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**Review Article**

# Efficacy and Safety of Esomeprazole for the Treatment of Reflux Symptoms in Patients with Gastroesophageal Reflux Disease: A Systematic Review and Meta-Analysis

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**Abstract**

**Background:** We investigated the efficacy of esomeprazole for the treatment of gastroesophageal reflux disease (GERD) in a meta-analysis of clinical trials results.

**Methods:** Medline, Embase, PubMed and Web of Science databases were systematically searched for suitable studies, and double-blind, randomized controlled trials (RCTs) were involved. A meta-analysis of RCTs was performed to analyze the efficacy of esomeprazole on clinical outcomes that associated with the severity of GERD.

**Results:** A total of 8 clinical trials were selected in our meta-analysis (N=4495, patients with GERD). Esomeprazole treatment yielded a significant improvement in clinical signs and symptoms of GERD compared to placebo group. Funnel plot and Egger test showed there was no significant bias in the publication. Cochrane collaboration tool and Jadad scale were used to indicate that all 8 RCTs were of high quality. The results of Galbraith radial plot showed that no study was the major source of heterogeneity. Esomeprazole treatment significantly decreased the relapse rates more than that of placebo group (RR = 0.729; 95% CI: 0.670 to 0.794; $P<0.001$). It seems to be lower rates of heartburn (RR = 0.747; 95%CI: 0.665-0.839; $P<0.001$) and epigastric pain (RR = 0.795; 95%CI: 0.679-0.932; $P=0.005$) in esomeprazole-treated group compared with the placebo group. Moreover, serious adverse events was less likely to happen after esomeprazole therapy (RR = 1.406, 95% CI: 1.030-1.918; $P=0.032$).

**Conclusion:** Compared with the control group, esomeprazole is a promising therapeutic agent that improves the management of patients with GERD.

**Keywords:** Esomeprazole; Meta-analysis; Gastroesophageal reflux disease; Clinical efficacy; Safety

## Introduction

Gastroesophageal reflux disease (GERD) is defined by esophageal and extraesophageal syndromes caused by the reflux of gastric contents (1-3). It is acceptable that symptoms induced by GERD seem to be more common now than 25 yr ago (4-6). GERD is prevalent worldwide with prevalence estimates showing greatest prevalence in North America (19.8%) and lowest in East Asia (5.2%) (7-10).

Acid suppression is recognized as the mainstay of treatment for GERD, and proton pump inhibitors (PPIs) therapy traditionally served as the

most rapid symptomatic relief in majority of patients (11-13). Recently, five PPIs were available for treating GERD, including omeprazole, pantoprazole, lansoprazole, rabeprazole and esomeprazole (14-18). Esomeprazole, as the isomer of omeprazole, has been developed and marketed with less adverse events compared with omeprazole (19, 20). All the PPIs are racemates, which leads to pharmacologically differences caused by their spatial disposition (21-23). Previous study was designed and suggested modest benefits of one drug over another (24-26). The efficacy of esomeprazole in patients with GERD symptoms control, include heartburn, acid regurgitation, dysphagia, and epigastric pain, remains controversial compared with other acid suppression drugs (27-32). Previous meta-analysis has been designed and suggests similar healing rates and relapse rates of omeprazole treatment compared with three other developed PPI drugs (pantoprazole, lansoprazole, rabeprazole) however not included esomeprazole (24).

We analyzed the efficacy of esomeprazole for GERD treatment in a meta-analysis of clinical trial results.

## Methods

This meta-analysis was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) statement as a guideline (http://www.prisma-statement.org/).

### *Search strategy and inclusion criteria*

On Nov 1st 2017, we conducted a systematic search of PubMed, Medline, Embase, and Web of Science databases for randomized controlled trials (published between Nov 1, 2000 and Nov 1, 2017; English publication only) using the search terms "esomeprazole" and "gastroesophageal reflux disease". All the enrolled studies using the strategy were checked independently by 2 authors; additionally, the articles that met all inclusion criteria were enrolled in this meta-analysis. The inclusion criteria were as follows: 1) patients were diagnosed of GERD and treated with esomeprazole; 2) double-blind, randomized, placebo-controlled studies; 3) outcome measures including relapse rate, heartburn rate and epigastric pain rate.

### *Testing for heterogeneity, risk of bias and sensitivity Meta-analysis*

Q test and I2 test were performed to analysis the heterogeneity of the studies that included in this meta-analysis. The Galbraith radial plot was made to indicate the cause of heterogeneity in studies using STATA 12.0 software. Each study was represented as a single dot with a central regression line through the plot. Moreover, Cochrane collaboration tool was used to evaluate the qualities of the included studies and the risk of bias, and the Egger test was performed which is a linear regression method to evaluate the bias in publication in our meta-analysis. Sensitivity analysis was described using STATA 12.0 software.

### *Data extraction and outcomes*

In our systematic review, the following variables were extracted: study, year, country, ages of esomeprazole/placebo group, numbers of esomeprazole-treated patients and control subjects, study type, name of the study, clinicaltrials.gov number, esomeprazole doses used, duration of study periods and outcomes.

### *Statistical Meta-analysis*

From the included studies in the analysis, we extracted for esomeprazole and placebo relapse rates, heartburn rates and epigastric pain rates (along with the corresponding 95% CI). The overall summary effect sizes were estimated using a random-effects model if heterogeneity was over 50% and fixed-effects model was used if heterogeneity was under 50%. The quantitative data was expressed as standardized mean difference (SMD), and numeration data was presented as relative risk (RR). Data was expressed as mean (range) or mean±SD, and a $P$ value of $< 0.05$ was considered to be statistically significant. Forest plots and data analysis were performed using Review Manager (RevMan version 5.3; Nordic Cochrane Centre, Copenhagen, Denmark) and

STATA (ver. 12.0; StataCorp, College Station, Tex) software.

## Results

### Study selection

The systematic search terms identified 791 original articles and the flow diagram of the studies was showed in Fig. 1. A total of 348 duplicates and 402 irrelevant articles were excluded, and 33 abstracts were removed as they did not meet the inclusion criteria in this meta-analysis. Finally, 8 RCTs were included for our meta-analysis (33-40). All 8 clinical trials are randomized controlled studies. All were published in English.

### Study characterization

The characteristics of the included RCTs are shown in Table 1. Three studies (33, 35, 40) were performed only in US, and other studies involved in different countries. All the studies were followed up 6 months and all the dosage of the esomeprazole was 20 mg/d. However, the drugs in the control group varied. All of the 8 trials were randomized, double-blinded, and placebo controlled trials.

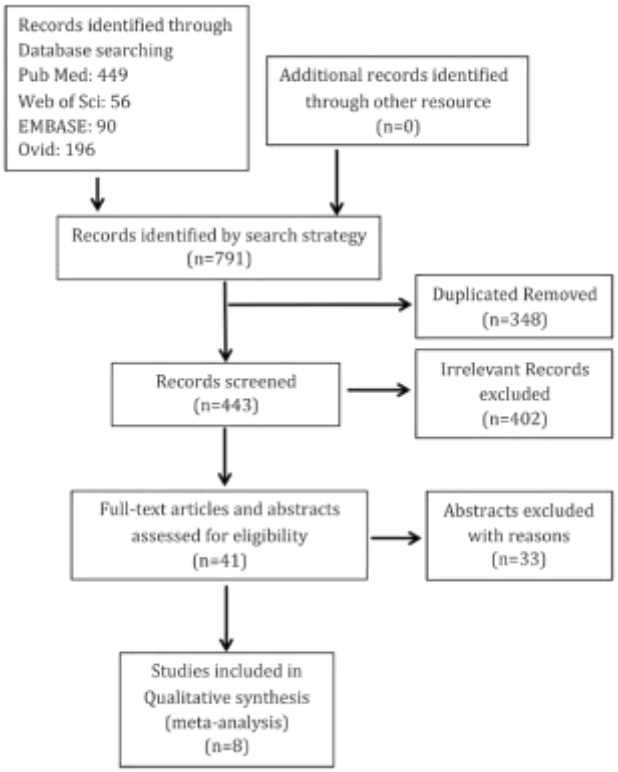


**Fig. 1:** Flow diagram of study selection. A total of 791 potentially relevant studies were collected, of which 8 RCTs were included in the meta-analysis

### Risk of bias, sensitivity analysis and quality assessment

Funnel plot was made to describe the bias in publications (Fig. 2). All of 8 RCTs enrolled in this meta-analysis unfolded a low risk of bias. Cochrane collaboration tool was used to show the risk of bias of 8 RCTs shown in Fig. 3. They all applied random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment and had low risk of incomplete outcome data and selective reporting.

**Table1:** Characteristics of the included RCTs

| *Study* | *Study type* | *Country* | *Follow up* | *Esomeprazole* | | | *Control* | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | *N (M/F)* | *Age, years* | *Admin-istration* | *N (M/F)* | *Age, years* | *Admin-istration* |
| Devault 2006 (33) | RCT | US | 6 months | 501 (297/204) | 47.5 (18-75) | 20 mg/d | 500 (293/207) | 47.9 (18-78) | Lan: 15 mg/d |
| Goh 2007 (34) | RCT | multi-countries | 6 months | 667 (396/271) | 48.8±14.5 | 20 mg/d | 636 (373/263) | 49.0±14.1 | Pan: 20 mg/d |
| Johnson 2001 (35) | RCT | US | 6 months | 82 (51/31) | 46.3 (21-81) | 20 mg/d | 82 (48/34) | 46.9 (19-73) | Eso: 40 mg/d |
| Labenz 2005 (36) | RCT | multi-countries | 6 months | 1377 (888/489) | 50.2±14.1 | 20 mg/d | 1389 (856/533) | 50.7±13.8 | Pan: 20 mg/d |
| Lauritsen 2003 (37) | RCT | Europe and South Africa | 6 months | 615 (388/227) | 49.3 | 20 mg/d | 609 (356/253) | 49.2 | Lan: 15 mg/d |
| Talley 2001 (38) | RCT | Denmark, Fenland, Norway and Sweden | 6 months | 170 (94/76) | 49 (19-78) | 20 mg/d | 172 (98/74) | 49 (21-79) | placebo |
| Talley 2002 (39) | RCT | UK, Ireland and Canada | 6 months | 282 (135/147) | 48.4 | 20 mg/d | 293 (135/158) | 48 | Eso: 40 mg on demand |
| Vakil 2001 (40) | RCT | US | 6 months | 92 (51/41) | 47.1 (18-84) | 20 mg/d | 98 (58/40) | 45.2 (19-76) | Eso: 40 mg/d |

All the RCTs were double-blinded: study subjects and investigators were both blinded. The clinical outcome data in the included studies were based on specific guideline, and their baselines were similar. Funnel plot and Egger test showed there was no significant bias in the publication (Fig. 4). Sensitivity analysis plot was performed to analyze the sensitivity of the included trials of this meta-analysis, indicating the stable results. The study qualities of each RCT were evaluated using the Jadad scale, and all 8 studies were of high quality. All 8 randomized controlled trials reported adequate randomization, and no RCT was stopped early. Jadad scale showed the study qualities of each randomized control trial (Table 2).

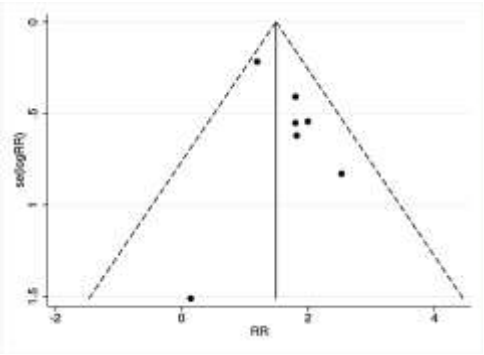


**Fig. 2:** Risk of publication bias for each trial. Both the funnel plot and Egger test showed no significant evidence of bias in the publication

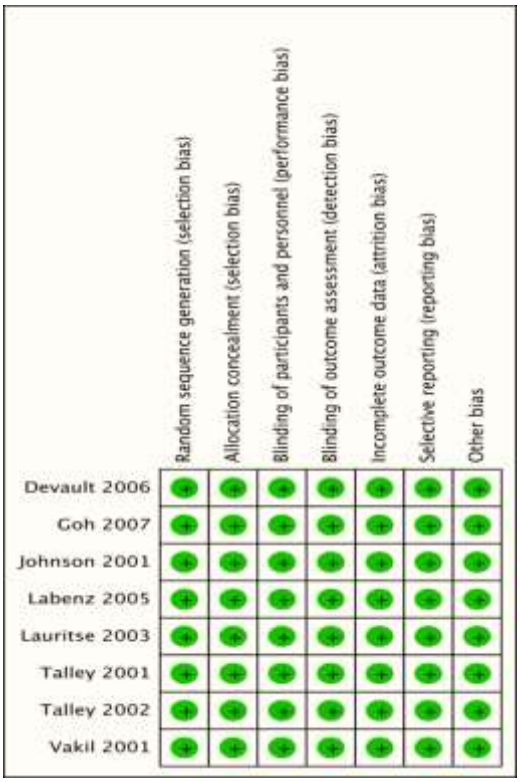


**Fig. 3:** Risk of bias assessment. The qualities of the included studies were evaluated using Cochrane collaboration tool, indicating that there is no significant risk of bias in the included trials of this meta-analysis

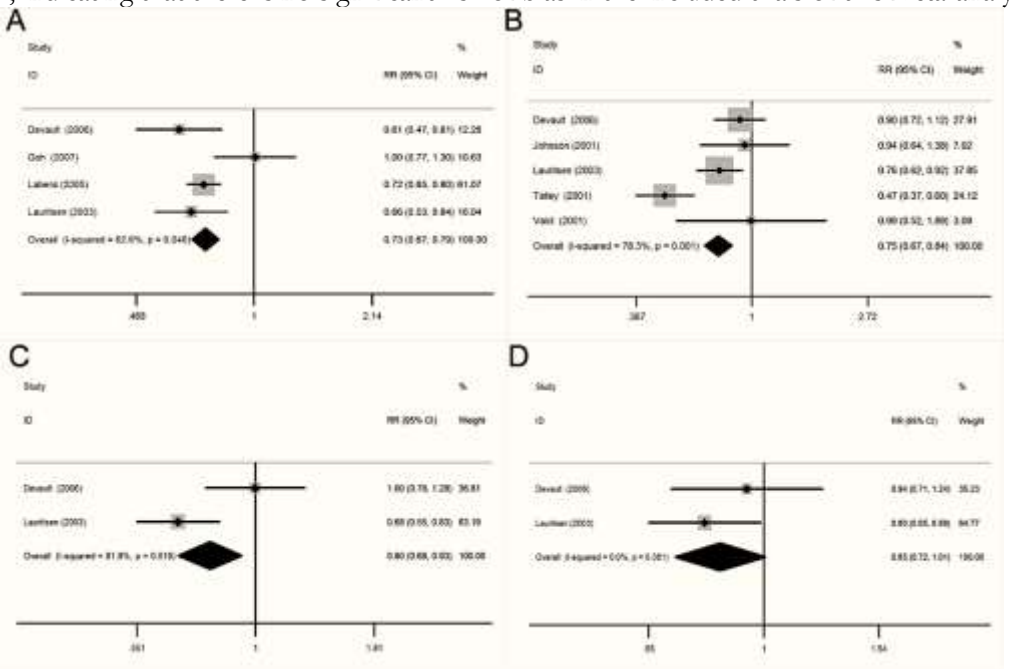


**Fig. 4:** Forest plot of the 8 RCT studies. (A)relapse rates; (B)heartburn; (C)acid regurgitation; (D)epigastric pain. Black dots represent the standardized mean difference (SMD), and Horizontal lines represent 95%Cls of the SMD estimates. Diamonds stand for summary effect estimate of the meta-analysis

**Table 2:** The study qualities of each RCT were evaluated using the Jadad scale

| *reference* | *Year* | *Representation of randomization* | *Appropriateness of method for randomization* | *Representation of double blinding* | *Appropriateness of method for double blinding* | *Representation of withdrawals* | *Total score* |
|---|---|---|---|---|---|---|---|
| Devault | 2006 | 1 | 1 | 1 | 1 | 1 | 5 |
| Goh | 2007 | 1 | 1 | 1 | 1 | 1 | 5 |
| Johnson | 2001 | 1 | 1 | 1 | 1 | 1 | 5 |
| Labenz | 2005 | 1 | 1 | 1 | 1 | 1 | 5 |
| Lauritsen | 2003 | 1 | 1 | 1 | 1 | 1 | 5 |
| Talley | 2001 | 1 | 1 | 1 | 1 | 1 | 5 |
| Talley | 2002 | 1 | 1 | 1 | 1 | 1 | 5 |
| Vakil | 2001 | 1 | 1 | 1 | 1 | 1 | 5 |

### *Efficacy outcomes of esomeprazole*

In a pooled analysis of all 8 RCTs, significant improvement of efficacy of esomeprazole was observed in various clinical indexes: relapse rates, heartburn, acid regurgitation and epigastric pain.

Four studies (33, 34, 36, 37) reported the relapse rates for esomeprazole treatment during six months. Heterogeneity test results showed that there was significant heterogeneity across individual studies ($P$= 0.046, I2 = 42.6%). Therefore, the random effects model was selected to pool RR from individual studies. Fig. 3A shows that esomeprazole treatment had better curative effects than treatment with other drugs (risk ratio (RR) = 0.73; 95% confidence interval (CI): 0.67-0.79; $P$< 0.001).

Five articles (33, 35, 37, 38, 40) reported heartburn symptoms of GERD reoccurrence after esomeprazole treatment. Significant heterogeneity between the studies ($P$< 0.001, I2 = 78.3%) was found. When we pooled data from the 5 studies, esomeprazole showed better a curative effect on heartburn compared with other treatments using random effects model (RR = 0.75; 95% CI: 0.67-0.84; $P$< 0.001) (Fig. 3B).

Two articles (33, 37) reported acid regurgitation symptom reoccurrence after esomeprazole treatment. According to the results of the heterogeneity test, heterogeneity across individual studies was found with statistical significance ($P$= 0.019, I2 = 81.9%). When data from the studies were pooled using the random effects model, results showed no significant difference on acid regurgitation occurrence between esomeprazole treatment and other drug treatment (RR = 0.80, 95% CI: 0.68-0.93; $P$= 0.005) (Fig. 3C).

Abdominal pain reoccurrence after esomeprazole treatment was reported in two papers (33, 37). Lower abdominal pain occurrence after esomeprazole treatment compared with other esomeprazole treatment was found using the fixed effect model (heterogeneity, $P$>0.05, I2=0%; RR=0.85, 95% CI: 0.72-1.00; $P$=0.058) (Fig. 3D).

### *Safety*

Adverse events occurrence is a key indicator for evaluating drug treatment (41). Here, we compared adverse events and serious adverse events during six months maintenance treatment between esomeprazole group and control group. Adverse events were reported in 6 studies. Fig. 5A shows no significant difference between esomeprazole treatment and other drug treatment on adverse events occurrence (RR = 1.07, 95% CI: 1.00-1.15; $P$= 0.068), and no significant heterogeneity was found across studies ($P$= 0.21, I2 = 30.1%).

Seven articles reported serious adverse events. As shown in Fig. 5B, we pooled data from the studies and found higher serious adverse events risk after other drug treatment than esomeprazole treatment (RR = 1.41, 95% CI: 1.03-1.92; p=

0.032) without significant heterogeneity (*P*= 0.61, I2= 0%).

### *Test of heterogeneity*

We generated to identify potential sources of heterogeneity of overall effects based on the forest plots, we discovered that the heartburn and acid regurgitation symptom can significantly affect the heterogeneity of outcome result; meanwhile, relapse rates and abdominal pain reoccurrence may not contribute to the data heterogeneity. To explore the source of heterogeneity, Galbraith radial plot was performed. No study was the major source of heterogeneity (Fig. 6).

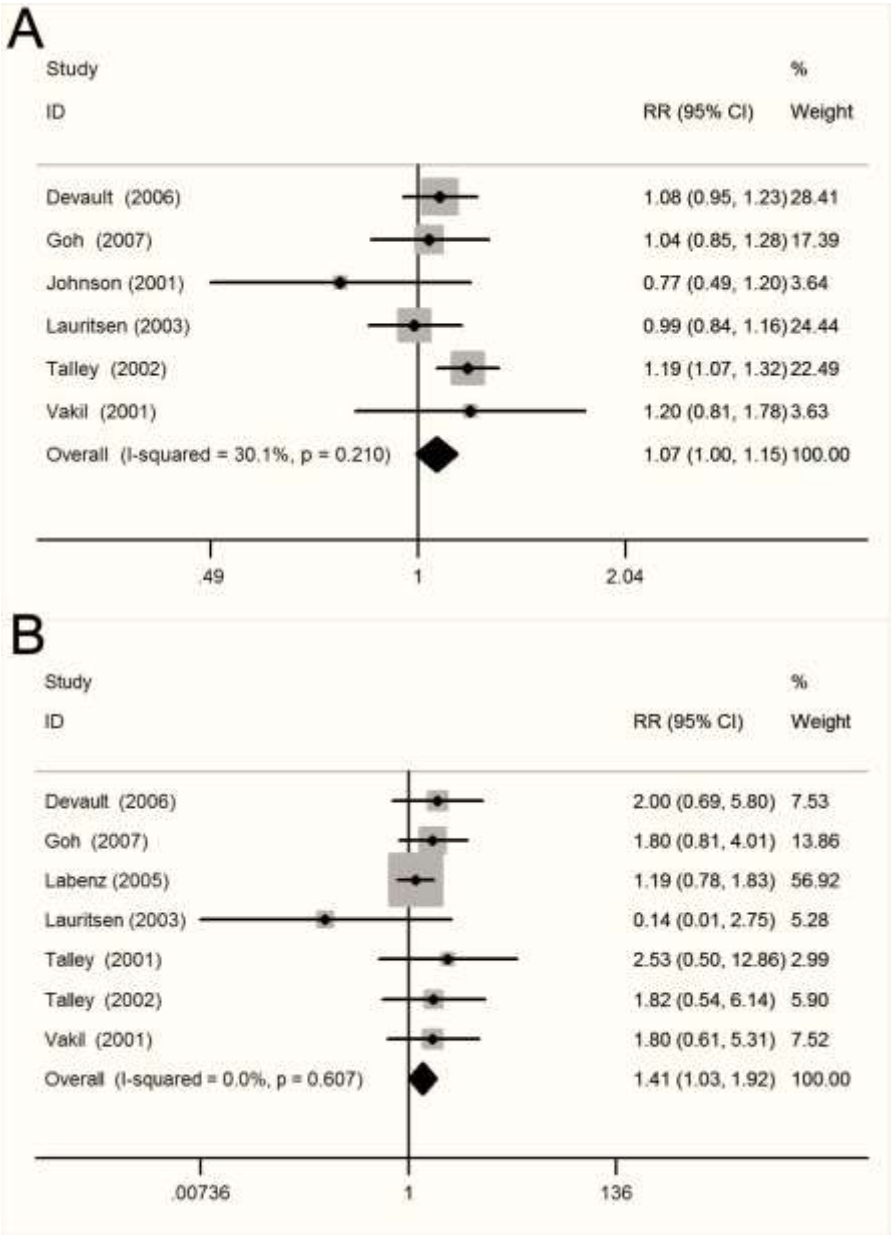


**Fig. 5:** Forest plot of the adverse events and serious adverse events of esomeprazole. (A) adverse events; (B) serious adverse events. Black dots represent the standardized mean difference (SMD), and Horizontal lines represent 95%Cls of the SMD estimates. Diamonds stand for summary effect estimate of the meta-analysis

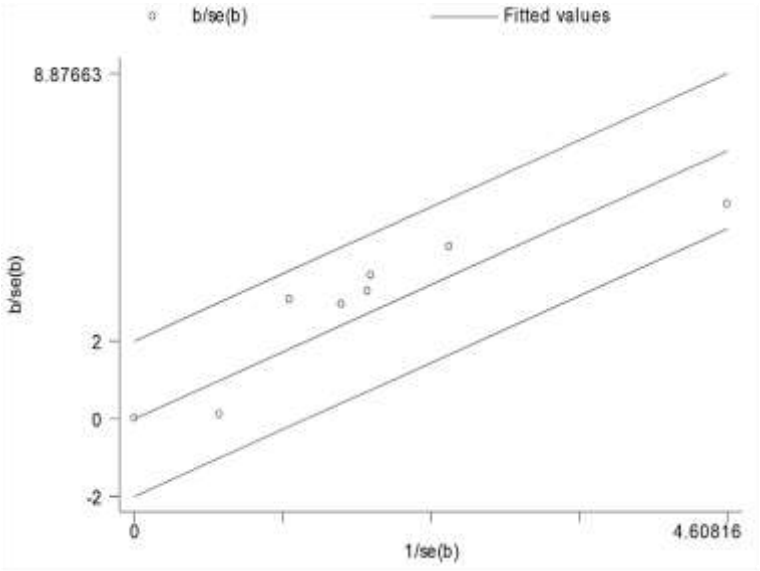


**Fig. 6:** Galbraith radial plot. The figures show the contribution of results from the different studies to the heterogeneity. No study was shown to be the main source of the heterogeneity

## Discussion

In this meta-analysis, our results demonstrated the efficacy and safety of esomeprazole in the treatment of patients with GERD across 8 RCTs. Esomeprazole was shown to be consistently more effective than placebo and has a placebo-like safety profile. This is the newest systematic analysis and comparison of all double-blinded RCTs data for the treatment of GERD.

The trials included have high consistency in the patients enrolled, randomization and masking, and treatment outcomes. The endpoints these clinical trials applied include objective indexes, subjective indexes, or both, which provide comprehensive assessment of the treatment responses. Relapse rates is objective assessment of the disease severity, whereas heartburn, acid regurgitation and epigastric pain combined both objective and subjective evaluation of GERD (42-45). The 8 trials included in this review are consistent in applying the similar objective and subjective clinical index, and the results from 8 trials are also consistent in that esomeprazole are effective and safe in the treatment of GERD, as evidenced not only by decreased symptoms of gastroesophageal reflux recurrence, but also by decreased side events occurrence.

The RCTs with esomeprazole did not show serious adverse events. Further clinical trials would provide more information on this issue. Overall, esomeprazole is a promising therapeutic agent that improves the management of patients with GERD. Most importantly, the esomeprazole treatment is very safe.

A limitation of this meta-analysis is the limited number of clinical trials (only 8) included in this study. However, all the trials were double-blinded, randomized, and placebo-controlled studies; therefore, they are of high quality. Furthermore, although almost all publications included in this study were from top journals with high impact factors, risks of bias e.g. funding from pharmaceutical industry may exist. Because of the restriction of ethics, it's not easy to carry out clinical trials in the population of children, which are the special population of GERD, and future study should address the potential application of esomeprazole in this population.

PPI drugs are still recommended by the current guidelines for the treatment of GERD when topic treatment or phototherapy is ineffective; however, the frequently occurring serious adverse events hinders the use of systemic anti-GERD treatment (45-50). Our finding clearly indicates that esomeprazole is a promising anti-GERD

medication, and would meet the need of treating GERD specifically and efficiently. Further investigations should prove the long-term stability, efficacy, and safety of esomeprazole in treating GERD.

## Conclusion

Esomeprazole is a promising therapeutic agent that improves the management of patients with GERD without serious adverse effects.

## Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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## Conflict of interest

The authors declare that there is no conflict of interest.

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