

Esomeprazole Versus Other Proton Pump Inhibitors in Erosive Esophagitis: A Meta-Analysis of Randomized Clinical Trials

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Background & Aims: There are limited data comparing the effectiveness of available proton pump inhibitors (PPIs) in erosive esophagitis (EE). We performed a meta-analysis to calculate the pooled effect of esomeprazole on healing rates, symptom relief, and adverse events versus competing PPIs in EE. **Methods:** We performed a structured electronic search of MEDLINE and EMBASE and reviewed published abstracts to identify English-language, randomized clinical trials from 1995–2005, comparing rates of endoscopic healing, symptom relief, and adverse events with esomeprazole versus alternative PPIs in the treatment of gastroesophageal reflux disease (GERD)/EE. We then performed meta-analysis to compare the relative risk (RR) of EE healing, symptom relief, and adverse events between study arms and calculated the absolute risk reduction and number needed to treat (NNT) for each outcome. **Results:** Meta-analysis was performed on 10 studies ($n = 15,316$). At 8 weeks, there was a 5% (RR, 1.05; 95% confidence interval, 1.02–1.08) relative increase in the probability of healing of EE with esomeprazole, yielding an absolute risk reduction of 4% and NNT of 25. The calculated NNTs by Los Angeles grade of EE (grades A–D) were 50, 33, 14, and 8, respectively. Last, esomeprazole conferred an 8% (RR, 1.08; 95% confidence interval, 1.05–1.11) relative increase in the probability of GERD symptom relief at 4 weeks. **Conclusions:** As compared with other PPIs, esomeprazole confers a statistically significant improvement, yet, clinically, only a modest overall benefit in 8-week healing and symptom relief in all-comers with EE. The clinical benefit of esomeprazole appears negligible in less severe erosive disease but might be important in more severe disease.

Proton pump inhibitors (PPIs) are very effective and safe when used to treat gastroesophageal reflux disease (GERD).^{1,2} However, there are few head-to-head data regarding the efficacy of competing PPIs in healing and symptom relief of GERD patients with erosive esophagitis (EE). Both intragastric pH studies and clinical trial data in patients with EE suggest that esomeprazole might have an efficacy advantage over other PPIs.^{3–9} The determinants, magnitude, and clinical relevance of this benefit remain uncertain. Because all PPIs are effective, head-to-head clinical trials must be extremely large to demonstrate statistically significant and clinically relevant differences between competing agents. Therefore, relying on underpowered comparative studies might lead to a type II error, in which a true difference between agents exists but cannot be detected because of

inadequate sample size. The risk of committing a type II error might be overcome by performing a meta-analysis of pooled data, an accepted methodology that increases the ability to detect small yet statistically significant and perhaps clinically relevant differences.

On the basis of the existing physiologic and clinical data supporting the efficacy of esomeprazole, we hypothesized that as compared with other PPIs, esomeprazole provides superior healing rates and symptom relief in patients with EE. Moreover, we further hypothesized that in certain patient populations with EE (eg, those with more severe disease), observed differences in healing and symptom relief might be clinically important. We tested these hypotheses in a systematic review and meta-analysis of published randomized controlled trials of esomeprazole versus other PPIs, evaluating healing rates, symptom relief, and adverse events in EE.

Methods

Search Strategy and Inclusion Criteria

We performed a structured electronic search of MEDLINE and EMBASE along with a review of published abstracts from 3 major subspecialty journals to identify English-language, randomized clinical trials from 1995–2005, comparing rates of endoscopic healing, symptom relief, and adverse events with esomeprazole versus alternative PPIs in the treatment of GERD/EE. In addition, we manually searched the bibliographies of key review articles for references not captured by our search strategy and reviewed the websites of the manufacturers of the PPIs to search for other unpublished clinical trial data that might have existed. Table 1 displays the search strategy we used to conduct the systematic review. Two reviewers (I.M.G., B.M.R.S.) assessed the generated titles for relevancy and only rejected titles that fulfilled the following explicit exclusion criteria: (1) not written in English, (2) not concerning a clinical question regarding human subjects, and (3) not related to GERD/EE. The reviewers then individually assessed the relevancy of all abstracts corresponding with the remaining titles and excluded

Abbreviations used in this paper: ARR, absolute risk reduction; CI, confidence interval; EE, erosive esophagitis; GERD, gastroesophageal reflux disease; NNT, need to treat; PPI, proton pump inhibitor; RR, relative risk.

Table 1. Search Strategy

Group	Search terms	Significance of grouping
1	MEDLINE or EMBASE	Targeted bibliographic database
2	(Randomized-controlled-trial or Controlled-clinical-trial or Randomized-controlled-trials or Random-allocation or Double-blind-method or Single-blind-method or Clinical-trial or Clinical-trials or (Clin* Near Trial*) or ((Singl* or Doubl* or Trebl* or Tripl*) Near (Blind* or Mask*)))	Filter to identify randomized controlled trials
3	Esomeprazole [tw]	Targeted proton pump inhibitor
4	(Lansoprazole or Omeprazole or Rabeprazole or Pantoprazole or Proton Pump Inhibitor* or PPI)	Comparator proton pump inhibitors
5	(Gastroesophageal Reflux [MeSH] or Esophageal Reflux or Gastro-Esophageal Reflux or Gastro Esophageal Reflux or Reflux, Gastro-Esophageal or Gastro-oesophageal Reflux or Gastro oesophageal Reflux or Reflux, Gastro-oesophageal or Gastroesophageal Reflux Disease or GERD or Reflux, Gastroesophageal or Regurgitation, Gastric or Gastric Regurgitation or Heartburn [MeSH] or Pyros* or Esophagitis, Peptic [MeSH] or Esophagitis [MeSH])	Targeted disease content
6	(TG = Animal or Letter [pt] or Editorial [pt] or Review [pt] or News [pt])	Excluded study types and content

NOTE. Search = 1 and 2 and 3 and 4 and 5 not 6.

abstracts for the following reasons: (1) fulfilled one or more of the title exclusion criteria, (2) was not a randomized clinical trial, and (3) did not compare esomeprazole with one or more alternative PPIs. The reviewers then independently assessed the relevancy of all articles corresponding with the remaining abstracts and included articles only if they fulfilled all the previous criteria and included data regarding prespecified symptoms of gastroesophageal reflux, including “acid reflux,” “heartburn,” and “pyrosis.” Each study was then independently abstracted for data by these same 2 investigators, and the results were entered onto a standardized electronic data abstraction form. In addition, the abstractors assigned a score for methodologic quality by applying the Jadad scale, which is a standardized instrument focusing on features related to internal validity¹⁰ (Table 2). In addition, we measured inter-rater agreement for each aforementioned step with a κ statistic and adopted a threshold of >0.7 as the definition for acceptable agreement.¹¹ Disagreements were settled by discussion and consensus between the 2 primary reviewers and a third arbiter (M.B.F.).

Statistical Analysis

Before conducting statistical analysis, we first constructed evidence tables and performed a qualitative assessment for homogeneity by comparing key study features including patient demographic characteristics (age, gender), indication for treatment, concurrent use of antacids or histamine₂-receptor antagonists, and *Helicobacter pylori* status. If the studies were qualitatively homogeneous, we then performed meta-analysis with Stata (Stata Corporation, College Station, Texas) statistical software v8.0 to compare the relative risk (RR) of EE healing, symptom relief, and adverse events between study arms.^{12,13} We then calculated the absolute risk reduction (ARR) and number needed to treat (NNT) with esomeprazole versus alternative PPI for each outcome.¹⁴ We performed a statistical test for heterogeneity and adopted a *P* value of greater than .05 as evidence for homogeneity.^{12,13} If the data were homogeneous, we then selected a fixed effects model.^{12,13} If the data were heterogeneous, we performed both a fixed and random effects model.^{12,13}

We performed a qualitative appraisal of publication bias by constructing a funnel plot and observing for evidence of asymmetry.¹⁵ In a funnel plot, larger studies that provide a more precise estimate of an intervention’s effect form the spout of the funnel, whereas smaller studies with less precision form the cone end of the funnel. Asymmetry in the funnel plot indicates potential publication bias. In addition, we performed a quantitative appraisal for publication bias by conducting an Egger’s test.¹⁶ We assumed there was evidence for publication bias if there was a qualitative lack of small “negative” studies on the funnel plot, or if the *P* value for the Egger’s test was less than .05.^{15,16}

Results

Study Selection and Data Collection

We identified 84 titles, of which 11 were selected for final review (κ >0.8 for agreement) (Figure 1). Meta-analysis was performed on 10 studies that included n = 15,316 total subjects. These 10 studies included 8 peer-reviewed, full-text manuscripts, 1 published abstract, and 1 manufacturer package insert^{7-9,17-23} (Table 3). In our methodologic assessment of the

Table 2. Jadad Scale for Quality Assessment of Controlled Clinical Trials¹⁰

Quality indicator	Points assessed
Was the study described as “randomized”?	If yes, score +1 If no, score 0
If randomization was performed, was there concealed allocation?	If yes, score +1 If no, score -1
Was the study described as “double blind”?	If yes, score +1 If no, score 0
If blinding was performed, was it appropriate?	If yes, score +1 If not, score -1
Was there a description of withdrawals and dropouts?	If yes, score +1 If no, score 0

NOTE. Poor-quality studies are defined as those with a cumulative score <3, and high-quality studies are defined as those with a cumulative score ≥3.

Table 3. Evidence Table

Study 1 st author, reference no., y	Publication type	N	Age (mean, y)	Gender (% male)	% <i>Helicobacter pylori</i> positive	Treatment groups	Los Angeles grade of EE, % (A-D)	GERD symptom relief measured?	Study duration, wk	Jadad score (1-5)
Kahrilas, ⁷ 2000	Full-text manuscript	1304	46	60	NA	ESO, 40 mg, n = 654; OME, 20 mg, n = 650	34, 39, 20, 7	Yes	8	5
Richter, ⁸ 2001	Full-text manuscript	2425	47	61	8	ESO, 40 mg, n = 1216; OME, 20 mg, n = 1209	33, 41, 21, 5	Yes	8	5
Castell, ⁹ 2002	Full-text manuscript	5241	47	57	15	ESO, 40 mg, n = 2624; LAN, 30 mg, n = 2617	36, 40, 18, 6	Yes	8	5
Howden, ¹⁷ 2002	Full-text manuscript	284	47	56	28	ESO, 40 mg, n = 141; LAN, 30 mg, n = 143	0, 61, 30, 9	Yes	8	3
Scholten, ¹⁸ 2003	Full-text manuscript	217	54	58	22	ESO, 40 mg, n = 105; PAN, 40 mg, n = 112	0, 73, 27, 0	Yes	4	3
Gillessen, ¹⁹ 2004	Full-text manuscript	227	53	61	27	ESO, 40 mg, n = 114; PAN, 40 mg, n = 113	0, 83, 17, 0	Yes	10	3
Fennerty, ²⁰ 2005	Full-text manuscript	999	47	66	9	ESO, 40 mg, n = 498; LAN, 30 mg, n = 501	0, 0, 79, 21	Yes	8	5
Labenz, ²¹ 2005	Full-text manuscript	3151	51	63	27	ESO, 40 mg, n = 1562; PAN, 40 mg, n = 1589	32, 44, 19, 5	Yes	8	1
Package insert (AstraZeneca), ²²	Package insert	1148	NA	NA	NA	ESO, 40 mg, n = 576; OME, 20 mg, n = 572	Not reported	Yes	8	NA
Sierra, ²³ 2005	Abstract	320	NA	NA	NA	ESO, 40 mg, n = NA; OME, 40 mg, n = NA	Limited to LA grades C & D but exact breakdown not reported in abstract	NA	8	NA

ESO, esomeprazole; OME, omeprazole; LAN, lansoprazole; PAN, pantoprazole; NA, not able to determine from information provided by investigator.

quality of selected clinical trials for meta-analysis, 7 of 8 published trials were “high quality” (Jadad score = 3-5), and 1 trial was of “low quality” (Jadad score = 1-2).¹⁰ We were unable to assess methodologic quality on either the published abstract or unpublished clinical trial data reported in the manufacturer’s package insert.^{22,23}

Healing of Erosive Esophagitis

In comparing rates of healing of EE at both 4 and 8 weeks, we found a 10% (RR, 1.10; 95% confidence interval (CI), 1.05-1.15) and 5% (RR, 1.05; 95% CI, 1.02-1.08) relative increase in the probability of healing, respectively, with esomeprazole versus alternative PPIs (Figures 2 and 3). At 8 weeks, there was an ARR of 4% and NNT of 25 (Figure 4). In other words, 25 patients with EE would need to be treated with esomeprazole in lieu of an alternative PPI to achieve 1 additional case of healed EE. We also found that the effectiveness of esomeprazole was inversely proportional to baseline EE severity. The calculated NNTs by Los Angeles grade of EE (grades A-D) were 50, 33, 14, and 8, respectively (Figure 5).

Gastroesophageal Reflux Disease Symptom Relief

We found that esomeprazole conferred an 8% (RR, 1.08; 95% CI, 1.05-1.11) relative increase in the probability of GERD symptom relief at 4 weeks. This translates into an ARR of 4% and NNT of 25. Here again, 25 patients with EE would need to be treated with esomeprazole instead of an alternative PPI to provide GERD symptom relief in 1 additional patient with EE after 4 weeks of treatment (Figure 6).

Adverse Events

There was a 22% relative increase in the reported incidence of headache with esomeprazole compared with

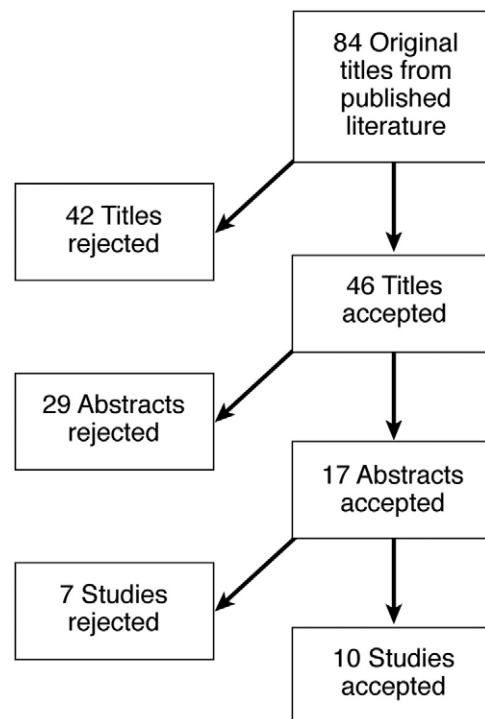


Figure 1. Results of literature search.

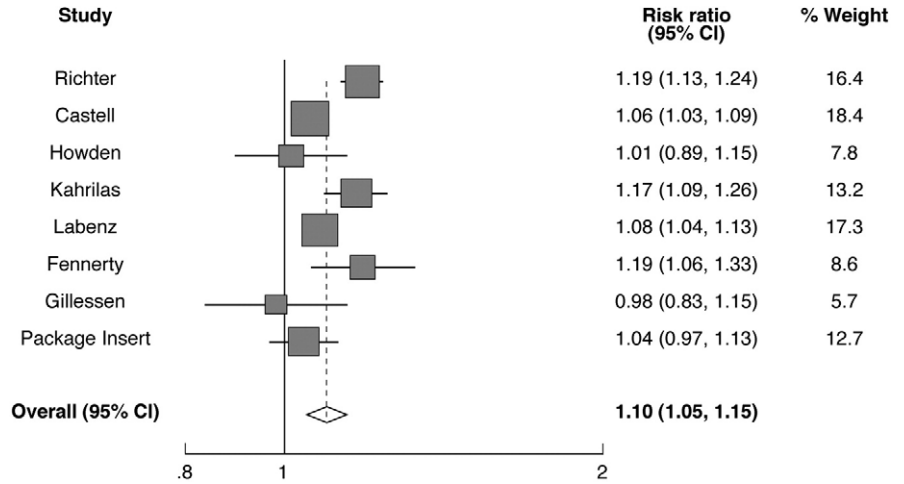


Figure 2. Relative risk reduction forest plot (random effects model) demonstrating healing of erosive esophagitis at 4 weeks (n = 14,779).

other PPIs (RR, 1.22; 95% CI, 1.03–1.44), but there was no observed difference in the reported rates of diarrhea, abdominal pain, nausea, or total adverse events between the various PPIs.

Publication Bias

There was no observed publication bias (Figure 7). A qualitative inspection of the Begg’s funnel plot showed the distribution of included studies to be relatively symmetric, thus no apparent publication bias. Further evaluation for publication bias in a quantitative manner by using the Egger’s test was also statistically nonsignificant, *P* = .21.

Discussion

This meta-analysis of randomized clinical trials comparing esomeprazole versus alternative PPIs in the treatment of EE found that in the healing of EE, there was a modest overall benefit of esomeprazole. Specifically, at 8 weeks of healing, we found an ARR of 4%, yielding an NNT of 25. However, when analyzing by specific LA grade of EE, we found that as the severity of EE grade increased, the NNT decreased. These data suggest that as compared with other

available PPIs, esomeprazole provides greater effectiveness in EE healing in patients with more severe erosive disease (eg, LA grade C, NNT = 14 and LA grade D, NNT = 8). This finding might help clinically validate the 24-hour intragastric pH data that have demonstrated physiologic superiority of esomeprazole.^{4–6} We found similar results in evaluating GERD symptom relief. As compared with alternative PPIs, esomeprazole again provides a modest improvement in GERD symptom relief at 4 weeks. Unfortunately, these studies did not stratify the outcome of GERD symptom relief by baseline grade of EE; thus we were unable to evaluate whether there was a similar benefit in GERD symptom relief with esomeprazole by baseline EE grade as was observed in EE healing. We also evaluated adverse events and found that there was a significantly higher (22% relative increase) reported incidence of headaches with esomeprazole use. However, there were no differences in reported rates of diarrhea, abdominal pain, nausea, or total adverse events. Last, we performed additional pooled analyses of the data with only high-quality studies as defined by Jadad et al.¹⁰ We found no difference in the study findings (data not presented).

There are limited published data comparing the effectiveness of the individual available PPIs for the treatment of

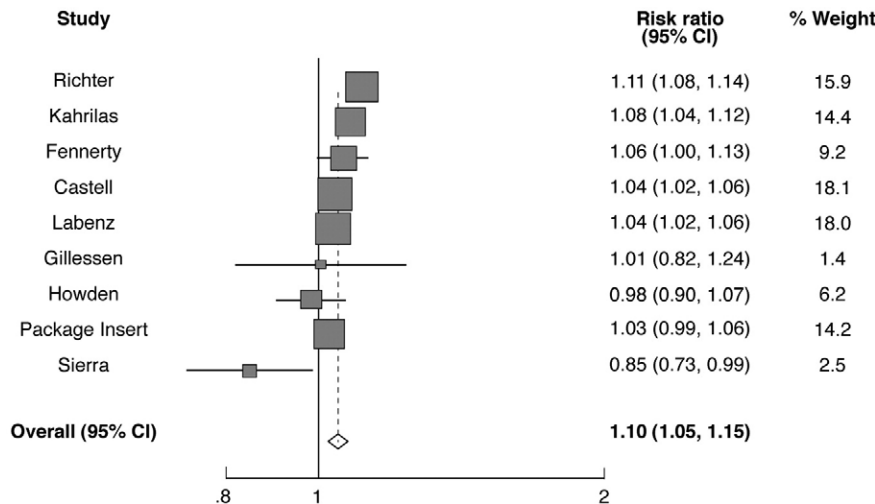


Figure 3. Relative risk reduction forest plot (random effects model) demonstrating healing of erosive esophagitis at 8 weeks (n = 15,099).

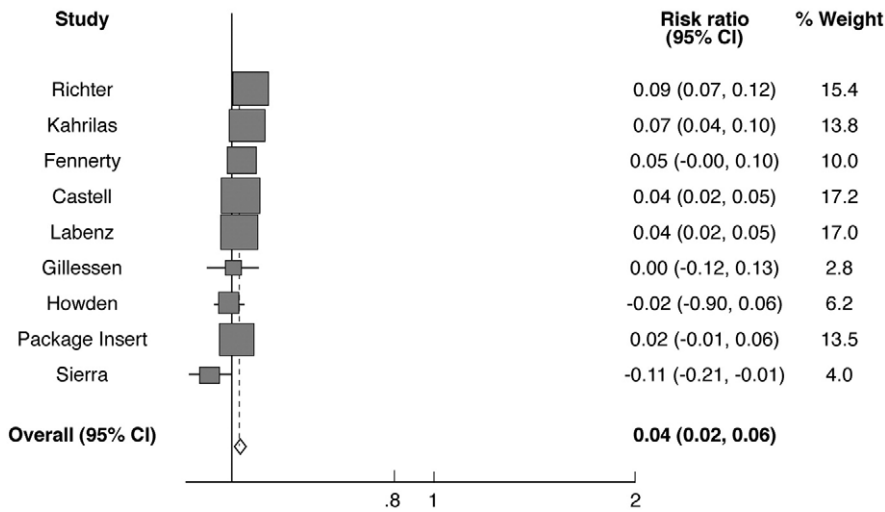


Figure 4. Absolute risk reduction forest plot in healing of erosive esophagitis at 8 weeks (n = 15,099). ARR = 4% yielding an NNT = 25.

GERD and EE.²⁴ In an earlier report, Bell et al³ demonstrated improved healing of EE caused by GERD as directly related to the percentage of time during a 24-hour period that the intragastric pH is maintained above 4.0. More recent published data have demonstrated superiority of esomeprazole as compared with other PPIs in controlling intragastric pH.⁴⁻⁶ In a randomized study of 38 patients with GERD, Lind et al⁴ found that both esomeprazole 40 mg and 20 mg once daily in oral dosing provided significantly better 24-hour intragastric pH control (pH >4 at steady-state on day 5) as compared with omeprazole 20 mg daily. They concluded that esomeprazole demonstrated more effective acid control than omeprazole and thus offered the potential for improved efficacy in acid-related diseases. In a study of 130 patients with GERD, Rohss et al⁵ similarly reported that esomeprazole 40 mg once daily demonstrated a significantly greater mean percentage of the 24-hour period with an intragastric pH >4 as compared with omeprazole 40 mg once daily. In a United States population, Miner et al⁶ conducted a randomized, open-label comparative 5-way crossover study evaluating the 24-hour intragastric pH profile of esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, and rabeprazole 20 mg once daily in 34 *H pylori*-negative GERD patients. They found that at steady state, the intragastric pH was maintained at greater than 4.0 for a mean of 14.0 hours with esomeprazole, statistically significantly higher than as compared with the other PPIs ($P \leq .001$). All these studies, however, are limited by relatively small numbers of subjects and the evaluation of an intermediate study end point (eg, 24-hour intragastric pH) that might not correlate with more clinically relevant patient outcomes in GERD symptom relief and healing of EE.

Prior pooled analyses comparing the relative benefits of PPIs for the treatment of GERD and EE have yielded similar results.^{25,26} Raghunath et al²⁵ reviewed pooled data limited to clinical trials comparing esomeprazole with lansoprazole in the acute healing of EE. Similar to our findings in this present meta-analysis, there was a modest incremental benefit in healing rates with esomeprazole of 5% and 4% at the 4-week and 8-week healing end points, respectively. However, there were no reported data evaluating EE healing by severity

of erosive disease. Vakil and Fennerty²⁶ also examined this topic in a systematic review and found that as compared with standard dose omeprazole, lansoprazole, and pantoprazole, esomeprazole provided earlier relief of GERD symptoms and superior healing of EE.

This present analysis has several strengths. First, we used a standardized and systematic search strategy (electronic and manual search), including both MEDLINE and EMBASE, to identify relevant studies (full text and published abstracts). Second, we performed all steps of the analysis in parallel by 2 abstractors blinded to each other's status. Third, the studies in our pooled analyses included a large number of subjects (n = 15,316) and did not show evidence of publication bias. Last, all but one study included for meta-analysis was of high methodologic quality. The one low quality study was to the right of the meta-analytic point estimate, suggesting that if it were removed, then the effect of esomeprazole would be even more modest.²¹ Of course, there are also limitations to this study. We limited our literature search to English-language studies only and thus might not have captured all

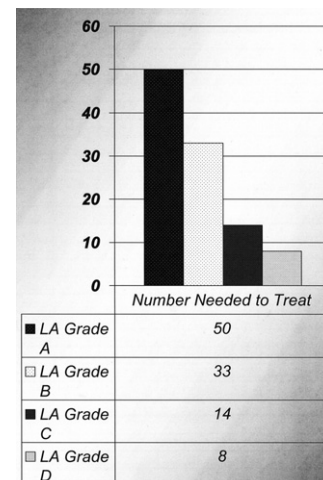


Figure 5. NNTs for Los Angeles grades A-D. NNTs decrease as LA Grade severity of EE increases.

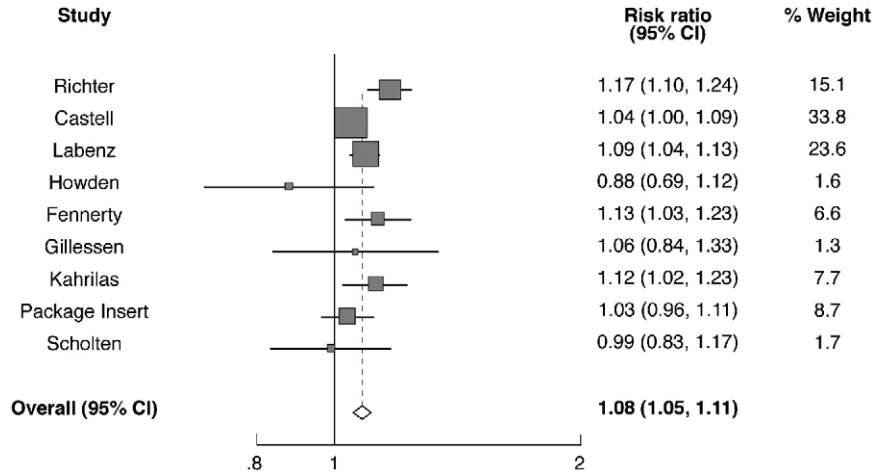


Figure 6. GERD symptom relief at 4 weeks: esomeprazole vs comparator PPIs relative risk forest plot with fixed effects model, n = 14,996.

relevant foreign language published studies. There might also have been additional unpublished data per the PPI manufacturers that we were unable to identify. Last, because there are no reported clinical trials directly comparing esomeprazole and rabeprazole for the treatment of EE, this analysis is limited to comparisons of esomeprazole with the other 3 available PPIs (omeprazole, lansoprazole, and pantoprazole). However, on the basis of published physiologic data, we do not believe that rabeprazole would behave significantly different in clinical efficacy than the other comparator PPIs, and that these meta-analytic findings therefore might be extrapolated to all available PPIs.⁶

In summary, we found that as compared with alternative PPIs, esomeprazole provides a statistically significant but only modest degree of improved effectiveness in the healing of EE, and this appears to be largely limited to those individuals with more severe erosive disease (LA grades C and D). In addition, we found no evidence of what we believe would be considered a clinically meaningful improvement in symp-

tom relief with esomeprazole compared with alternative PPIs, although clinical meaningfulness is subjective, is determined by each individual practitioner, and might vary widely. We believe that appropriately designed outcome studies in this patient population, including an a priori definition of what is a “clinically meaningful improvement,” are needed to evaluate whether any potential clinical advantage is provided by esomeprazole. Moreover, although there was a higher relative rate of reported headaches with esomeprazole, no significant differences in overall adverse events compared with other PPIs was detected. These data indicate that although esomeprazole is a more effective agent in healing and symptom relief in patients with EE, any advantage is largely found in those with more severe disease. As such, the choice of PPI used to manage a patient with GERD is likely best made on the basis of a number of factors including the patient’s disease presentation but also other factors such as drug cost, formulary availability, and patient tolerability of the drug.

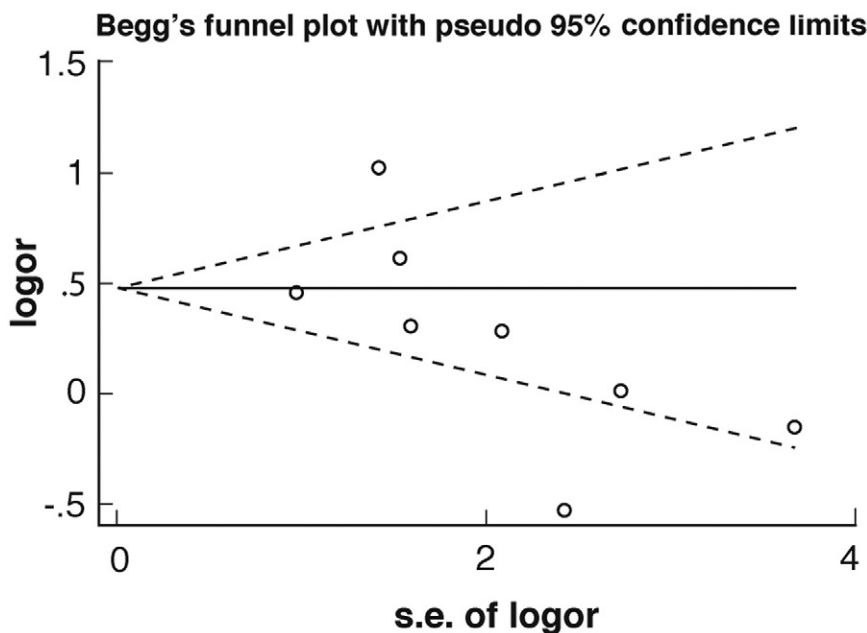


Figure 7. Begg’s funnel plot of studies reporting EE healing at 8 weeks selected for meta-analysis. No evidence of publication bias, *P* = .21 by Egger’s test, n = 15,099.

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M.B.F. is a consultant for TAP Pharmaceuticals, Santarus, AstraZeneca, Atlanta, and Axcan.

Supported by VA HSR&D Advanced Research Career Development Award and VA HSR&D IIR 01-191-1 (I.M.G.); supported by VA HSR&D Research Career Development Award RCD 03-179-2 and by the CURE Digestive Diseases Research Center (NIH 2P30 DK 041301-17) (B.M.R.S.); and by a grant from EBMed with funding for the grant obtained from AstraZeneca.