice daily, 3 for prevention of relapse of healed esophagitis and 1 for prevention of recurrence of symptoms of gastroesophageal reflux disease.[229,230,223, 225] After 12 months, proton pump inhibitor therapy (pantoprazole 10 mg, 20 mg, or 40 mg and omeprazole 20 mg daily) resulted in lower relapse rates compared with ranitidine therapy. In 2 studies, more patients remained healed on pantoprazole at all doses than on ranitidine, and the rate of relapse was related to the dose of pantoprazole: Relapse occurred in 60%, 32%, and 18% of the 10 mg, 20 mg, and 40 mg groups, respectively. A second study of the same doses of pantoprazole and ranitidine found similar results.[230] During the first 12 months of maintenance treatment, healing was maintained in 78% of patients treated with pantoprazole 40 mg, 55% of patients treated with pantoprazole 20 mg, 46% of patients treated with pantoprazole 10 mg, and 21% of those treated with ranitidine. This study is planned for 3 years, but only the first 12 months have been reported so far. With omeprazole, at 12 months 89% remained in remission compared with 25% on ranitidine ($P<0.001$).[225] In those with symptoms suggestive of gastroesophageal reflux disease, 72% had relief of symptoms after 6 months of esomeprazole 20 mg daily compared with 33% taking ranitidine (statistical analysis not presented).

Additionally, a study of famotidine 20 mg twice daily compared with lansoprazole 15 mg daily, both as step down therapy from lansoprazole 30 mg daily for treatment of erosive esophagitis, found the proton pump inhibitor to be superior in preventing recurrence of regurgitation and heartburn, but not dysphagia or assessment of esophagitis grade after 8 weeks of maintenance treatment.[231] Fifty percent of patients taking famotidine experienced recurrence of heartburn, and 79% experienced recurrence of regurgitation compared to 0% and 7%, respectively, with lansoprazole 15 mg daily.

Comparison of esomeprazole administered orally compared to esomeprazole administered intravenously

A trial conducted in 246 ambulatory patients compared esophagitis healing rates at 4 weeks in patients given esomeprazole 40 mg either orally, via intravenous injection, or via intravenous infusion.[232] Patients were randomized to either 1 week of intravenous esomeprazole (injection or infusion) followed by 3 weeks of oral esomeprazole or 4 weeks of oral esomeprazole. The study was blinded using multiple placebos. After 4 weeks, there was no difference in healing rates among the 3 treatment groups (approximately 80%). The frequency and type of adverse events were also similar among the treatment groups.

Comparison of a reduced-dose proton pump inhibitor with an H2 receptor antagonist in children

One fair-quality randomized trial compared reduced-dose omeprazole with ranitidine for longer-term treatment of erosive gastroesophageal reflux disease in children (Evidence Table 6).[233] Children who had been treated with omeprazole and shown by endoscopy to be healed after 3 months began treatment with omeprazole 0.7 mg/kg daily (half the starting dose for the healing phase), ranitidine 10 mg/kg daily, or nothing for 6 months. Although no statistically significant difference was found among the groups at baseline, children in the group receiving no treatment had slightly less severe esophagitis and slightly lower symptom scores than children in the other groups. They were also slightly older at enrollment and at age of symptom onset. Follow-up

endoscopy at 3 months after the end of maintenance treatment was blinded. No statistically significant differences were seen in endoscopic or histologic grade or in symptom scores. One patient in the no treatment group had a relapse of erosive esophagitis (Hetzel and Dent grade 3). Twelve (25%) had mild symptoms at study endpoint and remained untreated, 6 in the no treatment group, 1 in the ranitidine group, and 5 in the omeprazole group. While the differences at baseline between the no treatment group and the drug groups may result in confounding results of those comparisons, there is no apparent difference between the drug groups in maintenance of remission of esophagitis and symptoms and in the number of patients requiring no further treatment.

Taper off proton pump inhibitor

A group of 97 patients with at least 8 weeks of daily use of a proton pump inhibitor with no history of peptic ulcer or esophagitis, and no evidence of esophagitis on endoscopy were enrolled in a 3 week trial of tapering the proton pump inhibitor dose prior to discontinuation or abrupt discontinuation.[234] In this study, patients were assigned to take omeprazole 20 mg daily for 3 weeks or to a blinded taper of omeprazole 20 mg daily for 1 week, 10 mg daily for 1 week, and 10 mg every other day for 1 week. Symptoms were assessed 1 week after discontinuation of drug, and the rate of resumption of proton pump inhibitor therapy was measured after 1 year. The mean duration of proton pump inhibitor treatment at study entry was 48 months. No statistically significant differences were found between tapering and non-tapering groups on symptom scores at 4 weeks, or the rate of resumption of treatment at 1 year.

Key Question 6. What is the comparative safety of different proton pump inhibitors in patients being treated for symptoms of gastroesophageal reflux disease, peptic ulcer, and nonsteroidal anti-inflammatory drug-induced ulcer?

Summary

- The comparative evidence on long-term adverse effects was limited. There was no long-term, head-to-head comparative studies (clinical or observational) specifically designed to monitor adverse effects.
- Two long-term (48 weeks to 5 years) maintenance studies found no difference between omeprazole and lansoprazole in adverse events or withdrawals due to adverse events, and a 6-month study comparing esomeprazole 20 mg with lansoprazole 15 mg found no difference in adverse event rates.
- In follow-up studies of individual drugs, no important differences in long-term findings were apparent, but comparisons across these studies are not clear.
- Short-term, head-to-head comparative studies indicate that the incidence of all and serious adverse events and the drop-out rate due to adverse events for all the proton pump inhibitors is low. No consistent differences between the proton pump inhibitors were seen in these trials.
- Evidence on long-term harms in children is limited. No serious adverse events were seen in observational studies. Serum gastrin levels were found to be elevated in >70% of children after 1 year of treatment regardless of which proton pump inhibitor was taken. Evidence on elevation of serum liver enzymes was more varied. A study of lansoprazole found elevated

aspartate aminotransferase in 4% of infants or neonates after 5 days of treatment for symptoms of gastroesophageal reflux.

- Studies indicated a potential for increased risk of clostridium difficile diarrhea associated with proton pump inhibitor use, but hospitalizations related to clostridium difficile diarrhea were not significantly associated.
- Evidence suggested an increased risk of osteoporotic bone fractures, including hip fracture, with longer duration exposure to proton pump inhibitors. However, 1 study found no association among patients with any major risk factors for fracture.
- Evidence on the association between community acquired pneumonia and proton pump inhibitor use was mixed.

Detailed Assessment

There were no head-to-head, long-term trials designed to compare adverse events between proton pump inhibitors. In long-term (6 months or longer) maintenance studies of patients with gastroesophageal reflux disease, there was no difference in the number of adverse events or number of withdrawals due to adverse events in the different proton pump inhibitor groups.[71, 78, 235] Reports of adverse effects in head-to-head comparisons of proton pump inhibitors for short-term treatment of gastroesophageal reflux disease and ulcer are shown in Evidence Table 12. The proportion of patients withdrawing due to adverse events in these studies was very low, with most studies reporting 1% to 3%. No study found significant differences among treatment groups in the rate of withdrawals for adverse effects. Reports of serious adverse events were uncommon and generally balanced among the drugs. Many of these incidences could be associated with preexisting diseases.

Several reports of long-term (ranging from 1 year up to 11 years) follow-up of individual proton pump inhibitors (omeprazole, lansoprazole, pantoprazole, and rabeprazole) have been published.[214, 225, 236-250] They studied potential adverse events including enterochromaffin-like cell hyperplasia, enterochromaffin-like cell carcinoids tumors, atrophic gastritis, intestinal metaplasia, N-nitrosamine formation (with overgrowth of gastric bacteria), enteric infections, malabsorption syndromes, and diarrhea. The risk of enteric infection may, rarely, be increased with sustained acid suppression.[251] The other concerns have not been observed in these long-term, noncomparative studies. While enterochromaffin-like cell hyperplasia has been seen to occur, no increased risk of enterochromaffin-like cell carcinoids has been observed. Likewise, atrophic gastritis is increased with long-term use of proton pump inhibitors, but progression to intestinal metaplasia and gastric cancer has not been shown. Overgrowth of gastric bacteria does occur, but a related higher rate of gastric adenocarcinoma has not been observed.

Using a pharmacovigilance database in Spain, the risk of adverse events (reported by organ system) was reported for each proton pump inhibitor compared to all other drugs in the database (Table 16).[252] Using this analysis, increased risk of adverse events were found associated with specific proton pump inhibitors, as below. The authors note “A direct relationship was found between consumption and the number of reports.” Without controlling for this difference in the analysis, these results should be interpreted cautiously.

Table 16. Risk of adverse events for proton pump inhibitors compared with other ulcer drugs (Salgueiro 2006)[252]

Adverse event by organ system	Proton pump inhibitor	Odds ratio (95% CI)
Skin and appendage disorders	Omeprazole Rabeprazole	1.4 (1.2 – 1.7) 1.9 (1.1 – 3.2)
Urinary system	Lansoprazole	2.7 (1.2 – 6.2)
Reproductive female	Lansoprazole	4.2 (1.5 – 11.4)
Endocrine disorders	Lansoprazole	4.0 (1.3 – 12.7)
Liver and biliary system disorders	Lansoprazole Pantoprazole	2.4 (1.1 – 5.1) 3.0 (1.7 – 5.5)
Musculoskeletal system disorders	Esomeprazole Omeprazole	2.9 (1.2 – 7.4) 1.8 (1.3 – 2.4)
Vision disorders	Pantoprazole Rabeprazole Esomeprazole	3.0 (1.5 – 6.1) 4.0 (1.6 – 10.0) 3.4 (1.1 – 11.1)
Gastrointestinal system disorders	Omeprazole Lansoprazole	1.8 (1.5 – 2.1) 2.4 (1.6 – 3.7)

Diarrhea

A nested case-control study of 10 008 lansoprazole users followed for 4 years found a dose-related trend for diarrhea (5%, 4%, and 3% of patients using 60 mg or more, 30 mg, and 15 mg or less, respectively; P=0.08).[248] In 42% of patients reporting diarrhea the lansoprazole dosage was reduced or discontinued as a response. Cases had a higher current use of oral antibiotics than controls with no diarrhea (adjusted odds ratio, 2.7; 95% CI 1.0 to 6.9).

Two case control studies examined the relationship between clostridium difficile associated diarrhea and acid suppression, including proton pump inhibitors.[253, 254] The first, based on 1672 cases and 16720 controls, found a significantly increased risk of community acquired clostridium difficile diarrhea in patients who were currently using a proton pump inhibitor (relative risk 2.9; 95% CI 2.4 to 3.4).[253] However, the second, based on 1389 cases and 12303 controls, did not find a significant association between hospitalization due to clostridium difficile diarrhea and exposure to a proton pump inhibitor within 90 days (odds ratio 0.0.9; 95% CI 0.8 to 1.1).[254] Neither study examined differences between proton pump inhibitors.

Bone fractures

Four nested case control studies examined the association between exposure to proton pump inhibitors and risk of fracture.[255-258] Three of the studies found statistically significant increased risk of fracture associated with proton pump inhibitor use, although they differed in the duration of exposure that was found significantly associated with increased risk. The largest included 124 655 cases and 373 962 controls drawn from Danish registers of National Board of Health, the Danish Medicines Agency, and the National Bureau of Statistics.[256] Cases included any patient with a fracture in the year 2000. An increased risk of *any fracture* was associated with last use of a proton pump inhibitor within 1 year of the index date (adjusted odds ratio 1.18; 95% CI 1.12 to 1.43). Exposure that ended more than 1 year prior to the fracture was not significantly associated,

and a dose-response effect was not found. Cumulative dose was used as a proxy for duration of exposure, and the increased risk was found to be similar across exposure groups (≤ 25, 26-99 and ≥ 100 defined daily dosages). Similar results were found for specific fracture sites (hip, forearm and spine). This study controlled for exposure to multiple drug classes, but was not able to control for calcium or vitamin D and did not differentiate types of fracture.

In contrast, 2 studies involving 13 566 and 15 792 cases found increased risk based on duration and dose of proton pump inhibitor use in patients 50 years and older.[255, 257] One identified patients older than 50 years, who had been exposed to a proton pump inhibitor for at least 1 year prior to the index date (date of hip fracture). After 1 year of use, an increased risk was found; adjusted odds ratio of 1.44 (95% CI 1.30 to 1.59), increasing by year to 1.59 (95% CI 1.39 to 1.80) at 4 years of use.[255] The risk increased again with higher daily dosages of proton pump inhibitor, with adjusted odds ratios of 1.40 (95% CI 1.26 to 1.54) for those using ≤ 1.75 average daily doses, and 2.65 (95% CI 1.80 to 3.90) for those using ≥ 1.75 average daily doses. Multiple potential confounding factors were controlled for; including several groups of drugs know to influence bone metabolism, including calcium or vitamin D. The second study included patients with vertebral, wrist or hip fractures, again controlling for multiple potential confounders, including drugs (but not calcium or vitamin D).[257] No increase in risk was found with durations of exposure up to 6 years. The risk for any osteoporotic fracture was increased only with 7 or more years of exposure (adjusted odds ratio 1.92; 95% CI 1.16 to 3.18). The risk of hip fracture alone was increased after 5 years of exposure (adjusted odds ratio 1.62; 95% CI 1.02 to 2.58) although the magnitude of risk increased again with 6 and 7 years of exposure.

The fourth study limited the population of cases and controls to those with no major risk for hip fracture.[258] With 1098 cases and 10 923 controls, this was the smallest study. No association was found between proton pump inhibitors and incidence of hip fractures. The estimated relative risk of hip fracture for those who received *one or more* proton pump inhibitor prescriptions before the index date was 0.9 (95% CI 0.7 to 1.1), compared with those who received no prescriptions. This study also evaluated individual proton pump inhibitors and found similar results for each drug. The discordant results of this study compared to the other 3 may be due to smaller numbers and a differing selection process in that patients with as little as 1 prescription for a proton pump inhibitor were included and further stratification of exposure or dose were not undertaken.

Community acquired pneumonia

Two studies examined the association between proton pump inhibitor use and community acquired pneumonia, coming to somewhat different conclusions.[259, 260] A large, good-quality nested case-control study identified 80 066 cases and 799 881 controls drawn from a cohort of patients from a general practice research database.[260] The adjusted odds ration for the association of recent (within 30 days) use of a proton pump inhibitor and a diagnosis of community acquired pneumonia was 1.02 (0.97–1.08). This study did find, however, that the risk was significantly increased if the patient had started the proton pump inhibitor within 2 or 14 days, but not with longer durations of therapy. The other study, fair quality, identified 475 cases and 4960 controls from a cohort of patients who had all been exposed to an acid reducing drug during the study period.[259] The exposure was then stratified into recent (within 30 days) or past (>30 days since exposure). This study found an increased risk among current users of a proton pump inhibitor, with an adjusted relative risk of 1.89 (95% CI 1.36 to 2.62) compared to those who had stopped taking a proton pump inhibitor 30 or more days ago.[259] This study did report an analysis of each

proton pump inhibitor with enough cases to conduct an analysis, finding an increased risk with omeprazole and pantoprazole, adjusted odds ratios 1.74 (95% CI 1.28 to 2.35) and 2.29 (95% CI 1.43 to 3.68), respectively, but not with lansoprazole 0.91 (95% CI 0.35 to 2.34). However, because there were few cases for each drug, these results should be interpreted with caution.

A study combining data from all Phase II-IV trials of esomeprazole examined the risk of respiratory tract infections in 16 583 patients assigned to esomeprazole and 12 044 assigned to placebo or other acid suppressing drugs.[261] Compared to placebo, this analysis did not find a difference in risk of any respiratory tract infection (relative risk 0.93; 99% CI 0.78 to 1.11); lower respiratory tract infection (relative risk 0.92; 99% CI 0.59 to 1.42); or pneumonia (relative risk 0.94; 99% CI 0.29 to 3.07). Analyses of the relative risk with esomeprazole compared with omeprazole, lansoprazole, or ranitidine did not indicate statistically significant differences. Because this is a pooled analysis of selected studies without a systematic review, the quality of this study is undetermined and the results should be interpreted with caution.

Colorectal cancer

A nested case control study of 4432 cases and 44 292 controls from the General Practice Research Database (UK) evaluated the association between duration of proton pump inhibitor use and incidence of colorectal cancer.[262] While multiple durations of exposure were examined, the one showing a statistically significant increased risk was diagnosis of colorectal cancer with less than 1 year exposure to a proton pump inhibitor with an adjusted odds ratio of 2.6 (95% CI 2.3 to 2.9). Less than 1 year of exposure, more than 12 months prior to the index date, and 1 to 2, 2 to 3, 3 to 4, 4 to 5, or >5 years of proton pump inhibitor use were not statistically significantly associated with colorectal cancer. The adjusted odds ratio for ≥5 years of proton pump inhibitor exposure was 1.1 (95% CI 0.7 to 1.9). Among high-dose proton pump inhibitor users (≥1.5 defined daily doses/day), there was a nonstatistically significant trend toward an increased risk with increasing duration of use (test for trend, P=0.2).

Serum gastrin levels

Serum gastrin level were monitored in several studies and found to be significantly elevated above baseline although the magnitude of increase was small and generally not considered clinically significant. A dose-related difference was found in some studies, but there were no differences between different proton pump inhibitors. Likewise, when studied, the effect of different proton pump inhibitors on *Helicobacter pylori*-related gastritis was similar, worsening gastritis in the corpus and improving gastritis in the antrum.[263]

Adverse events in children

Reporting of adverse events in children was limited to short-term trials and 2 open-label uncontrolled studies with longer follow-up.[264, 87, 88, 188, 189, 209-212 265] In short-term trials of omeprazole no serious adverse events were reported.[87, 209, 214]

Lansoprazole was studied in infants and neonates in 2 similar trials of children with symptoms of gastroesophageal reflux disease. [265] The infants, age > 28 days by but < 1 year, were given a suspension of lansoprazole dosed at 1 or 2 mg/kg/day and the neonates (up to 28 days after birth) were given 0.5 to 1.0 mg/kg/day for 5 days. Twenty-four neonates and 24 infants were enrolled. Mean age in the infant group was 24 weeks, and 3.7 weeks in the neonate group. While most neonates were white, 50% of the infants were black. While a large number of

adverse events were reported (58%) 4 in the neonates (8%), and 1 in the infant group (4%) were considered related to the drug. In neonates, the adverse events were anemia, flushing (2 patients), and elevated aspartate aminotransferase level and were considered mild or moderate in severity. One infant also had elevated an aspartate aminotransferase level. The increases in aspartate aminotransferase occurred in the higher dose groups for each age group (0.5 and 2.0 mg/kg/day, respectively).

A retrospective chart review of 113 children identified from a registry-type database examined children with erosive esophagitis who received a proton pump inhibitor for at least 1 year.[264] The majority (66%) was taking lansoprazole, followed by omeprazole (22%), and few were taking pantoprazole, rabeprazole, or esomeprazole. Overall, 88% of the children had no adverse event while taking a proton pump inhibitor, with a range of 80% to 100% for specific proton pump inhibitors. The most frequent adverse events recorded in patients' charts were constipation (4%) and diarrhea (5%). Serum gastrin level was elevated (>90 pg/mL) in 73% of children, with no statistically significant differences by specific proton pump inhibitor, dose, dosing frequency, or treatment duration. No elevation in liver enzymes was reported.

In a before-after study of omeprazole for esophageal reflux, 15 children were followed for a mean of 12 months. Seven (47%) had elevation of liver enzymes. Eleven (73%) had hypergastrinemia.[213] A short-term before-after study of pantoprazole reported elevated liver enzymes in 1 of 18 children exposed for 28 days and 5 of 18 (28%) had hypergastrinemia.[211] In a 2-week study of lansoprazole in children (mean age 11 years) only mild gastric adverse events were reported.[212]

Two short-term trials compared lower dose and higher dose esomeprazole in children with gastroesophageal reflux disease. These trials made no comparison to placebo or other drugs. In 148 adolescents aged 12 to 17 years assigned 20 or 40 mg esomeprazole daily for 8 weeks, 15% experienced an adverse event considered related to esomeprazole; headache (8%), abdominal pain (3%), nausea (2%), and diarrhea (2%).[266] In 108 younger children, aged 1 to 11 years, who were assigned to 5 or 10 mg esomeprazole if weight < 20 Kg or 10 or 20 mg if weight > 20 Kg, 9% reported an adverse event considered related to esomeprazole; diarrhea (2.8%), headache (1.9%), and somnolence (1.9%).[267] Serious adverse events thought to be related to esomeprazole were not reported in either study.

Key Question 7. Are there subgroups of patients based on demographics, other medications, or comorbidities for which a particular medication or preparation is more effective or associated with fewer adverse effects?

Summary

- Head-to-head comparison studies did not adequately describe or analyze subgroups for differences in effectiveness. However, 2 studies assessed adverse effects in subgroups of age, gender, and race and found no difference among groups.
- Studies suggested that a lower dose of proton pump inhibitor 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% to 25% of Asians). Only 1 of these studies was a head-to-head comparison, omeprazole compared with lansoprazole, but no difference was found between the drugs.

- While the effects of the proton pump inhibitors may differ by demographics, there was inadequate data to identify any of these differences.
- Based on a cohort study of more than 8000 patients, use of a proton pump inhibitor concomitant with clopidogrel following acute coronary syndrome increased the risk of death or rehospitalization for acute coronary syndrome with adjusted odds ratio of 1.25 (95% CI 1.11 to 1.41).
    - Similarly, use of a proton pump inhibitor concomitant with clopidogrel following acute myocardial infarction can increase the risk of readmission for recurrent myocardial infarction within 90 days with adjusted odds ratio 1.27 (95% CI 1.03 to 1.57) based on a smaller nested case-control study of 734 cases and 2057 controls. Analysis of the subgroup taking pantoprazole indicated no increased risk, while analysis of the other proton pump inhibitors (as a group) indicated a similar increase in risk.

Detailed Assessment

Age and sex

In included head-to-head studies, the enrolled patients were middle aged, with mean ages ranging from 43[268] to 70[162] years. From 38% to 89% of the patients were male. The ethnicity of participants was stated in only 5 trials.[4, 25, 75, 108, 268] The majority of studies included mostly white populations. In those studies with greater variation subgroups were too small for meaningful analyses by racial or ethnic group.

An open-label, single-center trial conducted in 320 patients over age 65 compared 4 proton pump inhibitors for healing and symptom resolution in erosive esophagitis.[269] This was the only head-to-head trial conducted exclusively in elderly patients. The mean age of the group was 77.4 years (standard deviation 7.9 years, range 65-93 years). Nineteen patients withdrew from the study (5.9%), 2 due to adverse events. Patients were randomized to omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, or rabeprazole 20 mg. After 8 weeks of treatment, the healing rate in the overall group was 85% (intention-to-treat). Healing rates in the pantoprazole (90%) and rabeprazole (89%) groups were significantly higher than the omeprazole group (75%; P=0.022 and P=0.040, respectively). No difference was found between omeprazole and lansoprazole (75% and 85%; P=NS). Pantoprazole and rabeprazole were also superior to omeprazole and to lansoprazole for resolution of heartburn (rates 100% for pantoprazole and rabeprazole, 87% for omeprazole, and 82% for lansoprazole). The frequency of adverse events was low (4 patients; 1.3%), and there were no differences between treatment groups in the prevalence of adverse events.

There was 1 small, 12-month, placebo-controlled trial in which pantoprazole 20 mg was effective for maintenance treatment of gastroesophageal reflux disease in patients age 65 or older.[270] 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, 2 trials did assess the impact of age, gender, and race on the incidence of adverse effects.[5, 106] There were no differences between proton pump inhibitors (omeprazole, rabeprazole, esomeprazole) on the basis of these characteristics. The effect of age on eradication rate was also evaluated.[198] This study found higher eradication rates among patients older than 50 years than patients younger than 50, but proton pump inhibitors were not compared.

In trials comparing a proton pump inhibitor with another drug, the same general statements can be made, but a few findings deserve comment. Studies looking at healing or prevention of nonsteroidal anti-inflammatory drug-induced ulcer included more women than men, with the proportion of women ranging from 62% to 67% and 64% to 83% in the respective types of study. This is most likely due to the greater prevalence among women of diseases requiring long-term nonsteroidal anti-inflammatory drug treatment. However, no gender-based analyses were presented.

Genotype

The proton pump inhibitors are all metabolized, largely by the CYP2C19 and CYP3A4 liver enzymes. Theses enzymes are estimated to be deficient in 3% of white and African Americans and 17% to 25% of Asians. The deficiency results in a significantly longer half-life of proton pump inhibitors, 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[184, 271] and that rapid metabolizers may have a higher rate of failure to eradicate *Helicobacter pylori*[176, 177, 187] and to heal esophagitis.[272] Subgroup analysis found no effect by race in 1 study of esomeprazole and lansoprazole in healing of erosive esophagitis.[4] A small study (N=80) found no statistically significant difference at 8 weeks in rate of ulcer healing between rabeprazole 10 mg daily and omeprazole 20 mg daily among patients with differing CYP2C19 genotype.[108] The few adverse events were not analyzed by genotype. A trial of omeprazole in Japanese patients with recurrent esophagitis found no difference in efficacy or safety by genotype.[273]

Older patients also metabolize proton pump inhibitors more slowly, resulting in significantly higher drug levels and half-lifes. However, accumulation has not been shown, and dose adjustments are not recommended. One reanalysis of data from 2 trials comparing omeprazole with either ranitidine or cimetidine for reflux esophagitis compared effect in patients age 65 or older with those under age 65.[274] In this analysis there was no difference in healing rate or symptom resolution at 4 or 8 weeks, with a slightly higher proportion of older patients both healed and symptom-free. Withdrawals due to adverse event were higher in the older group, 7.6% compared with 2.5%. Similar data are not available for other proton pump inhibitors.

Comorbidity

In an uncontrolled, non-randomized open-label study, patients with peptic ulcer and comorbid liver disease were given 6 to 8 weeks of rabeprazole 10 mg to 20 mg.[275] Eleven of 108 patients (10%) reported 21 adverse drug events, resulting in 5 withdrawals (5%) and an additional 5 patients with an adverse event were lost to follow up. Two patients (2%) had adverse events that were rated as serious, 1 had an elevated bilirubin level, and the other had hepatic encephalopathy. Analysis by dose was not conducted.

Concomitant medications

Two good quality observational studies assessed the impact of a potential drug interaction between proton pump inhibitors and clopidogrel following an acute coronary syndrome (ACS).[276, 277] Clopidogrel is activated by a liver enzyme system known as P450 C19, and proton pump inhibitors can inhibit this system. A cohort study of 8205 patients who were discharged after an ACS and were prescribed clopidogrel between October 2003 and January 2006 were examined to

determine if the rate of death or rehospitalization for ACS was affected by concomitant use of a proton pump inhibitor.[276] Of these patients, 64% were prescribed a proton pump inhibitor. Multivariable analysis found that there was an increased risk of death or rehospitalization for ACS in those patients taking both clopidogrel and a proton pump inhibitor; adjusted odds ratio 1.25 (95% CI 1.11 to 1.41). The analysis controlled for multiple variables, included demographic characteristics, comorbidities, previous cardiac history, and other medications. In patients who had period with and without a proton pump inhibitor, but continued clopidogrel use, the risk of the primary outcome was also increased during the proton pump inhibitor periods; adjusted odds ratio 1.27 (95% CI 1.10 to 1.46). In addition to the primary outcome, secondary outcomes were evaluated. The risk of rehospitalization for ACS was increased (adjusted odds ratio 1.86 95% CI 1.57 to 2.20); the risk of a revascularization procedure was increased (adjusted odds ratio 1.49 95% CI 1.30 to 1.71); however risk of all-cause mortality was not significantly increased (adjusted odds ratio 0.91 95% CI 0.80 to 1.05). The authors also conducted a nested case-control analysis with these data in an attempt to confirm their findings, resulting in an adjusted odds ratio of 1.32 (95% CI 1.1.4 to 1.54) for the risk of death or rehospitalization for ACS. Multiple sensitivity analyses were conducted, with no meaningful change to the results. This study was conducted using data from the Veteran's Affairs hospitals, and no patients were taking esomeprazole. Too few patients were taking pantoprazole or lansoprazole to be able to conduct individual analyses, but omeprazole and rabeprazole resulted in increased adjusted odds ratios for the primary outcome (adjusted odds ratios: 1.24 95% CI 1.08 to 1.41 for omeprazole, N=3132; 2.83 95% CI 1.96 to 4.04, N=151 for rabeprazole). Analysis by dose of proton pump inhibitor indicated did not indicate a dose-response relationship.

A population-based nested case-control study examined data from all patients in Ontario, Canada who were prescribed clopidogrel after hospital discharge following a myocardial infarction between April 2002 and December 2007.[277] In this study, 13 636 patients were identified. Among this group, cases were identified as patients who were rehospitalized for myocardial infarction within 90 days of discharge (N=734), while controls were those who were not. Controls were identified in a 3:1 ratio to cases and matched on age, percutaneous coronary intervention, and a validated risk score (N=2057). Proton pump inhibitor exposure was defined as current (within 30 days of rehospitalization), previous (31 to 90 days) or remote (91 to 180 days). The logistic regression analysis controlled for demographic variables, socioeconomic status, Charlson comorbidity index, length of stay during initial admission for myocardial infarction, and 9 comorbid conditions (for example diabetes). A similar adjusted odds ratio was found in this study as the cohort study; 1.27 (95% CI 1.03 to 1.57) for current users of a proton pump inhibitor. Previous or remote use was not associated with an increased risk of recurrent myocardial infarction. All-cause mortality was again not affected statistically significantly (adjusted odds ratio 0.82 95% CI 0.57 to 1.18). Analysis of recurrent myocardial infarction within 1 year of initial discharge also indicated an increased risk with current proton pump inhibitor use; odds ratio 1.23 (95% CI 1.01 to 1.49). Because pantoprazole does not inhibit the P450 2C19 enzyme system responsible for activation of clopidogrel, it has been suggested that it may not result in a clinically-relevant drug interaction. An analysis of pantoprazole alone (N=cases 46, controls 125) found no statistically significant increase in risk (adjusted odds ratio 1.02 95% CI 0.70 to 1.47). Analysis of all other proton pump inhibitors (which inhibit the P450 2C19 enzyme system to varying degrees) together resulted in increased risk; adjusted odds ratio 1.40 (95% CI 1.10 to 1.77; N=cases 148, controls 299). Analysis stratified further by individual proton pump inhibitor was not undertaken; insufficient data may have prevented such analysis.

Because these are post-hoc sub-group analyses of small groups, further research is needed to confirm these findings.

Pregnancy

A multicenter, prospective cohort study enrolled 410 pregnant women who had sought counseling after exposure to omeprazole (N=295), lansoprazole (N=62), or pantoprazole (N=53) between 1992 and 2001.[278] Details of exposure were collected during pregnancy before pregnancy outcome was known, and follow-up was performed in the neonatal period. A control group of 868 women who had been counseled during pregnancy about exposures known to be nonteratogenic served as a control group. There were some differences between control and treatment groups at baseline (for example, number of children was larger in then treatment than the control group), and confounders were not controlled for in the analysis. There was a higher rate of elective termination of pregnancy in the omeprazole and lansoprazole groups than the control group. Two of these terminations in the omeprazole group, 1 in the lansoprazole group, 0 in the pantoprazole group, and 5 in the control group were because of prenatal diagnosis of anomalies. There was no difference in the rate of major anomaly between each of the 3 groups and the control group; the relative risk was 0.95 (95% CI 0.46 to 1.98) for omeprazole, 1.04 (95% CI 0.25 to 4.21) for lansoprazole, and 0.55 (95% CI 0.08 to 3.95) for pantoprazole. Median birth weight was lower by 60 grams in the omeprazole group than the control group, but no difference was seen between groups for median gestational age at delivery or rates of preterm birth, miscarriage, ectopic pregnancy, or stillbirth.

Applicability

Applicability of most trials to community practice was difficult to determine. These studies generally excluded patients who had serious medical conditions. In addition, although most treatment and control groups received standard doses of anti-ulcer drug, there were instances where doses were higher or lower than typical. In trials comparing maintenance treatment or different strategies for longer-term treatment of gastroesophageal reflux disease, patients were enrolled on the basis of a successful response to acute treatment. This preselection may have resulted in a group of patients who were adherent to treatment, who were able to tolerate any side effects, and whose disease was less severe in comparison with patients who were not enrolled. Another concern is that of studies that stated their funding source, most were funded by the pharmaceutical industry, and industry employees often served as co-authors.

SUMMARY

Table 17 summarizes the evidence for this report.

Table 1. Summary table

Key Question	Strength of evidence	Conclusion
Key Question 1. Gastroesophageal reflux disease, short-term efficacy		
Erosive gastroesophageal reflux disease: Symptoms	Good	In 16 head-to-head trials, the only difference between proton pump inhibitors on the outcome of complete

Key Question	Strength of evidence	Conclusion
		symptom relief at 4 weeks was in the comparison of esomeprazole 40 mg with omeprazole 20 mg; the pooled risk difference in 3 trials was 8% (95% CI 3 to 13), with a number needed to treat of 13. Time to relief of heartburn was similar for all proton pump inhibitors in head-to-head trials, but the methods used to measure and report this outcome varied in the 14 studies.
Erosive gastroesophageal reflux disease: Esophagitis healing	Good	Good evidence shows no difference between omeprazole, lansoprazole, pantoprazole, and rabeprazole for healing of esophagitis. Thirteen head-to-head trials found these 4 proton pump inhibitors to be equally effective in healing at 4 and 8 weeks. Pooled analysis of 4- and 8-week healing rates from 4 trials of esomeprazole 40 mg compared to omeprazole 20 mg indicate esomeprazole to be superior; risk difference 7% (95% CI 1 to 12) and a number needed to treat of 14 and 5% (95% CI 1 to 9), number needed to treat = 20, respectively. Three trials compared esomeprazole 40 mg with lansoprazole 30 mg. The pooled difference in healing rate was significantly greater with esomeprazole at 4 and 8 weeks, risk differences 5% (95% CI 2 to 7) and 3% (95% CI 1 to 5), respectively. Four trials compared esomeprazole 40 mg and pantoprazole 40 mg. Pooled difference in healing rate was significantly greater with esomeprazole at 4 weeks, but not at 8 weeks, risk differences 5% (95% CI 2 to 8) and 1% (95% CI –3 to 5).
Healing in moderate to severe erosive esophagitis	Fair	Esomeprazole 40 mg was more effective at healing esophagitis at 4 and 8 weeks than omeprazole 20 mg and lansoprazole 30 mg. The pooled risk difference in 3 studies comparing omeprazole 20 mg with esomeprazole 40 mg was 16% at 4 weeks and 13% at 8 weeks (number needed to treat = 6 at 4 weeks, 8 at 8 weeks).The pooled risk difference in 2 studies comparing lansoprazole 30 mg with esomeprazole 40 mg was 8% at 4 weeks and 9% at 8 weeks (number needed to treat = 13 at 4 weeks, 11 at 8 weeks). Evidence is mixed on differences between esomeprazole 40 mg and pantoprazole 40 mg. At 4 weeks, esomeprazole 40 mg had a higher healing rate \than pantoprazole 40 mg - pooled risk difference (2 studies), 14% (95% CI 7 to 20). At 8 weeks, no difference was found in a single small study. Lansoprazole 30 mg (2 studies) and esomeprazole 20 mg (1 study) were no different to omeprazole 20 mg at 4 or 8 weeks.
Erosive gastroesophageal reflux disease: Prevention of relapse	Good	For maintenance of healed esophagitis, there is good evidence that no difference exists between omeprazole, lansoprazole, and rabeprazole. The longest study (over 5 years) compared omeprazole with rabeprazole. No difference was found between esomeprazole 20 mg and pantoprazole 20 mg in combined symptomatic and endoscopic remission rates after 6 months. Esomeprazole 20 mg was found to have lower relapse rates than pantoprazole 20 mg in 2 6-month studies.
Non-erosive or empirically-treated gastroesophageal reflux	Fair	Three head-to-head trials in patients with endoscopy-negative gastroesophageal reflux disease found no

Key Question	Strength of evidence	Conclusion
disease: Symptoms		difference between esomeprazole 20 mg and omeprazole 20 mg, pantoprazole 20 mg, and rabeprazole 10 mg. These studies used different outcome measures. Limited indirect evidence from placebo- and active-controlled trials suggests similar efficacy for heartburn resolution and complete symptom relief for the 5 proton pump inhibitors.
Non-erosive or empirically-treated gastroesophageal reflux disease: Prevention of relapse	Fair to Poor	In a 6-month head-to-head trial of on-demand esomeprazole compared with daily lansoprazole 15 mg, more patients discontinued lansoprazole.. On-demand rabeprazole 10 mg, on-demand esomeprazole 20 mg, and daily omeprazole 10 mg were more effective than placebo in prevention of relapse of symptoms over 6 months in patients with endoscopy negative gastroesophageal reflux disease.
Gastroesophageal reflux disease: Evidence in Children	Poor	There are no direct comparisons of proton pump inhibitors for reflux esophagitis in children. A fair quality placebo-controlled trial in infants did not find omeprazole to be superior to placebo.
Key Questions 2, 3, 4. Peptic ulcer, *Helicobacter pylori* eradication		
Duodenal Ulcer	Fair	All newer proton pump inhibitors have been compared to omeprazole. The evidence from 10 head to head trials suggests no difference between the proton pump inhibitors in healing rates or symptom relief.
Gastric Ulcer	Fair	Three head-to-head studies were found, comparing rabeprazole to omeprazole. No significant differences in healing rate was found. Minor improvements in symptom relief were found with a higher dose of rabeprazole (20 mg) compared to omeprazole 20 mg, but not with a lower dose (rabeprazole 10 mg). There are no other direct comparisons.
Nonsteroidal anti-inflammatory drug-induced ulcer	Poor	No head-to-head studies. In trials of omeprazole and lansoprazole compared with ranitidine, no difference in healing rates or symptom resolution rates were apparent.
Prevention of nonsteroidal anti-inflammatory drug induced ulcer	Poor	Direct comparison of pantoprazole 20 mg, 40 mg and omeprazole 20 mg daily did not indicate statistically significant differences in rates of therapeutic or endoscopic failure at 6 months in a group of patients taking nonsteroidal anti-inflammatory drugs regularly for arthritic conditions. There are no other direct comparisons.
Eradication of *Helicobacter pylori*	Fair	Five fair quality systematic reviews and 29 more recent trials indicate that eradication rates among the proton pump inhibitors do not differ significantly. Pooled analysis of eradication rates stratified by number of days of treatment and dose comparison did not find statistically significant differences in eradication rate among the proton pump inhibitors. Differences between the antibiotic regimens, participants and study designs limit the strength of this evidence. In children, evidence is extremely limited, with only 2 trials of lansoprazole versus placebo. Neither trial found the addition of lansoprazole to result in higher eradication rates than antibiotic therapy alone.

Key Question	Strength of evidence	Conclusion
Key Question 5. Dosing strategies for maintenance therapy in gastroesophageal reflux disease		
Standard dose compared with low-dose proton pump inhibitor	Good	Based on 11 studies, time in remission was longer for higher doses compared with lower doses for omeprazole and rabeprazole, but the same for higher and lower doses of lansoprazole. Evidence on esomeprazole was inconclusive. Rates of endoscopically verified remission at study end were greater with the higher dose of rabeprazole compared with the lower dose, but no different between dose strategies for omeprazole and lansoprazole. Rates of relapse of symptoms were generally higher with lower doses of omeprazole, lansoprazole, and rabeprazole.
Standard dose compared with intermittent or on-demand proton pump inhibitor	Fair	In 3 studies of patients with healed erosive esophagitis, a regimen of daily proton pump inhibitor was superior in preventing relapse of esophagitis or recurrence of symptoms compared with 3 days a week or on-demand regimens at 6 months. In 3 studies of patients with nonerosive esophagitis, assessments of symptom severity or relapse of symptoms was not different between daily and on-demand regimens. Patient satisfaction and quality of life ratings at study end were also not different, although the mean change in quality of life score from baseline was better with daily therapy. In 2 studies of patients presenting with symptoms of gastroesophageal reflux disease, but without endoscopic assessment, evidence is mixed.
Proton pump inhibitor compared with H2 receptor antagonist	Fair	Daily proton pump inhibitor therapy was found superior to daily H2 antagonist therapy (rantidine 300 mg daily) in preventing relapse of erosive esophagitis, or symptoms of gastroesophageal reflux disease in 4 studies. In children, at 3 months omeprazole 0.7 mg/kg daily was not different to ranitidine 10 mg/kg daily or placebo.
Key Question 6. Adverse events		
Long-term studies	Comparative evidence = Poor	Three comparative trials. Evidence from single-drug follow-up studies indicates no differences between the proton pump inhibitors. A pharmacovigilance study found increased risk of adverse events related to specific PPIs – study limitations indicate a need for further study. Noncomparative evidence indicates a potential for increased risk of colorectal cancer (1 study), clostridium difficile diarrhea (2 studies), and fracture (4 studies). Mixed evidence was found on the risk of community acquired pneumonia with proton pump inhibitor use.
Short-term studies	Fair	Evidence from short-term head-to-head comparison trials does not indicate a difference in the rate of overall adverse events, serious adverse events or the rate of dropouts due to adverse events. These studies are very short-term and include highly selected patient populations; evidence may not be generalizable to patients with co-morbidities and longer-term treatment.

Key Question	Strength of evidence	Conclusion
Key Question 7. Subpopulations		
	Fair	2 studies found no difference in adverse effects in subgroups of age, gender, and racial groups A single open-label study of 320 patients with mean age of 77 years with erosive esophagitis found that that pantoprazole 40 mg and rabeprazole 20 mg were superior to omeprazole 20 mg in healing rate at 8 weeks, no difference compared to lansoprazole 30 mg. Pantoprazole and rabeprazole were superior to both omeprazole and lansoprazole in symptom relief at 8 weeks. These results differ to those found in younger populations and need confirmation. Based on a cohort study of more than 8000 patients, use of a proton pump inhibitor concomitant with clopidogrel following acute coronary syndrome can increase the risk of death or rehospitalization for acute coronary syndrome with adjusted odds ratio of 1.25 (95% CI 1.11 to 1.41). Similarly, use of a proton pump inhibitor concomitant with clopidogrel following acute myocardial infarction can increase the risk of readmission for recurrent myocardial infarction within 90 days with adjusted odds ratio 1.27 (95% CI 1.03 to 1.57) based on a smaller nested case-control study of 734 cases and 2057 controls. Analysis of the subgroup taking pantoprazole indicated no increased risk, while analysis of the other proton pump inhibitors (as a group) indicated a similar increase in risk. No other comparative evidence in subgroups.

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Appendix A. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

Absolute risk: The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

Add-on therapy: An additional treatment used in conjunction with the primary or initial treatment.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse drug reaction: An adverse effect specifically associated with a drug.

Adverse event: A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

Adverse effect: An **adverse event** for which the causal relation between the intervention and the event is at least a reasonable possibility.

Active-control trial: A trial comparing a drug in a particular class or group with a drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Applicability: see *External Validity*

Before-after study: A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Bioequivalence: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

Black box warning: A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The U.S. Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

Blinding: A way of making sure that the people involved in a research study — participants, clinicians, or researchers —do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an

illness. Blinding is used to make sure that knowing the type of treatment does not affect a participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinical diversity: Differences between studies in key characteristics of the participants, interventions or outcome measures.

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Combination Therapy: The use of two or more therapies and especially drugs to treat a disease or condition.

Confidence interval: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report was hypothetically repeated on a collection of 100 random samples of studies, the resulting 100 95% confidence intervals would include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Control group: In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Crossover trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

Dosage form: The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage

forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

Effectiveness: The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

Effectiveness outcomes: Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a "real-world" population.

Effect size/estimate of effect: The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

Efficacy: The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

Equivalence level: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

Exclusion criteria: The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

External validity: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Fixed-dose combination product: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: See *External Validity.*

Half- life: The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See *Adverse Event*

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group with another in the same class or group.

Health outcome: The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

I^2: A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I^2 suggest heterogeneity. I^2 is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as (Q-(n-1))/Q, where n is the number of studies.

Incidence: The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

Indication: A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

Intention to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intention to treat despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the interval validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (hear attack).

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Masking: See *Blinding*

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Mixed treatment comparison meta analysis: A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

Monotherapy: the use of a single drug to treat a particular disorder or disease.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N-of-1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Noninferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Nonrandomized study: Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

Null hypothesis: The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

Number needed to harm: The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

Number needed to treat: An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

Observational study: A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

Off-label use: When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

Outcome: The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the effectiveness of care/ treatment/ rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Outcome measure: Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

One-tailed test (one-sided test): A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intention-to-treat analyses.

Pharmacokinetics: the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

Placebo: An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

Placebo controlled trial: A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo controlled clinical

trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

Point estimate: The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

Pooling: The practice of combing data from several studies to draw conclusions about treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Prevalence: How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

Probability: The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤ 0.05 is often used as a threshold to indicate statistical significance.

Q-statistic: A measure of statistical heterogeneity of the estimates of effect from studies. Large values of Q suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk: A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Risk difference: The difference in size of risk between two groups.

Risk Factor: A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

Run-in period: Run in period: A period before randomization when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

Safety: Substantive evidence of an absence of harm. This term (or the term ‘‘safe’’) should not be used when evidence on harms is simply absent or is insufficient.

Sample size: The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how

robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Side effect: Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Standard treatment: The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

Statistically significant: A result that is unlikely to have happened by chance.

Study: A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

Study population: The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Superiority trial: A trial designed to test whether one intervention is superior to another.

Surrogate outcome: Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

Survival analysis: Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Tolerability: For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected.

The extent to which a drug’s adverse effects impact the patient’s ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

Treatment regimen: The magnitude of effect of a treatment versus no treatment or placebo; similar to "effect size". Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

Two-tailed test (two-sided test): A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Variable: A measurable attribute that varies over time or between individuals. Variables can be

- *Discrete*: taking values from a finite set of possible values (e.g. race or ethnicity)
- *Ordinal*: taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)
- *Continuous:* taking values on a continuum (e.g. hemoglobin A1c values).

Washout period: [In a cross-over trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

Appendix B. Search strategies

Search strategies: Update 4

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2005>
Search Strategy:
---
1 (gastroesophageal reflux or gerd).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1077)
2 (gastrooesophageal reflux or gord).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (87)
3 1 or 2 (1094)
4 (peptic ulcer$ or stomach ulcer$ or gastric ulcer$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (3038)
5 3 or 4 (4097)
6 (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (2632)
7 (proton pump$ adj3 (antagon$ or inhibit$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (616)
8 6 or 7 (2729)
9 5 and 8 (917)
10 from 9 keep 1-917 (917)

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

Database: Ovid MEDLINE(R) <1996 to November Week 3 2005>
Search Strategy:
---
1 Gastroesophageal reflux/ or "gerd".mp. (7177)
2 exp peptic ulcer/ or "peptic ulcer".mp. (11820)
3 1 or 2 (18234)
4 Proton pump/ai (2118)
5 proton pump inhibitor$.mp. (2872)
6 (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. (4884)
7 4 or 5 or 6 (6850)
8 3 and 7 (3592)
9 limit 8 to (humans and english language) (2806)
10 limit 9 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial) (947)
11 exp clinical trials/ or clinical trial$.mp. (115736)
12 exp epidemiologic research design/ (288078)
13 observational stud$.mp. (9134)
14 11 or 12 or 13 (394813)
15 9 and 14 (784)
16 10 or 15 (1303)
17 limit 16 to yr="2005 - 2006" (107)
18 from 17 keep 1-107 (107)

Database: Ovid MEDLINE(R) <1996 to November Week 3 2005>
Search Strategy:
---
1 Gastroesophageal reflux/ or "gerd".mp. (7177)
2 exp peptic ulcer/ or "peptic ulcer".mp. (11820)
3 1 or 2 (18234)
4 Proton pump/ai (2118)
5 proton pump inhibitor$.mp. (2872)
6 (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. (4884)
7 4 or 5 or 6 (6850)
8 3 and 7 (3592)
9 limit 8 to (humans and english language) (2806)
10 limit 9 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial) (947)
11 exp clinical trials/ or clinical trial$.mp. (115736)
12 exp epidemiologic research design/ (288078)
13 observational stud$.mp. (9134)
14 11 or 12 or 13 (394813)
15 9 and 14 (784)
16 10 or 15 (1303)
17 limit 16 to yr="2003 - 2006" (409)
18 from 17 keep 1-409 (409)

Search strategies: Update 5

Database: Ovid MEDLINE(R) <1996 to September Week 3 2008>

Search Strategy:

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1 Gastroesophageal reflux/ or "gerd".mp. (10132)

2 exp peptic ulcer/ or "peptic ulcer".mp. (14612)

3 1 or 2 (23718)

4 Proton pump/ai (2933)

5 proton pump inhibitor$.mp. (4290)

6 (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. (6320)

7 6 or 4 or 5 (9389)

8 3 and 7 (4804)

9 limit 8 to (english language and humans) (3761)

10 limit 9 to (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial) (1198)

11 exp clinical trials/ or clinical trial$.mp. (371808)

12 exp epidemiologic research design/ (415174)

13 observational stud$.mp. (15812)

14 11 or 13 or 12 (717226)

15 9 and 14 (1429)

16 10 or 15 (1579)

17 (200511$ or 200512$ or 2006$ or 2007$ or 2008$).ed. (1896250)

18 16 and 17 (338)

19 from 18 keep 1-338 (338)

Database: Ovid MEDLINE(R) <1996 to November Week 2 2008>

Search Strategy:

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1 Gastroesophageal reflux/ or "gerd".mp. (10279)

2 exp peptic ulcer/ or "peptic ulcer".mp. (14721)

3 1 or 2 (23966)

4 Proton pump/ai (2938)

5 proton pump inhibitor$.mp. (4383)

6 (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. (6390)

7 6 or 4 or 5 (9527)

8 3 and 7 (4860)

9 limit 8 to (english language and humans) (3807)

10 limit 9 to (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial) (1210)

11 exp clinical trials/ or clinical trial$.mp. (375693)

12 exp epidemiologic research design/ (422624)

13 observational stud$.mp. (16191)

14 11 or 13 or 12 (728308)

15 9 and 14 (1444)

16 10 or 15 (1598)

17 (200808$ or 200809$ or 20081$).ed. (201730)

18 16 and 17 (32)

19 from 18 keep 1-32 (32)

Database: Ovid MEDLINE(R) <1996 to March Week 4 2009>

Search Strategy:

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1 Gastroesophageal reflux/ or "gerd".mp. (10634)

2 exp peptic ulcer/ or "peptic ulcer".mp. (15042)

3 1 or 2 (24624)

4 Proton pump/ai (2941)

5 proton pump inhibitor$.mp. (4624)

6 (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. (6556)

7 6 or 4 or 5 (9863)

8 3 and 7 (5010)

9 limit 8 to (english language and humans) (3919)

10 limit 9 to (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial) (1240)

11 exp clinical trials/ or clinical trial$.mp. (384769)

12 exp epidemiologic research design/ (439367)

13 observational stud$.mp. (17227)

14 11 or 13 or 12 (753726)

15 9 and 14 (1478)

16 10 or 15 (1640)

17 (200811$ or 200812$ or 2009$).ed. (267578)

18 16 and 17 (43)

19 from 18 keep 1-43 (43)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2009>

Search Strategy:

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1 (gastroesophageal reflux or gerd).mp. (1361)

2 (gastrooesophageal reflux or gord).mp. (111)

3 1 or 2 (1385)

4 (peptic ulcer$ or stomach ulcer$ or gastric ulcer$).mp. (3261)

5 3 or 4 (4607)

6 (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. (3146)

7 (proton pump$ adj3 (antagon$ or inhibit$)).mp. (837)

8 6 or 7 (3296)

9 5 and 8 (1156)

10 limit 9 to yr="2005 -Current" (257)

11 from 10 keep 1-257 (257)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <1st Quarter 2009>

Search Strategy:

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1 (gastroesophageal reflux or gerd).mp. (43)
2 (gastrooesophageal reflux or gord).mp. (17)
3 1 or 2 (49)
4 (peptic ulcer$ or stomach ulcer$ or gastric ulcer$).mp. (103)
5 3 or 4 (145)
6 (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. (31)
7 (proton pump$ adj3 (antagon$ or inhibit$)).mp. (42)
8 6 or 7 (51)
9 5 and 8 (35)
10 limit 9 to yr="2005 -Current" (31)
11 from 10 keep 1-31 (31)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2009>
Search Strategy:

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1 (gastroesophageal reflux or gerd).mp. (43)
2 (gastrooesophageal reflux or gord).mp. (5)
3 1 or 2 (43)
4 (peptic ulcer$ or stomach ulcer$ or gastric ulcer$).mp. (77)
5 3 or 4 (113)
6 (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. (78)
7 (proton pump$ adj3 (antagon$ or inhibit$)).mp. (86)
8 6 or 7 (110)
9 5 and 8 (68)
10 limit 9 to yr="2005 -Current" [Limit not valid; records were retained] (68)
11 from 10 keep 1-68 (68)

Appendix C. Excluded studies

Exclusion codes
1 = foreign language
2 = wrong outcome
3 = wrong drug
4 = wrong population
5 = wrong publication type
6 = wrong study design

Excluded studies	Exclusion code
Head-to-head trials	
Bigard MA, Genestin E. Treatment of patients with heartburn without endoscopic evaluation: on-demand treatment after effective continuous administration of lansoprazole 15 mg. Alimentary Pharmacology & Therapeutics. Oct 1 2005;22(7):635-643.	6
Castell D, Bagin R, Goldlust B, Major J, Hepburn B. Comparison of the effects of immediate-release omeprazole powder for oral suspension and pantoprazole delayed-release tablets on nocturnal acid breakthrough in patients with symptomatic gastro-esophageal reflux disease. Alimentary pharmacology & therapeutics. Jun 15 2005;21(12):1467-1474.	4
Frazzoni M, De Micheli E, Grisendi A, Savarino V. Effective intra-oesophageal acid suppression in patients with gastro-esophageal reflux disease: lansoprazole vs. pantoprazole. - Alimentary Pharmacology & Therapeutics. 17(2):235-41, 2003 Jan. 2003.	4
Janczewska I, Sagar M, Sjostedt S, Hammarlund B, Iwarzon M, Seensalu R. Comparison of the effect of lansoprazole and omeprazole on intragastric acidity and gastroesophageal reflux in patients with gastroesophageal reflux disease. Scandinavian Journal of Gastroenterology. 1998;33:1239-1243.	4
Johnson M, Guilford S, Libretto SE. Patients have treatment preferences: A multicentre, double-blind, crossover study comparing rabeprazole and omeprazole. Current Medical Research & Opinion. 2002;18(5):303-310.	6
Kumar R, Tandon VR, Bano G, et al. Comparative study of proton pump inhibitors for triple therapy in H. pylori eradication. Indian J Gastroenterol. Mar-Apr 2007;26(2):100-101.	5
Kuwayama H, Luk G, Yoshida S, et al. Efficacy of a low-dose omeprazole-based triple-therapy regimen for Helicobacter pylori eradication independent of cytochrome P450 genotype: The Japanese MACH study. Clinical Drug Investigation. 2005;25(5):293-305.	6
Labenz J, Tillenburg B, Peitz U, et al. Helicobacter pylori augments the pH-increasing effect of omeprazole in patients with duodenal ulcer. Gastroenterology. 1996;110(3):725-732.	2

Lind T, Rydberg L, Kyleback A, et al. Esomeprazole provides improved acid control vs. omeprazole in patients with symptoms of gastro-oesophageal reflux disease. Alimentary Pharmacology & Therapeutics. 2000;14(7):861-867.	4
Miehlke S, Hansky K, Schneider-Brachert W, et al. Randomized trial of rifabutin-based triple therapy and high-dose dual therapy for rescue treatment of Helicobacter pylori resistant to both metronidazole and clarithromycin. Alimentary Pharmacology & Therapeutics. Jul 15 2006;24(2):395-403.	6
Ormeci N, Sarioglu M, Sandikci M, et al. The effectiveness of omeprazole versus lansoprazole along with amoxillicin and clarithromycin in Turkish population with duodenal ulcer. Minerva Gastroenterol Dietol. 2003;49(2):147-153.	1
Regula J, Deckers CPM, Raps D, et al. Comparison of 20 mg and 40 mg Pantoprazole vs 20 mg Omeprazole in the prevention of the development of gastrointestinal lesions in rheumatic patients with continuous NSAID intake. Gut. Nov 2001;49(Suppl 3):1229.	6
Robinson M, Maton PN, Rodriguez S, Greenwood B, Humphries TJ. Effects of oral rabeprazole on oesophageal and gastric pH in patients with gastro-oesophageal reflux disease. Alimentary Pharmacology & Therapeutics. 1997;11(5):973-980.	4
Subei IM, Cardona HJ, Bachelet E, et al. One week of esomeprazole triple therapy vs 1 week of omeprazole triple therapy plus 3 weeks of omeprazole for duodenal ulcer healding in Helicobacter pylori-positive patients. Digestive Diseases & Sciences. Jun 2007;52(6):1505-1512.	6
Tursi A, Brandimarte G, Giorgetti GM, Modeo ME. Effect of Lactobacillus casei supplementation on the effectiveness and tolerability of a new second-line 10-day quadruple therapy after failure of a first attempt to cure Helicobacter pylori infection. Medical science monitor : international medical journal of experimental and clinical research. 2004;10(12):CR662-666.	6
Vakil NB, Traxler B, Levine D. Dysphagia in patients with erosive esophagitis: prevalence, severity, and response to proton pump inhibitor treatment. Clinical Gastroenterology & Hepatology. Aug 2004;2(8):665-668.	6
Wong BC, Wang WH, Wong WM, et al. Three-day lansoprazole quadruple therapy for Helicobacter pylori-positive duodenal ulcers: a randomized controlled study. Alimentary Pharmacology & Therapeutics. 2001;15(6):843-849.	6
Active-control trials	
Lansoprazole versus ranitidine in the treatment of reflux esophagitis. Multicentric study. Med Chir Dig. 1991;20(8):462-468."	1
Adachi K, Hashimoto T, Komazawa Y, et al. Helicobacter pylori infection influences symptomatic response to anti-secretory therapy in patients with GORD--crossover comparative study with famotidine and low-dose lansoprazole. Digestive & Liver Disease. Jul 2005;37(7):485-490.	6

Arkkila PE, Seppala K, Kosunen TU, et al. Helicobacter pylori eradication as the sole treatment for gastric and duodenal ulcers. European journal of gastroenterology & hepatology. 2005;17(1):93-101.	6
Awad RA, Camacho S, Dibildox M. Pantoprazole effectively controls intra-oesophageal pH and promotes oesophageal healing: Further evidence for ranitidine-induced tolerance in patients with gastro-oesophageal reflux disease. Clinical Drug Investigation. 2001;21(4):265-272.	6
Bardham KD, Muller-Lissner S, Bigard MA, et al. Symptomatic gastro-oesophageal reflux disease: Double blind controlled study of intermittent treatment with omeprazole or ranitidine. BMJ. 1999;British Medical Journal. 318(7182):502-507.	6
Bate CM, Green JR, Axon AT, et al. Omeprazole is more effective than cimetidine for the relief of all grades of gastro-oesophageal reflux disease-associated heartburn, irrespective of the presence or absence of endoscopic oesophagitis. Alimentary pharmacology & therapeutics. 1997;11(4):755-763.	6
Bigard MA, Isal JP, Galmiche JP, Ebrard F, Bader JP. Omeprazole versus cimetidine in short-term treatment of acute duodenal ulcer. Gastroenterol-Clin-Biol, Issn:. 1987;0399-8320. 11(11):753-757.	1
Bochenek WJ, Mack ME, Fraga PD, Metz DC. Pantoprazole provides rapid and sustained symptomatic relief in patients treated for erosive oesophagitis. Alimentary pharmacology & therapeutics. 2004;20(10):1105-1114.	6
Buzas GM, Gyorffy H, Szeles I, Szentmihalyi A. Second-line and third-line trial for helicobacter pylori infection in patients with duodenal ulcers: A prospective, crossover, controlled study. Current Therapeutic Research - Clinical and Experimental. 2004;65(1):13-25.	6
Cataldo MG, Brancato D, Donatelli M, Morici ML, Aspetti S, Spina P. Treatment of patients with duodenal ulcer positive for Helicobacter pylori infection: Ranitidine or omeprazole associated with colloidal bismuth subcitrate plus amoxicillin. Current Therapeutic Research Clinical and Experimental. 1996;57(3):168-174.	6
Cisternino M. Omeprazole 20 mg uid and ranitidine 150 mg bid in the treatment of benign gastric ulcer. Italian Cooperative Group on Omeprazole. Hepato-Gastroenterology. 1991;38(5):400-403.	6
Classen M, Dammann HG, Domschke W, et al. Short-duration treatment of duodenal ulcer with omeprazole and ranitidine: Results of a multi-centre trial in Germany. Dtsch-Med-Wochenschr. 1985;110(6):210-215.	1
Cucchiara S, Minella R, Iervolino C, et al. Omeprazole and high dose ranitidine in the treatment of refractory reflux oesophagitis. Archives of Disease in Childhood. 1993;69(6):655-659.	6
Dickman R, Schiff E, Holland A, et al. Clinical trial: acupuncture vs. doubling the proton pump inhibitor dose in refractory heartburn. Alimentary Pharmacology & Therapeutics. Nov 15 2007;26(10):1333-1344.	6

Figura N, Minoli G, Fedeli G, Cammarota G, Mazzilli D, Bayeli PF. Omeprazole versus ranitidine in the prevention of duodenal ulcer recurrence after eradication therapy. Current Therapeutic Research Clinical and Experimental. 1995;56(6):568-572.	6
Fujiwara Y, Higuchi K, Nebiki H, et al. Famotidine vs. omeprazole: a prospective randomized multicentre trial to determine efficacy in non-erosive gastro-oesophageal reflux disease. Alimentary pharmacology & therapeutics. Jun 2005;21 Suppl 2:10-18.	6
Hotz J, Kark W, Plein K, Wiedbrauck F, Guthke A, Otten O. Management of acute gastroduodenal peptic ulcer: Superiority of omeprazole to ranitidine in the early phase of ulcer healing. Leber Magen Darm. 1995;25(4):165-170.	1
Howden CW, Henning JM, Huang B, Lukasik N, Freston JW. Management of heartburn in a large, randomized, community-based study: comparison of four therapeutic strategies. American Journal of Gastroenterology. 2001;96(6):1704-1710.	6
Hsu PI, Lo GH, Lo CC, et al. Intravenous pantoprazole versus ranitidine for prevention of rebleeding after endoscopic hemostasis of bleeding peptic ulcers. World journal of gastroenterology : WJG. 2004;10(24):3666-3669.	3
Hu FL, Jia JC, Li YL, Yang GB. Comparison of H2-receptor antagonist- and proton-pump inhibitor-based triple regimens for the eradication of Helicobacter pylori in Chinese patients with gastritis or peptic ulcer. Journal of International Medical Research. 2003;31(6):469-474.	6
Hungin APS, Gunn SD, Bate CM, Turbitt ML, Wilcock C, Richardson PDI. A comparison of the efficacy of omeprazole 20 mg once daily with ranitidine 150 mg bd in the relief of symptomatic gastro-oesophageal reflux disease in general practice. British Journal of Clinical Research. 1993;4:73-88.	6
Itoh M, Matsuo Y, Choi KW, et al. Gastric ulcer treatment with intravenous human epidermal growth factor: a double-blind controlled clinical study.: A double-blind, randomized, parallel group study of omeprazole and ranitidine in Korean patients with gastric ulcer. J Gastroenterol Hepatol. 1994;9 Suppl 1(2):S78-83-118-123.	3
Jiang M, Chen ZM, Tsukahara H, et al. Relationship between gastric acid suppression and healing of peptic ulcers in children. International Medical Journal. 2001;8(3):199-203.	1
Kato S, Ritsuno H, Ohnuma K, Iinuma K, Sugiyama T, Asaka M. Safety and efficacy of one-week triple therapy for eradicating Helicobacter pylori in children. Helicobacter. 1998;3(4):278-282.	6
Kato S, Takeyama J, Ebina K, Naganuma H. Omeprazole-based dual and triple regimens for Helicobacter pylori eradication in children. Pediatrics. 1997;100(1):E3.	6

Kovacs TO, Wilcox CM, DeVault K, Miska D, Bochenek W, Pantoprozole USGSGB. Comparison of the efficacy of pantoprazole vs. nizatidine in the treatment of erosive oesophagitis: a randomized, active-controlled, double-blind study. Alimentary pharmacology & therapeutics. 2002;16(12):2043-2052.	6
Kuipers EJ, Nelis GF, Klinkenberg-Knol EC, et al. Cure of Helicobacter pylori infection in patients with reflux oesophagitis treated with long term omeprazole reverses gastritis without exacerbation of reflux disease: results of a randomised controlled trial. Gut. 2004;53(1):12-20.	6
Lewin-Van Den Broek NT, Numans ME, Buskens E, Verheij TJM, De Wit NJ, Smout A. A randomised controlled trial of four management strategies for dyspepsia: Relationships between symptom subgroups and strategy outcome. British Journal of General Practice. 2001;51(469):619-624.	6
Lin CK, Lai KH, Lo GH, et al. Efficacy of omeprazole versus famotidine in the short-term treatment of gastric ulcer. Chinese Journal of Gastroenterology. 1995;11(4):13-17.	1
Lundell L, Attwood S, Ell C, et al. Comparing laparoscopic antireflux surgery with esomeprazole in the management of patients with chronic gastro-oesophageal reflux disease: a 3-year interim analysis of the LOTUS trial. Gut. Sep 2008;57(9):1207-1213.	6
Mahon D, Rhodes M, Decadt B, et al. Randomized clinical trial of laparoscopic Nissen fundoplication compared with proton-pump inhibitors for treatment of chronic gastro-oesophageal reflux. The British journal of surgery. 2005;92(6):695-699.	5
Malfertheiner P, Dent J, Zeijlon L, et al. Impact of Helicobacter pylori eradication on heartburn in patients with gastric or duodenal ulcer disease - Results from a randomized trial programme. Alimentary Pharmacology & Therapeutics. 2002;16(8):1431-1442.	6
Michel P, Lemaire M, Colin R, et al. Short report: treatment of gastric ulcer with lansoprazole or ranitidine: a multicentre clinical trial. Alimentary pharmacology & therapeutics. 1994;8(1):119-122.	6
Miyake K, Ueki N, Suzuki K, et al. Preventive therapy for non-steroidal anti-inflammatory drug-induced ulcers in Japanese patients with rheumatoid arthritis: the current situation and a prospective controlled-study of the preventive effects of lansoprazole or famotidine. Alimentary pharmacology & therapeutics. Jun 2005;21 Suppl 2:67-72.	3
Okada M, Oki K, Shirotani T, et al. A new quadruple therapy for the eradication of Helicobacter pylori. Effect of pretreatment with omeprazole on the cure rate. Journal of Gastroenterology. 1998;33(5):640-645.	6
Pare P, Bailey RJ, Archambault AP, et al. Healing of benign gastric and prepyloric ulcers: A prospective, endoscopy-controlled, randomized, double-blind, Canadian multicentre study of omeprazole 20 and 40 mg daily and ranitidine 150 mg twice a day. Can J Gastroenterol. 1990;4(1):7-12.	6

Pilotto A, Di Mario F, Franceschi M, et al. Pantoprazole versus one week Helicobacter pylori eradication therapy for the prevention of acute NSAID related gastroduodenal damage in elderly subjects. Alimentary Pharmacology & Therapeutics. 2000;14:1077-1082.	6
Popovic O, Dzambas D, Tasic T, Bidikov V, Jesenski T, Janosevic S. Omeprazole 20 mg o.m. vs. famotidine 40 mg h.s. in the treatment of duodenal ulcer. Multicenter double-blind randomized trial. Gastroenterohepatoloski Arh. 1990;9(1):26-34.	1
Puig LG, Santaella RA, Aparicio PG, et al. Healing of gastric or pre-pyloric ulcers with once daily omeprazole 20 mg or ranitidine 300 mg. Journal of Drug Development and Clinical Practice. 1995;7(3):173-180.	6
Richter JE, Campbell DR, Kahrilas PJ, Huang B, Fludas C. Lansoprazole compared with ranitidine for the treatment of nonerosive gastroesophageal reflux disease. Archives of Internal Medicine. 2000;160:1803-1809.	6
Russo A, Dattilo M. Bedtime administration of lansoprazole does not modify its greater efficacy vs ranitidine in the acute and long term treatment of duodenal ulcer. Results from a multicentre, randomised, double blind clinical trial. Italian Journal of Gastroenterology & Hepatology. 1997;29:312-319.	6
Shi L, Zhu LY, Shi S, Shun GX. Contrastive Study of Effect of Lansoprazole and Ranitidine On Treatment in Gastric Ulcer Disease. Journal of Henan Medical Staff College. 2000;12(3):18-19.	1
Si J-M, Cao Q, Wu J-G. Quality of gastric ulcer healing evaluated by endoscopic ultrasonography. World Journal of Gastroenterology. Jun 14 2005;11(22):3461-3464.	3
Wada T, Sasaki M, Kataoka H, et al. Efficacy of famotidine and omeprazole in healing symptoms of non-erosive gastro-oesophageal reflux disease: randomized-controlled study of gastro-oesophageal reflux disease. Alimentary pharmacology & therapeutics. Jun 2005;21 Suppl 2:2-9.	6
Yang PJ, Chen RC, Wang TH. Eradication of Helicobacter pylori with omeprazole-amoxicillin combination therapy versus famotidine. A randomized, controlled study. Gastroenterological Journal of Taiwan. 1996;13(1):13-20.	2
Yeomans N, Wilson I, Langstrom G, et al. Quality of life in chronic NSAID users: a comparison of the effect of omeprazole and misoprostol. Scandinavian journal of rheumatology. 2001;30(6):328-334.	6
Placebo-controlled trials	
Avner DL, Dorsch ER, Jennings DE, Greski RPA. A comparison of three doses of lansoprazole (15, 30 and 60 mg) and placebo in the treatment of duodenal ulcer. Aliment Pharmacol Ther. 1995;9(5):521-528.	6
Bochenek WJ, Peters S, Fraga PD, et al. Eradication of Helicobacter pylori by 7-day triple-therapy regimens combining pantoprazole with clarithromycin, metronidazole, or amoxicillin in patients with peptic ulcer disease: results of two double-blind, randomized studies. Helicobacter. 2003;8(6):626-642.	6

Feng LY, Yao XX, Jiang SL. Effects of killing Helicobacter pylori quadruple therapy on peptic ulcer: a randomized double-blind clinical trial. World journal of gastroenterology : WJG. 2005;11(7):1083-1086.	6
Giral A, Ozdogan O, Celikel CA, Tozun N, Ulusoy NB, Kalayci C. Effect of Helicobacter pylori eradication on anti-thrombotic dose aspirin-induced gastroduodenal mucosal injury. J Gastroenterol Hepatol. 2004;19(7):773-777.	4
Gold BD. A randomized, double-blind, placebo-controlled study of gastroesophageal reflux disease therapy. ClinicalTrials.gov. 2005.	4
Hawkey C, Talley NJ, Yeomans ND, et al. Improvements with esomeprazole in patients with upper gastrointestinal symptoms taking non-steroidal antiinflammatory drugs, including selective COX-2 inhibitors. The American journal of gastroenterology. 2005;100(5):1028-1036.	2
Johnson DA, Orr WC, Crawley JA, et al. Effect of esomeprazole on nighttime heartburn and sleep quality in patients with GERD: a randomized, placebo-controlled trial. American Journal of Gastroenterology. Sep 2005;100(9):1914-1922.	6
Juul-Hansen P, Rydning A, Ditlef Jacobsen C, Hansen T. High-dose proton-pump inhibitors as a diagnostic test of gastro-oesophageal reflux disease in endoscopic-negative patients. Scandinavian Journal of Gastroenterology. 2001;36(8):806-810.	4
Lundell L. New information relevant to long-term management of endoscopy-negative reflux disease. Alimentary Pharmacology and Therapeutics, Supplement. 1997;11(2):93-98.	5
Richter JE, Kovacs TO, Greski-Rose PA, Huang B, Fisher R. Lansoprazole in the treatment of heartburn in patients without erosive oesophagitis. Alimentary Pharmacology & Therapeutics. 1999;13:795-804.	6
Richter JE, Peura D, Benjamin SB, Joelsson B, Whipple J. Efficacy of omeprazole for the treatment of symptomatic acid reflux disease without esophagitis. Archives of Internal Medicine. 2000;160:1810-1816.	6
Scholten T, Dekkers CPM, Schutze K, Korner T, Bohuschke M, Gatz G. On-demand therapy with pantoprazole 20 mg as effective long-term management of reflux disease in patients with mild GERD: the ORION trial. Digestion. 2005;72(2-3):76-85.	6
Wheeldon TU, Granstrom M, Hoang TT, Phuncarg DC, Nilsson LE, Sorberg M. The importance of the level of metronidazole resistance for the success of Helicobacter pylori eradication. Alimentary Pharmacology & Therapeutics. 2004;19(12):1315-1321.	6
Williams MP, Sercombe J, Hamilton MI, Pounder RE. A placebo-controlled trial to assess the effects of 8 days of dosing with rabeprazole versus omeprazole on 24-h intragastric acidity and plasma gastrin concentrations in young healthy male subjects. Alimentary Pharmacology & Therapeutics. 1998;12:1079-1089.	4
Yi C-H, Chen C-L, Kuo TBJ, Yang CCH. The effect of acid suppression on sleep and cardiac autonomic regulation in GERD. Hepato-Gastroenterology. Sep-Oct 2008;55(86-87):1649-1652.	4

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

Study quality is objectively assessed using predetermined criteria for internal validity, based on the combination of the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination criteria. This appendix lists questions that are posed for each included study in order to assess study quality. These quality-assessment questions differ for systematic reviews, controlled trials, and nonrandomized trials.

Regardless of design, all studies that are included are assessed for quality and assigned a rating of "good," "fair," or "poor." Studies with fatal flaws are rated poor quality. A fatal flaw is failure to meet combinations of criteria that may indicate the presence of bias. An example would be inadequate procedure for randomization or allocation concealment combined with important differences in prognostic factors at baseline. Studies that meet all criteria are rated good quality, and the remainder is 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 a true difference between the compared drugs.

Systematic Reviews

1. Does the review report a clear review question and inclusion/exclusion criteria that relate to the primary studies?
   A good-quality review should focus on a well-defined question or set of questions. These questions ideally are reflected in the inclusion/exclusion criteria, which guide the decision of whether to include or exclude specific primary studies. The criteria should relate to the 4 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, such as 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?
   If details of electronic database searches and other identification strategies are given, the answer to this question usually is yes. Ideally, search terms, dates, 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. For example, if only Medline was searched for a review looking at proton pump inhibitors then it is unlikely that all relevant studies were 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 (for example, how randomization was done, whether outcome

assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use 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 (how many reviewers were 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 judgment 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 sizes, patient characteristics, interventions, settings, outcome measures, follow-up periods, drop-out rates (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 provide 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 studies should be weighted in some way (for example, 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.

Controlled Trials

Assessment of internal validity

1. Was the assignment to treatment groups really random?
   Adequate approaches to sequence generation:
   - Computer-generated random numbers
   - Random-numbers table

   Inferior approaches to sequence generation:
   - Use of alternation, case record number, birth date, or day of week

   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

   Inferior approaches to concealment of randomization:
   - Use of alternation, case record number, birth date, or day of week

Open random-numbers list
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 (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 (giving numbers for each group)?

Assessment of external validity (applicability)

1. How similar is the population to the population to which 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 follow-up? (Give numbers at each stage of attrition.

Nonrandomized Studies

Assessment of internal validity

1. Was the selection of patients for inclusion unbiased? In other words, was any group of patients systematically excluded?

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

3. Were the investigated events specified and defined?

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

5. Was there unbiased and accurate ascertainment of events (independent ascertainers and validation of ascertainment technique)?

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

7. Did the duration of follow-up correlate with 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 which 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?

References:

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

Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med.* Apr 2001;20(3 Suppl):21-35.

Appendix E. Esophagitis grading scales used in randomized controlled trials

Savary-Miller

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

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

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

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

Modified Hetzel-Dent

Grade 0: Normal mucosa, no abnormalities found

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

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

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

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

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

Los Angeles Classification

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

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

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

Grade C: Mucosal breaks that are continuous between the tops of 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 squamocolumnar junction was evaluated

Grade 4: multiple erosions involving >50% of the distal 5 cm of the esophagus or a single ulcer > 5mm in diameter.