Esomeprazole versus other proton pump inhibitors in erosive esophagitis: a meta-analysis of randomized clinical trials
Gralnek I M, Dulai G S, Fennerty M B, Spiegel B M

CRD summary
This review concluded that while there was a statistically significant improvement with esomeprazole compared with other proton-pump inhibitors in healing and symptoms, the clinical benefit was modest and may be more important in severe than mild erosive esophagitis. The overall conclusion appears reliable but the conclusion about the influence of disease severity should be viewed with caution.

Authors' objectives
To assess the effect of esomeprazole compared with other proton-pump inhibitors (PPIs) on healing rates, symptom relief and adverse events in the treatment of erosive oesophagitis (EE).

Searching
MEDLINE and EMBASE were searched from 1995 to 2005 for English language articles; the search strategy was reported. Three sub-speciality journals, the bibliographies of review articles and manufacturers' websites were also searched.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Apart from one study of 4 weeks' duration and one of 10 weeks' duration, the studies lasted 8 weeks.

Specific interventions included in the review
Trials comparing esomeprazole with at least one other PPI were eligible for inclusion. All of the included studies used a 40-mg dose of esomeprazole. The comparator PPIs were omeprazole (20 or 40 mg), lansoprazole (30 mg) and pantoprazole (40 mg).

Participants included in the review
Studies of participants with EE or gastroesophageal reflux disease (GERD) were eligible for inclusion. In the included studies, the proportion of participants reported to be Helicobacter pylori positive ranged from 8 to 28%. The Los Angeles grade of EE varied between studies, though in most studies grade B appeared to be the most commonly reported grade; the majority of participants were graded between A and C. Where reported, the average age of the participants ranged from 46 to 54 years and the proportion of males ranged form 56 to 66%.

Outcomes assessed in the review
Studies reporting outcomes related to pre-specified symptoms of gastroesophageal reflux such as acid reflux, heartburn and pyrosis were eligible for inclusion.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for eligibility. Any disagreements were resolved by consensus.

Assessment of study quality
The Jadad scale was used to assess randomisation, allocation concealment, blinding, and withdrawals and drop-outs. A score of 0 to 5 was assigned and studies with a score of 3 or greater were defined as high quality. Two reviewers independently assessed study quality and any disagreements were resolved by consensus.
Data extraction
Two reviewers independently extracted the data and any disagreements were resolved by consensus. The relative risk (RR) and 95% confidence interval (CI) for each of the outcomes of interest were extracted for each study.

Methods of synthesis
How were the studies combined?
Studies that appeared qualitatively homogeneous were pooled in a meta-analysis using a fixed-effect model. Where there was statistical significant heterogeneity a random-effects model was also created. Publication bias was assessed by visual inspection of a funnel plot and the use of Egger's test.

How were differences between studies investigated?
The authors initially assessed heterogeneity qualitatively by comparing key study features. Heterogeneity was also assessed statistically, though the method employed was not reported; a p-value of 0.05 or less was classified as statistically significant heterogeneity. To investigate the influence of baseline disease severity on outcome, numbers-needed-to-treat (NNT) were calculated by baseline Los Angeles grade.

Results of the review
Ten RCTs (n=15,316) were included. One of these was a published abstract and one was of unpublished data reported in the manufacturer's package insert.

Seven of the studies were classified as high quality, with four of these studies receiving a score of 5. There was a statistically significant increase in the probability of healing of EE with esomeprazole compared with the other PPIs at 4 weeks (RR 1.10, 95% CI: 1.05, 1.15) and 8 weeks (RR 1.05, 95% CI: 1.02, 1.08). There was a statistically significant increase in the probability of relief of GERD symptoms at 4 weeks (RR 1.08, 95% CI: 1.05, 1.11). The risk of headaches was greater with esomeprazole than with the other PPIs (RR 1.22, 95% CI: 1.03, 1.44), but no difference was observed for other adverse events. The NNT decreased with increasing disease severity from 50 at grade A to 8 at grade D. The test for publication bias was not significant.

Authors' conclusions
There was a statistically significant improvement with esomeprazole compared with other PPIs but, clinically, the overall benefit in healing and symptom relief at 8 weeks was modest. The clinical benefit may be more important in severe than mild EE.

CRD commentary
The review question was clearly stated. A number of relevant electronic databases and other sources were searched. Unpublished data were sought but from one source only, therefore there is a risk of publication bias. This was investigated using relevant methods, but the results were probably limited by the small number of studies. In addition, there is a risk of language bias. Appropriate review processes were used to reduce error and bias in the study selection, data extraction and quality assessment processes. Appropriate details were given about the individual studies, though only the overall Jadad score was reported which has some limitations. Statistical heterogeneity was assessed but not reported, thus it was difficult to assess whether the treatment effect has broad generalisability. The authors' conclusion about overall benefit is appropriate given the evidence presented; however, the conclusion about greater benefit for more severe disease should be considered with caution given the limited details of the methods used and the results generated.

Implications of the review for practice and research
Practice: The choice of PPI is likely to be best made on multiple factors such as disease presentation, drug cost, availability and patient tolerability.

Research: Further research is required to establish whether any clinical advantage is provided by esomeprazole, using an
a priori definition of clinically meaningful improvement.

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